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*“Identification of options for the design of future instruments to limit pollution from PPs into water”*

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## Abbreviations

API	Active Pharmaceutical Ingredients
BLAC	German Federal and States' Committee for the Safety of Chemicals ( <i>Bund/Länderausschuss für Chemikaliensicherheit</i> )
BOD	Biological Oxygen Demand
DOOP	Disposal of old Pharmaceuticals
EEA	European Environmental Agency
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPA	Environmental Protection Agency
ERA	Environmental Risk Assessment
EU	European Union
HCWH	Health Care without Harm
NGO	Non-Governmental Organisation
LIF	Swedish Association of the Pharmaceutical Industry
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-counter
PBT	Polybutylenterephthalat
PEC	Predicted Environmental Concentration
PPs	Pharmaceutical products
SEK	Swedish Crowns
SEPA	Swedish Environmental Protection Agency
SRU	Sachverständigenrat für Umweltfragen
TKSG	Tweede Kamer der Staten-Generaal
UK	United Kingdom
UWWTP	Urban Waste Water Treatment Plant
WFD	Water Framework Directive
WWTP	Waste Water Treatment Plant

# 1 Introduction

## 1.1 Objectives and scope

This paper aims at identifying and assessing instruments that can be used to limit the occurrence of pharmaceutical products (PPs) in the European water environment in view of a possible future action programme.

The information presented is based on the review of currently available literature, reports prepared within the KNAPPE project as well as the conclusions of the KNAPPE expert workshop on policy instruments and ecopharmacostewardship to limit water pollution with PPs (York, 29-30 April 2008).

The scope of instruments discussed below ranges from technical management practices, e.g. related to the upgrading of wastewater treatment, to instruments that aim at better information/education of doctors and patients or at improved policy implementation. In chapter 3 an evaluation of the instruments is presented according to a set of relevant criteria, including environmental effectiveness and costs (when data available). Recommendations for further research as well as consultation to support the identification and assessment of the right mix of instruments that should be applied in the future are indicated in the final section of the paper.

Most aspects of the paper focus on human pharmaceuticals but several instruments are also relevant to the reduction of water pollution from veterinary drugs, e.g. good prescription practices, take-back schemes or ecolabels.

## 1.2 Is there a need for future action?

In view of preparing a possible future action programme to prevent and limit water pollution from PPs, the question of “whether there is a problem or not due to the discharge of PPs in water” comes at the centre of attention.

At the KNAPPE expert workshop in York (29-30 April 2008) (see summary Kampa (2008)), it was concluded that there is no clear picture yet within the industry of potential risks from PPs. However, risks cannot be excluded, which is why the use of the precautionary principle is called for in relevant policy and management discussions.

According to current literature, the occurrence of pharmaceutical products as trace environmental pollutants has become an important issue since the 1980s. Until now, more than 90 pharmaceuticals and their metabolites, out of 3000 registered in EU (Joss et al., 2006), have been found in environmental waters and sediments. Furthermore, the amount of PPs in the environment is expected to continue to grow. With regard to this prospect, Daughton (2003) mentions the following drivers: increase of per capita consumption of PPs, expanding population, expanding potential markets, patent expirations, new target age groups, inverting age structure in the general population and new use for existing drugs.

To date, only few cases of significant environmental impact of PPs have been confirmed, especially the case of vultures mortality due to diclofenac and the case of fish reproductive disruption due to estrogenic chemicals.

Specifically, in the early 1990s, vultures experienced dramatic population declines (as great as 99%) in Southern Asia – particularly India and spreading to Pakistan and Nepal. Various hypothesized causes ranged from pathogens to pesticides until researchers of the Washington

State University first discovered (in Pakistan) that the die-offs were strongly linked with exposure to diclofenac (Oaks et al., 2004). Diclofenac was used in veterinary medicine in certain countries. In India, it was used for cattle, whose carcasses were a major food source for vultures (*Gyps spp.*). Diclofenac seems to be selectively toxic to *Gyps spp.* versus other carrion-eating raptors. As of 2006, India, Nepal, and Pakistan banned the veterinary use of diclofenac (now replaced by meloxicam). This case thus indicated the unanticipated responses of non-target organisms when acutely exposed to high levels of single stressors (Daughton, 2008).

Furthermore, over the past 15 years, scientists have discovered that natural and synthetic estrogenic chemicals in sewage water effluent, including 17 $\alpha$ - ethinylestradiol from birth control pills, can affect the reproduction and development of wild fish living in the waters downstream.<sup>1</sup> Data from a recent study on a model fish species (minnows) revealed a clear link between estrogens present in effluents and diverse, adverse, and sex-related health impacts. The findings also highlighted the need for an improved understanding of interactive effects of chemical toxicants on biological systems for understanding health effects of environmental mixtures (Filby et al. 2007).

Except for such clear examples of impacts of PPs on non-target living organisms, our knowledge on the nature and extent of the environmental impact of PPs is still limited. The lack of knowledge and uncertainties on this issue complicates discussions on possible future action. In this context, it becomes clear that we need a better understanding, better data and further research on PPs in the aquatic environment. Some of the key areas for further research include the fate and effects of PPs in the environment, low-level effects and chronic effects of PPs as well as the cumulative effects of mixtures of PP substances (Kampa et al., 2008).

As concerns impacts on human health, current literature concludes that human health is not at risk from PPs via surface and drinking water (Christensen, 1998; Schulman et al. 2002; Schwab et al. 2005; Webb et al. 2003). However, although the environmental concentration of PPs is considered to be too low to have an effect on human health, the public demand for drinking water of good quality cannot be overlooked by water managers. In addition, the following remarks are worth keeping in mind: 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; current 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); current 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).

Despite our limited current understanding of this emerging environmental issue, the scientific community tends to agree that, for the sake of the precautionary principle, we should already explore ways of limiting the input of PPs into the environment, thus, anticipating possibly needed actions in the near future (Kampa et al. 2008).

A wide range of protective/proactive actions can be implemented in order to reduce or minimize the introduction of pharmaceutical compounds to the environment (Daughton, 2003). Next to progress that can be made with respect to improving wastewater, sludge or water treatment technologies, there is a wide variety of other actions that can be initiated such

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<sup>1</sup> Environmental Health News, 7-9-2007, <http://www.environmentalhealthnews.org/newscience/2007/2007-0905philbyetal.html>.

as better risk communication, better implementation of relevant regulations, targeted therapy and others as elaborated in the next section.

At the same time, it is important to be sure that the appropriate level of scientific evidence of risk be accumulated before costly precautionary measures are invoked. Relevant criteria should be communicated and more transparency is required for proposed actions. In general, the industry (but also governments) need to know what is defined as a problem, before they can give an opinion on what types of PPs are of most concern (Kampa, 2008).

The need for future action on the issue of PP occurrence in the environment is also increasingly recognised on the political level of some European countries. For example, in the Netherlands, the emission of pharmaceutical residues to the environment has been getting attention since 1999. At that point, the screening and monitoring of pharmaceuticals started. In 2004, the Minister of Environment initiated a working group in which different stakeholders met, including the ministry responsible for drinking water, the ministry responsible for water quality, the ministry responsible for pharmaceuticals and health care, the drinking water companies, some research institutes and the pharmaceutical industry. Firstly, a chain analysis was made for human and veterinary pharmaceuticals. This analysis resulted in a list of possible actions for emission reduction, with an advice for the most promising actions. From 2007 on, the most promising actions started to be implemented or investigated at a pilot scale, such as the promotion of restrictive PP use by more information to users and new packaging, green pharmacy, the application of an environmental classification system for PPs, pilot projects on treatment and emission reduction at health care units as well as research on wastewater treatment systems (Roorda et al., 2008).

### **1.3 Structure of report**

The following section 2 describes good management practice options and possible instruments that may be used to reduce PP occurrence in the water environment, based on discussions of the KNAPPE partners and stakeholders. Subsequently, section 3 presents a preliminary assessment of the proposed instruments based on selected criteria that are relevant to the environmental effectiveness as well as the costs of different options. The preliminary instrument assessment is based on the limited information available at present on these aspects. Section 5 identifies issues that need to be further researched and assessed in the future, in order to support the selection and to guide the design of the most cost-effective instruments and management practices.

## 2 Identification of possible instruments to reduce PP occurrence

In the following, good management practices options that were identified at a KNAPPE expert workshop in York (29-30 April 2008) are discussed in more detail, while certain new aspects are also added (e.g. collection and treatment of wastewater in hospitals) based on current literature. The following list of key instruments and management practices is grouped into technical instruments, instruments addressing prescriber and/or consumer behaviour, policy and economic instruments. These categories are only meant as a broad systematization based on (one of) the main operating principle(s).

a) Technical instruments:

- Upgrade of wastewater treatment plants
- On-site collection & treatment of wastewater at health care units, esp. hospitals
- Take-back schemes of PPs

b) Instruments targeting prescriber and consumer behaviour:

- Environmental classification of PPs as means of improved risk communication
- Good prescription practices
- Ecolabels for PPs
- Consideration of environmental risk criteria in hospital procurement
- Partnerships, e.g. between WWTP operators and prescribers

c) Economic and policy instruments:

- Economic instruments based on the polluter-pays principle (e.g. sewage treatment fees and tax systems)
- Economic incentives for the production/consumption of “greener” PPs
- Improving the implementation of the current policy framework

With the exception of the instrument of drug take-back schemes, other approaches that fall under pharmaceutical product stewardship for lowering the environmental impact of PPs, as well as “ecopharmacovigilance”, are not discussed here in detail, since they have been discussed to great extent in other reports of the KNAPPE project (see Summerton et al. (2008); Clark et al. (2007)). Nonetheless, some approaches related to incentives for the industry are discussed below.

### 2.1 Technical instruments

#### Upgrade of wastewater treatment plants

Although the limitation of PPs at source should be our first choice, it is argued that this will not be a sufficient action considering the very large amounts of PPs in circulation already. On the other hand, it is also emphasised that if action is limited to treatment only, there will be no or little incentives to change PP release at source.

At present, municipal wastewater is treated mainly for the removal of BOD, suspended solids, nitrogen and phosphorus. The removal of pharmaceuticals is not intended and the treatment plants are not designed to remove these substances.

Thus, WWTPs are not able to remove all PP substances during treatment. For this reason pharmaceutical residues and other chemicals are found in WWTP effluents. Those substances which are not degraded or go straight through the plant end up in the sludge. In the WWTPs, concentrations of PPs are reduced between 0 and 100 % depending on the kind of substance (SEPA, 2008).

There is a lot of research carried out currently on pharmaceutical residue in WWTPs. All in all, upgrade of existing WWTP seems to be necessary in order to improve PPs removal (Buntner et al. 2008).

The extension of nitrogen treatment or increasing the sludge age in the activated sludge process by a couple of days can reduce the concentration of a number of substances, but not all (SEPA, 2008). Using pre- or post-treatment, such as ozonation, activated carbon, UV light or nanofiltration are available solutions, however, they increase the costs and in some cases involve the danger of toxic metabolite emission to the environment (see section 3.2). Therefore, it is recommended that the major improvements of existing wastewater treatment systems rely on modifications of chosen parameters. It has been proven that the removal efficiency of PPs in WWTPs varies with regard to following parameters: sludge retention time, hydraulic retention time and the reactor configuration (Zabczyński et al. 2008).

As far as the policy framework for treatment is concerned, the most relevant EU policy at present 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. Firstly, the full implementation of the Directive in all EU Member States would contribute to a larger-scale removal of PPs from water at the treatment phase. Secondly, 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 (Kampa et al. 2008).

It should be mentioned that next to upgrading technology of WWTPs, requiring all municipal WWTPs to have secondary treatment as minimum is required by European legislation and would in itself be a measure contributing to less PP emissions to the water environment.

### **On-site collection & treatment of wastewater in hospitals**

In hospitals, a large variety of chemical substances (e.g. pharmaceuticals, radionuclides, solvents and disinfectants) are in use for medical purposes such as diagnostics and research. After application, diagnostic agents, disinfectants and non-metabolized pharmaceuticals excreted by patients, reach the wastewater. In the same time, hospitals consume an important volume of water per day, giving significant volumes of wastewater, which in turn, may generate risks for aquatic organisms. Hospital wastewaters are also responsible for the spread of antibiotic resistance in the environment. The concentration of antibiotics in hospital wastewater is 4 to 100 times higher than in municipal wastewater. The reason is that about 25% of antibiotics for human application are being used in hospitals (summarised by Zabczyński et al. (2008)).

In the Netherlands, the emission route via hospitals has been calculated to account for up to 20% of the total load of human pharmaceuticals in the environment. For this reason, the 130 hospitals in the Netherlands are called a hot spot for pharmaceutical emissions, related to the

more diffuse emission route via 7 million households. In addition, although the wastewater volume of Dutch hospitals only accounts for 0.4% of the total wastewater volume, the amount of specific pharmaceutical compounds originating from hospitals can be from 30% up to 50% of the total amount discharged to the sewage system (Roorda et al. 2008).

Another recent report by the Swedish EPA also indicates that the highest concentrations of pharmaceutical residues are found in hospital sewage systems. However, it is emphasised that the largest amounts of PPs are found in the inflow to the WWTPs (SEPA, 2008), which should be considered in investment decisions for the treatment of wastewater loaded with PPs.

The wastewater from hospitals and other health care units is usually collected in the municipal sewer system and treated together with other municipal wastewater.

Because of the variety and load of hazardous pollutants, several researchers propose that wastewater from hospitals requires on-site treatment to prevent contaminating the municipal sewer system and environmental waters. Additionally, sludge from on-site plants should be managed with the same precautions as municipal waste sludge and should not be used as manure, unless properly treated (Gautam et al., 2007).

Roorda et al. (2008) also suggest that, instead of removing the contaminants from more than 100 times diluted urine and faeces within the municipal WWTPs, these substances can be removed from the undiluted urine and/or faeces at the hospital.

Hospital wastewater could be successfully treated by photo-Fenton process, reverse osmosis, activated carbon, ozonation, submerged hollow fiber membrane bioreactor, coagulation/flocculation (+ filtration + disinfection) (summarized by Zabczyński et al. (2008)).

Roorda et al. (2008) discuss the following collection and treatment methods for (waste)water from health care units like hospitals in the Netherlands:

- Conventional collection and treatment with other municipal wastewater. The situation as it is in most developed countries.
- Separate collection and treatment of urine, considering that up to 70-90% of all pharmaceuticals are excreted via the urine. One example is the installation of urine separation toilets in a newly build hospital. Another example is houses for elderly, where pharmaceuticals from urine are removed by applying proper treatment techniques.
- Separate collection and treatment of black water or toilet water. Almost 98% of all pharmaceuticals are excreted in urine and faeces. In several hospitals the collection and treatment of toilet water is being discussed.
- Next to these options, combinations of new sanitation options are under development. One very promising idea is the Pharmafilter concept in which all waste streams in a hospital are combined.

### **Drug take-back schemes**

The development and set up of take-back schemes for unused/expired medication has been receiving increasing attention as a post-pharmacy stewardship approach for reducing the discharge of pharmaceutical products into waters.

Next to the environmental benefits of the correct disposal of unused PPs (the effectiveness of which is however sometimes questioned due to lack of concrete data; see chapter 3), take-

back schemes help address other, more high-profile public health issues such as unintentional poisonings of children and elderly, substances abuse, etc. These drivers were actually behind the setting up of take-back schemes in several European countries during the 1990s; short-term campaigns for returning unused drugs can be traced back at least to the 1970s (Langley et al., 2005)). By the late 1990s, France, Germany, Sweden, and England all counted with return systems in pharmacies; Spain followed in 2002. Returned drugs are customarily subjected to high-temperature incineration; this is satisfactory from an environmental point of view due to break-down of active ingredients in this process. In some cases (e.g. France), the portion of returned drugs in satisfactory condition were to be donated to NGOs for distribution to poor people or in poor countries. This possibility has also been discussed in research in other countries such as England (Mackridge and Marriott, 2007). In the case of France, however, scandals concerning the re-sale of returned drugs by pharmacists caused changes to the system: currently all drugs are to be destroyed “under secured conditions” (Grass and Lalande, 2005).

At the European level, take-back schemes for unused or expired medicine are required since 2004 by EU legislation. For veterinary products, the requirement to have appropriate collection systems based on European legislation dates from 2001. In those countries which counted with take-back systems (see above), these were simply maintained; in the case of those countries facing the requirement to implement new systems, several have not yet complied. According to Taylor and Poulmair (2007), 20 European countries (out of 28 countries surveyed) have a drug take-back scheme in place. However, seven countries have no scheme,<sup>2</sup> and no information was available for Luxembourg. Eleven of the schemes in place are managed by pharmacies, six are co-ordinated nationally and five locally. The majority of the returned material is incinerated.

Take-back surveys are viewed positively by most stakeholders involved, including the pharmaceutical industry. In a survey of expert stakeholders’ views, which compiled the opinions of 27 stakeholders working in government, academia, pharmaceutical and consulting industries, the implementation of take-back schemes was put forward as the most popular risk management strategy for pharmaceuticals in the environment (Doerr-MacEwen & Haight, 2006). In this context, take-back schemes were seen best coupled with public education. Although the size of the contribution of improper pharmaceutical disposal to the environmental loading of pharmaceutical products is not well understood (see discussion in chapter 3), one of the interviewed stakeholders explained that take-back schemes are seen as a positive management response because disposal of unused and expired medicine seems like a logical, easy portion to remove from the environmental loading.

## **2.2 Instruments targeting prescriber and consumer behaviour**

### **Risk communication, especially environmental classification scheme**

Risk communication is seen as a promising strategy within source-control approaches. It is seen as having the potential to influence compound choice, i.e. opting for the environmentally friendly choice in case of alternative compounds being available with comparable effectiveness. The main risk communication scheme for PPs, the “Swedish model”, has taken the form of an environmental classification and information scheme. There has been an on-going discussion on the possibility of extending this scheme to the rest of Europe.

The scheme relies on information on the environmental hazards and on the associated risks of Active Pharmaceutical Ingredients (APIs). The information on risk/hazard is presented

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<sup>2</sup> Bulgaria, Cyprus, Greece, Latvia, Malta, Romania and Slovenia.

differently for three target groups with different levels of expertise: patients, prescribers, and specialists (scientists, experts, etc.). The information is not placed on the packaging due to European restrictions on the information that can be added to packaging of medication. The relevant information/labels are placed on websites; Stockholm County Council provides both a detailed book on the subject background and booklets with the latest classifications (Clark et al., 2007).

The outcome of the information scheme is presented to the pharmaceutical expert groups of the Stockholm County Council; these use this information – as well as considerations regarding therapeutic efficiency, side effects, price, etc. – in selecting the drugs that are recommended for use in the County Council health care. According to an early evaluation of the Stockholm County Council, doctors displayed a high obedience (around 75%) to the recommendations of these pharmaceutical expert groups. Doctors would also receive training in the information system.

The presumed achievements of the model were that doctors, healthcare staff and patients increase their awareness of possible environmental impacts of pharmaceuticals, and that the industry increases its efforts to design new biodegradable and not bioaccumulating drugs.

### **Good prescription practices**

The promotion of good prescription practices aims at a wiser use of PPs (e.g. of animal antibiotics in a balanced way for prophylaxis and treatment) and at limiting over prescription.

Stockpiling and over prescription of medicines is a huge issue. There is a need to educate doctors and pharmacists but also patients because over prescription is very often a patient problem as they want the doctor to prescribe medication (that is not always necessary). It is considered that health insurers and health agencies could drive change in this area (Summerton et al. 2008).

The promotion of improved prescription practices could be combined with the development of more targeted therapy and the education of physicians themselves. In this context, one potential way to reduce the presence of pharmaceuticals in the environment is to develop personalised medicines. This would require a reduced dose (increased efficacy) and would lead to improved prescription practices as there would be less trial and error to find which works best for the patient. Improved stock control to minimise drugs in the market place would also minimise waste (Summerton et al. 2008).

Synergies are also obvious with instruments that promote risk communication for both the public and prescribers, such as environmental classification systems (see further below).

Both physicians and the public could be made more aware and better informed as to the medical and environmental consequences of overprescribing medications. Guidelines could be developed and promulgated for minimising inappropriate drug use. Regarding the linkage between human and environmental health, progress on this front has been most developed for the issue of antibiotics, where physician knowledge and patient expectations are commonly at odds and antibiotics are sometimes prescribed (because of patient expectations) in situations where they are not justified. Others who should attempt to minimise the misuse of antibiotics are veterinarians, aquaculturists and agriculturists to lessen the incidence of resistance development in native bacteria and human pathogens (Daughton 2003).

Furthermore, drug manufacturers could provide the medical community with more easily implementable information (and unit doses) to tailor drug dosages for the individual (Daughton 2003). Consideration could be given to providing a broader selection of package

sizes of PPs, e.g. smaller start-up packs. Some PPs are more likely to be discarded because they are prescribed or purchased in quantities too great to be used before expiration. On the other hand, also patients need to be further educated regarding appropriate drug use in order to reduce patient non-compliance.

## **Ecolabels**

Ecolabels are important instruments in an environmental policy mix. Compared to command and control mechanisms, they are more flexible and their introduction is easier if supported by stakeholders. To our knowledge, there are no ecolabels of the classical kind that address the issue of pharmaceutical products in the environment. It is, however, questionable if they are appropriate for targeting the problem of the presence of PPs in the environment (see below and chapter 3).

Contrary to the classification and information approach implemented in Sweden (see above), which targets individual active substances, ecolabels target products; the labelling information should correspondingly appear on product packaging. It is often the case that chemicals of very different origin and purpose (e.g. active substance and other chemical compounds necessary for stabilising the intake of the drug) are mixed in a pharmaceutical product, and as a consequence released jointly into the environment. By addressing the product as a whole, an ecolabel could be a step towards more sustainable chemistry in pharmaceuticals; this is often termed “green pharmacy”.

Based on their characteristics as well as on the experience with their use in other areas, ecolabels seem to be appropriate for evaluating the sustainability or “greenness” of the *production processes* of a particular medication (Summerton et al., 2008). This, however, would not provide information that would allow comparing the behaviour of the relevant APIs once released into the environment. For the specific aim of reducing the impact of PP input into the environment, then, ecolabels would prove to be of limited value (although interesting from the altogether different perspective of reducing the environmental footprint of the pharmaceutical industry). A relatively minor link is given between both areas in the fact that ecolabels could *inter alia* address the release of APIs into the environment from pharmaceutical factories via discharge waters.

## **Consideration of environmental risk criteria in hospital procurement**

This proposed action would involve making large orders of PPs, e.g. by hospitals, also on the basis of environmental risk criteria. This could be considered as an extension of current greener purchasing initiatives of certain hospitals, e.g. with respect to packaging plastics. The argument related to this is that when there are two similar drugs (efficacy, safety, ease of use, etc), the environmental profile could well be the deciding factor in purchasing decisions. Difficulties could arise when a very cheap drug with a bad profile is chosen based solely on price. In this scenario, total costs (total lifecycle and externalities) should be considered but this obviously adds to the complexity of the decision (pers.comm, J.Page, HCWH, 5.8.2008).

It is argued that large customers of PPs, such as hospitals and health authorities, could be crucial in driving a trend towards drugs with less environmental impact. For example, the National Health Service in the UK is beginning to look at sustainability issues and if it were to demand demonstrably greener drugs in their tenders/contracts, then a system could potentially be developed to measure „greenness”. However, it is believed that this would only

work for on-patent prescription PPs but not for off-patent prescription PPs or OTCs (Summerton et al. 2008).

In any case, guiding principles behind green procurement should include the fact that all patients should be allowed best available pharmaceutical treatment and that other things being equal, the medicine's PBT<sup>3</sup> profile should be considered when purchasing (Page, 2007).

In Stockholm and in some other counties of Sweden, where the Swedish environmental classification system for pharmaceuticals is applied, a condition was set up in PP procurement to hospitals, that the producer should be loyal with the environmental classification system. This implies that the producers agree to deliver data to the database operated by the producers' own branch organisation (LIF, Swedish Association of the Pharmaceutical Industry). This organisation collects data and an external independent organisation audits the classification and approves it if it follows the guidelines agreed upon. Since this system operated by the producers themselves now runs without any problems, authorities only need to remind producers that they have to be loyal to the system if they want to sell drugs to the hospitals (pers.comm, A. Wennmalm, Stockholm County Council, 4.8.2008).

## **Partnerships**

Partnerships have been put forward as a good management practice option in order to reduce discharge of PPs at source. For instance, partnerships could be created between operators of urban wastewater treatment plants (for whom water pollution with PPs is an "upstream" issue) with pharmacists and doctors in their region in order to provide better information to prescribers on this issue.

In the Netherlands, already a covenant has been negotiated between government, pharmaceutical industry, health sector and drinking water companies, aiming at emissions reduction of iodine x-ray media (iopamidol and amidotrizoic acid), the anti-epileptic carbamazepine and the contraceptive pill (17alpha-ethinyloestradiol) (Roorda et al., 2008). In the context of a national emissions reduction strategy of PPs put recently on the Dutch policy agenda, this covenant targets substances which are considered to have proven environmental & health impacts (TKSG, 2007).

## **2.3 Economic and policy instruments**

### **Economic instruments: Polluter pays principle**

The application of the polluter-pays-principle is being promoted across Europe in the context of the Water Framework Directive implementation. Certain economic instruments can also be considered to support PP pollution prevention action as well as to support the financing of end-of-pipe treatment solutions. These approaches have to be seen in the context of the complex discussion on who is the actual polluter in this case (the pharmaceutical companies, the patient/consumer, or even the prescriber).

Options that may be considered include sewage treatment fees and tax systems. Taxes may be applied to the PP products themselves and/or to the industrial process; in either way, taxes should be ear-marked so that revenue is used to fund activities to reduce and prevent water pollution from PPs. Theoretically, taxes can be considered to be to the detriment of industry (if this increase is not reflected in the consumers' end-price), to the detriment of the consumer (if the price increase is passed on in its entirety to the consumer), or, in the case of a middle

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<sup>3</sup> PBT stands for persistence, bio-accumulation and toxicity.

position between these two poles, to affect both groups. The sewage treatment fees can be applied on consumers, the healthcare sector as well as industry.

Concerning taxes on polluting substances, there is a considerable body of documented experience in OECD countries, e.g. with taxes targeting pollution due to pesticides and fertilisers (Pearce & Kondouri, 2003). The taxes on these products appear to have played a role, albeit a limited one, in reducing pesticide and fertiliser use (the study highlights the difficulty of disentangling tax effects from other policy effects). On the one hand, pesticides and fertilisers can be expected to be over-used due to risk aversion among farmers, i.e. farmers will prefer to over-use rather than under use them, due to the possibility of unacceptable increases in the variance of crop yield. On the other hand, estimations of the sensitivity of consumer behaviour to price change of pesticides and fertilisers (price elasticity estimates) indicate low sensitivity, suggesting comparatively limited effects in terms of quantity reductions unless they are set at very high rates (relative to price) (ibid.). Pearce and Kondouri (2003) suggest that the effectiveness of the taxes rests on the uses given to the tax revenues.

Although a similar low effect of price change on purchasing behaviour has been suggested for pharmaceuticals due to the comparatively high priority of health issues to consumers, general statements on the matter are complicated by the major influence of national health systems and/or insurance coverage (e.g. deductibles, co-insurance provisions, maximum expenditure limits, etc.).

Sewage treatment fees are a widespread economic instrument. It frequently has the function of collecting charges e.g. for wastewater treatment, of being an instrument for reducing pollution (typically that originating from industry), or both (EEA Report No 2/2005). A sewage treatment fee, or a modification of existing fees, can be designed to target specific types of sewage water, with an appropriate mix of simplicity and target-specificity. The Netherlands' sewage treatment fee for instance makes a simple distinction between single households, charged for 1 pollution equivalent (equivalent to the amount of pollution one person produces per year), and normal households, which are charged for 3 pollution units. Industry can be charged on the basis of proxies such as production or number of employees, or in the case of the healthcare sector, number of beds. Non-residential users are often already charged differently according to their type of business, due to their producing wastewater of different "strength" (determined on the basis of Biological Oxygen Demand).

Both taxes and fees as economic instruments can be linked to the upgrade of wastewater treatment discussed previously. This is particularly the case if the same holds true for taxes on PPs as was suggested for taxes on pesticides and fertilisers, namely that the effectiveness of the taxes rests on the uses given to the tax revenues. A sewage treatment fee differentiated for various substances including drugs may also show similar behaviour.

### **Economic instruments: incentives for the production/consumption of "greener" PPs**

A different approach to economic instruments based on the polluter-pays-principle is the creation of incentives for the production and/or use of PPs that have a significantly improved environmental performance. The discussions on the subject have identified two possible types of incentives.

One type would focus on supporting the development of greener PPs by R&D pharmaceutical companies, by providing clear economic incentives. A possibility is that of patent extension (which would work as an effective incentive even if the extension period is a very short one). However, it should be kept in mind that this proposal is not likely to be well received by generics companies (Summerton et al. 2008).

The second type would focus on the support of consumer purchase of “greener” pharmaceuticals. This could take the form of a government subsidy that could for instance cover the price differential between a more expensive PP which has a significantly improved environmental performance, and a cheaper but environmentally more damaging equivalent PP.

### **Improving the implementation of the current policy framework**

As far as the current policy framework is concerned, the right mechanisms are already there in Europe in order to deal with the environmental impacts of PPs. The **environmental risk assessment (ERA) guidelines** of the EMEA and the Technical Guidance Documents are considered as very complete and the most strict in the world (Kampa, 2008).

However, there are some gaps in the current framework concerning particular classes of compounds that have not been tested at all in terms of their environmental risk (mainly compounds that were authorised prior to the issuing of ERA requirements and guidelines). For these cases, at the KNAPPE York workshop, it was proposed that a representative compound should be tested (see summary Kampa (2008)).

In addition, the low quality of data currently 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 many authorised substances are missing (Kampa et al. 2008).

In general, ERA has to continually improve to incorporate new knowledge on open issues, e.g. metabolites. Especially 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.

Additionally to the ERA policy framework, the **EU Water Framework Directive (WFD)** provides an overall framework for water protection from chemicals in Europe. The WFD includes important innovative elements such environmental quality standards combined with emission limit values, regular risk assessment of the status of water bodies and the drafting of river basin management plans, which can all be used to keep track of the role of PPs in the water environment.

All in all, the current policy framework at EU level is considered to be sufficient to deal with the issue of PP occurrence in the water environment. However, the need for better implementation of the existing framework in practice is recognised. Gaps in practical aspects of policy implementation should be targeted in future efforts addressing the presence of PPs in the environment. For instance, there are certain constraints which decrease the effectiveness of possible risk mitigation measures that may be taken for veterinary medicine (see discussion in Kampa et al. (2008)).

As far as EU directives going beyond medicinal regulations are concerned, they do not yet adequately take account of the precautionary and prevention principles on the issue of pharmaceuticals in water and the environment in general. Although a suitable EU policy framework is already in place, more explicit consideration of the issue of PPs and practical implementation of relevant policy aspects are needed. Especially as concerns the WFD, its respective mechanisms (e.g. identification of specific pollutants discharged in significant quantities in river basins) and its 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 further below).

The initial WFD identification of pressures and impacts on water bodies (completed in 2005) has to be updated by 2013 and every 6 years thereafter. PPs can be incorporated into this scheme once more data have become available on their occurrence and ecological impacts in water bodies failing to reach the WFD objectives. On the basis of the identification of water pressures and impacts, decisions for future monitoring of substances and relevant necessary water management measures are taken.

As far as targeted environmental monitoring of PPs is concerned, it has been intensively discussed within work package 5 of the KNAPPE project on ecopharmacovigilance. For more detailed information on this topic as well as a summary of expert discussions conducted at a workshop in York (April 2008), please refer to the deliverables of this work package available on the project website ([www.knappe-eu.org](http://www.knappe-eu.org)).

An additional key issue linked to EU and also national policies is the presence of PPs in sewage sludge that can 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). At present, there are no limits for PP concentrations 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 their preoccupation with the issue of contaminants in sludge, including pharmaceuticals, the application of sewage sludge on agricultural fields has been prohibited.

### 3 (Preliminary) assessment of possible instruments

#### 3.1 Assessment criteria

Before applying new instruments to limit PP occurrence in the water environment, socio-economic research is needed to assess the cost-effectiveness of existing and newly proposed management options. Indeed, investment and efforts are best spent on the most cost-effective approaches. The following criteria are proposed to be used as the basis for a first preliminary assessment of the effectiveness and costs of the different instruments proposed in the previous section.

<b>Criteria</b>	<b>Description &amp; possible indicators</b>
Impacts and effectiveness (regarding reduction of PP occurrence in water)	<i>Effectiveness in removing PPs from water</i>
Other environmental benefits	<i>Qualitative description and possibly specific indicators depending on type of consequence</i>
Environmental costs	<i>Qualitative description and possibly specific indicators depending on type of consequence. E.g. upgrading wastewater treatment may raise energy demand in the treatment process</i>
Costs	<i>Differs depending on instrument. E.g. EUR/lit of wastewater treated (upgrading treatment) EUR/tn of drugs recovered (take-back schemes)</i>
Possible limitations/obstacles to application	<i>Qualitative description</i>
Time until effectiveness	<i>This refers to the time needed for an effect to be measured in the water environment</i>

Only a preliminary assessment of instruments is possible in the context of the KNAPPE project due to limited currently available information and literature. In general, there is not sufficient information available yet for a full assessment of all options. It is expected that more information on the costs and benefits of different instruments and options will be available at a later stage, as more progress is made in ongoing pilot projects on a national level.

#### 3.2 Assessment findings

##### Upgrade of wastewater treatment plants

##### Impact/effectiveness

There is a lot of ongoing research on the removal efficiency of different WWTPs technologies with regard to PPs (e.g. in the context of EU projects such as POSEIDON and KNAPPE). Unfortunately, current lack of data limits proper comparison of the removal efficiency of most compounds according to a variety of treatment technologies (Zabczyński et al. 2008). Particularly, extracting water soluble pharmaceuticals from wastewater poses a problem to conventional WWTPs (Meißner, 2008).

According to current knowledge and available data:

- Conventional wastewater treatment does not provide full pharmaceutical products removal. When the treatment system uses the most suitable parameters (hydraulic retention time, sludge retention time, etc.), some of the substances achieve removal above 90% (e.g. ibuprofen or paracetamol), but some substances (e.g. contrast media, carbamazepine) do not show even partial elimination (see also Ternes et al., 2007).
- In case of upgrading treatment with the ozonation step, 5 mg/L of the ozone allows to eliminate some persistent substances (e. g. carbamazepine), however the contrast media remain present in wastewater (see also Ternes et al., 2003).
- Contrast media can be removed by means of activated carbon (see also Metzger et al., 2005).

Literature suggests that treatment methods such as ozonation and membrane filtration can achieve removal rates of more than 95% for most PPs (Heberer et al. 2002; Sedlak and Pinkston 2001; Ternes et al. 2003; Westerhoff et al. 2005; Zwiener and Frimmel 2000; in Doerr-MacEwen & Haight 2006), compared with an average of 60% for secondary WWTPs (Ternes 1998). Advanced treatment methods would be especially appropriate in large municipalities producing high volumes of waste, with existing infrastructure to support the advanced technology.

#### Other environmental benefits

There are many micro-pollutants in wastewater other than PPs. The upgrade of treatment technology in WWTPs in order to reduce PPs in wastewater effluent would also bring benefits in terms of reducing other micro-pollutants. According to SEPA (2008), the possible additional treatment steps of ozonation, UV/hydrogen peroxide, UV/titanium oxide, membrane filtration, and activated carbon filtration are new methods for PP reduction which also reduce the presence of other organic molecules.

#### Environmental costs

Firstly, additional treatment in WWTPs (e.g. ozonation or activated carbon) to further reduce PPs involves increased energy demand of the treatment process (see table below) compared to the energy demand of conventional treatment. According to a recent report of the Swedish EPA, the energy consumed by wastewater treatment plants would at least be doubled if additional treatments for pharmaceuticals were introduced (SEPA, 2008). Furthermore, the rise of energy consumption does not only increase impact on the environment but also involves additional financial costs, as explained further below.

Secondly, additional treatment technologies can reduce PPs but at the same time lead to the formation of undefined by-products, which may be toxic to the environment (see more details below).

**Table 1 Options for advanced wastewater treatment**

	Energy kWh m <sup>-3</sup>	Costs €m <sup>-3</sup>	By products	Power Consumption (total 6000 W person <sup>-1</sup> )	Cost per person and year (100 m <sup>3</sup> water pers. <sup>-1</sup> year <sup>-1</sup> )
<b>Ozonation (with postfiltration)</b>	0.1-0.2	0.05-0.15	Toxico- logy unknown	1-2.5 W pers. <sup>-1</sup>	5-15 € pers. <sup>-1</sup> year <sup>-1</sup>
<i>Piloting results</i>					
<b>Activated Carbon</b>	<<0.05	0.08-0.20	None	<<1 W pers. <sup>-1</sup>	8-20 € pers. <sup>-1</sup>
<i>Literature, lab scale</i>					

Source: Busch & Mickols (2004); & Joss et al. (2007).

### Costs

The cost of additional treatment technologies could be very high. Thus, there is a need to assess relevant costs in detail.

At present, there are different estimations of costs, some of which are summarised below.

Recently, a rough estimation of the extra cost of reducing pharmaceutical residues from wastewater under Swedish conditions was made. This estimation indicated an extra cost of between 0.08 € and 1.58 € (SEK 0.75 and 15) per cubic metre, depending upon the choice of technique and size of the wastewater treatment plant. The cost of current treatment of wastewater in Sweden lies between 0.21 € and 0.84 € (SEK 2 and 8) per cubic metre depending on the size of the wastewater treatment plant. Taking into account all of the wastewater treatment plants in Sweden, the total cost would amount to a sum total between 0.16 mill € and 1.05 bill € per year (SEK 1.5 and 10 billion), which is equivalent to 21 € and 137 € per person per year (SEK 200 to 1,300). The reduction of pharmaceutical residues would at best involve an increase of 10 percent of the current cost, and in the worst case a near doubling of the cost for water supply and sewage system (SEPA, 2008).

The cost of advanced treatment technologies has also been calculated by several other authors, in the context of pilot projects as well as literature-based and lab-based studies (see table 1 above for costs of the technology of ozonation and activated carbon).

### Limitations & obstacles to application

In general, there are concerns related to the expense and energy requirements of advanced treatment technologies, the end-of-pipe nature of this management strategy, as well as the potential for the generation of reaction products (Doerr-MacEwen & Haight, 2006).

Indeed, advanced treatment technologies to further reduce PPs in WWTP effluents involve raised costs, as compared to costs under existing conventional treatment. Considering the high costs involved and for the sake of more cost-effective treatment, it is often suggested to separate strongly contaminated waters at source, e.g. via appropriate sewage canals in nursing homes (instead of allowing them to be diluted in the large amounts of wastewater reaching the WWTPs) (Meißner, 2008).

Regarding the formation of undefined by-products, especially in case of treatment with advanced oxidation processes, there is a risk of introducing toxic metabolites to the environment (Zabczyński et al. 2008). In general, however, there is a lack of research at present on the resulting by-products when using advanced treatment technologies to limit PP occurrence in WWTP effluents.

An issue related to this instrument that requires further assessment is its *time until effectiveness*.

## **On-site collection & treatment of wastewater in hospitals**

### Impact/effectiveness

In the Netherlands, different sanitation concepts for emission reduction of PPs from health care units like hospitals have been evaluated for their effectiveness and for the costs of the system. The indicative results are presented in table 2 below.

The effectiveness of urine and/or faeces collection and hospital treatment systems is about 10%, as on an average about 10% of the pharmaceutical are excreted in hospitals. This is a function of the flow of hospital wastewater related to the flow at the receiving municipal wastewater treatment plant where also wastewater from households and stormwater is collected and treated. The implementation of new sanitation systems at a large hospital that discharges its wastewater to a small WWTP will have a higher impact on the total pharmaceutical reduction than is the case at a small hospital discharging to a relatively large WWTP (Roorda et al. 2008).

A comparison has also been made to the removal of PPs by advanced treatment at the WWTP. The maximum removal efficiency is calculated at about 75% but with higher investment costs compared to the other sanitation concepts assessed (Roorda et al. 2008).

**Table 2 Expected effect and calculated costs of sanitation concepts for PP emission reduction**

<b>Scenarios</b>	<b>Costs/year</b>	<b>Effect</b>	<b>Costs per amount of pharmaceuticals</b>
<b>Urine</b>	Pharmaceuticals: 100 k€ All: 200 k€	10 %	1,0
<b>Urine and faeces</b>	Pharmaceuticals: 150 k€ All: 300 k€	10 %	1,5
<b>Hospital wastewater</b>	Pharmaceuticals: 150 k€ All: 300-350 k€	>10 %	1,5
<b>Hospital wastewater (concentrated part)</b>	Pharmaceuticals: 125 k€ All: 200 k€	>10 %	1,3
<b>WWTP</b>	Pharmaceuticals: 1300 k€	75 %	1,9
<b>Pharmafilter</b>	Cost<Benefit*	> 10%	?

\*Estimation based on calculation for fully implemented system

Source: Roorda et al. (2008)

Note: "All" refers to the removal of PPs plus removal of other substances like N, P etc.

### Other environmental benefits

An integrated treatment approach of all waste streams in a hospital, such as the Pharmafilter developed in the Netherlands, could contribute to an overall more sustainable waste disposal of hospitals.

### Environmental costs

These could also be similar to the environmental costs identified for the upgrade of wastewater treatment plants, including elevated energy demand (compared to energy spent when all wastewater is treated in the municipal treatment plants) as well as the formation of undefined post-treatment by-products.

### Costs

Costs of different sanitation concepts for emission reduction of PPs from health care units like hospitals in the Netherlands were summarised in table 2 above.

The costs for removal of PPs per amount of removed pharmaceuticals are highest at the wastewater treatment plant, although the total removal efficiency there is the highest. The costs for the Pharmafilter concept (combined treatment of all waste streams in a hospital) are still preliminary (Roorda et al. 2008).

An issue related to this instrument that requires further assessment is its *time until effectiveness*.

## **Drug take-back schemes**

### Impact/effectiveness

The extent of the contribution of improper PP disposal to the environmental loading of PPs, and in consequence the current and maximum effectiveness of take-back schemes, is not known, due to the lack of a comprehensive data basis and of representative surveys of consumer behaviour. The question of a measurable reduction in environmental residues in case all leftover medications are prudently collected is probably dependent on the particular Active Pharmaceutical Ingredient (API) (Daughton, 2008). Figures available for take-back schemes, on the other hand, are mostly expressed in tonnes/year, do not make clear if they include or exclude packaging, and provide no possibility of comparison with e.g. total sales. The following discussion presents results obtained indirectly via e.g. consumer surveys.

On the one hand, the possible impact and effectiveness of take-back schemes are related to the proportion of pharmaceuticals that go unused, and on the other hand are related to the extent to which other possible pathways of disposal are used; the two predominant ones are disposal via toilet or sink, or disposal as part of domestic garbage.

In the case of prescription medicine, unused medication is generated due to non-compliance (i.e. medication that is not or only partially used by the patient, against doctor's instruction), medication change (e.g. due to side-effects), and as left-overs after a completed therapy. Available figures for unused medication vary strongly. Non-compliance is estimated in Germany at between 20 and 30% for prescribed medications (SVR Gesundheitswesen 2002; in Götz and Keil, 2007). In France, Grass and Lalande (2005) estimate that on average one out of two prescribed medicines (i.e. 50%) is not consumed, whereas in Sweden the proportion of drugs which never get used is placed at as low as "about 5 per cent" (Apoteket, 2006).

As concerns the manner of disposal of unused medication, in Germany, a representative survey of 2,000 people indicated that 43% of the interviewees discard at least occasionally

liquid pharmaceuticals via sink or toilet (with 10,2% answering “always”); in the case of pills, up to 16% discarded them occasionally via the toilet (Götz and Keil, 2007). In a survey in England, 12% of the interviewees claimed to discard unneeded medication via toilet or sink (Bound & Voulvoulis 2005; in Götz and Keil, 2007); a parallel survey in England put this figure at 16% (Mackridge and Marriott, 2006). These surveys imply that the disposal of unused medication via the toilet or sink is not an infrequent practice.

Household waste is also a major disposal pathway for PPs. For the English surveys cited above, the amount of respondents disposing pharmaceutical products via the household waste was placed at 63% and 34%, respectively. Accordingly, landfills can be an important source of PPs over very long periods of time, and research has determined high concentrations of PPs in their leachate water (e.g. BLAC, 2003). Nevertheless, this pathway of disposal is *not always* problematic from an environmental point of view, for instance in the case of household waste being subject to incineration as a stage of pre-treatment, as is currently the case in practically all of Germany (Götz and Keil, 2007). The best disposal pathway is nevertheless still considered to be the high-temperature incineration that is usually applied in take-back schemes.

The extent to which the population has knowledge of existing take-back schemes varies strongly, even in the case of well-established schemes of comparable age. Whereas a 2006 survey in Sweden indicated that 73% of the public knows and uses the national take-back scheme (Apoteket, 2006), in England 77% indicated that they were *not* familiar with the English Disposal of Old Pharmaceuticals (DOOP) scheme (Mackridge and Marriott, 2006). (Of these, 89% stated they would use the service now they were aware of it.) In Germany, the low levels of public information and the differing and partly contradictory recommendations for disposal of PPs that are provided at city and *Länder* level are considered possible motives for the improper disposal of PPs analysed above (Götz and Keil, 2007).

In summary, the figures for the proportion of medicine that goes unused (only available for prescription medicine) seem to vary strongly from country to country, and in general only limited information is still available on drug consumer behaviour and manner of unused drug disposal. It can be assumed that consumer behaviour when discarding unused pharmaceuticals also greatly varies from country to country, and is dependent on behaviour regarding pharmaceutical intake, the type of take-back scheme (if existent) for medications and consumers’ knowledge of it, recycling behaviour of the population, official recommendations for disposing of pharmaceuticals, etc. The above discussion also makes evident that the results of take-back schemes are strongly linked to good levels of clear and non-contradictory public information, both regarding the existence of the take-back scheme and its benefits, as well as of the environmental consequences of disposal of PPs via alternative pathways.

All in all, given the lack of data at present, it cannot be argued with certainty whether the incorrect disposal of unused PPs is a significant or insignificant source of environmental loading of PPs. It is argued, nonetheless, that based on the precautionary principle, the most adequate way of disposal of PPs from an environmental perspective is collection and high-temperature incineration, for which a take-back scheme is ideally suited. There are strong possibilities for synergies of take-back schemes with other high-profile topics, such as unintentional poisonings of children and elderly, substances abuse, etc.

#### Other environmental benefits (e.g. in terms of soil or other micropollutants)

Some environmental benefit is to be expected by the higher rates of recycling of pharmaceutical packaging that would accompany a well-functioning take-back scheme. Other additional environmental benefits have not been identified.

Improved public information on PPs in the environment could cause additional environmental benefits due to a general higher awareness of the consequences of PPs presence in the environment. Synergy effects with other management approaches of PPs in the environment can be expected, for instance with possible risk management approaches such as the Swedish information scheme.

#### Environmental costs

Additional environmental costs are related to the logistics of the system, particularly transport. Increased levels of packaging recycling can be expected; this is clearly beneficial from the point of view of raw materials, but not necessarily from an energy perspective.

#### Costs

Information on the costs of take-back schemes is very limited so far. Data from 7 European countries which counted with figures for their costs give the following results (provided by the EFPIA, Taylor & Poulmair, 2007):

- From 7 countries surveyed with available cost figures, these ranged from €0.25m for Belgium to €15m for Denmark. (This strong variability is probably a function of the particular characteristics of the scheme, e.g. number of collection points, frequency of collection, etc., as well as the degree to which the public knows of and uses the system, that is, generates waste to be disposed.)
- Cost/tonne is usually in the range €400 to €4000

#### Limitations & obstacles to application

There are no direct limitations or obstacles to application of take-back schemes, as these are indeed required by EU legislation. Nevertheless, enforcement of current legislation is still a problem in most countries.

Stakeholders present at the KNAPPE Workshop in York (April 2008) identified the possibility of an EU guideline on how to set up and operate take-back schemes as a way to further support this management practice. For instance, standardised guidance on recommended routes for disposal could be developed for use regarding package labelling/inserts.

The question of informing the public of the existence of take-back schemes and of the environmental consequences of other disposal routes is a central one. Related to this question is that of the responsibility for the communication of information. The possibilities are varied, and include the respective national health services, doctors, pharmacists, councils and NGOs.

#### Time until effectiveness

The two main pathways for unused PPs to reach the environment are via the wastewater system or via landfills.

Before reaching the environment, wastewater is subjected to treatment; the removal rate ranges widely, from near-nil to almost complete depending on the particular compound. The remaining PPs thus enter the environment as part of wastewater treatment plants discharge. The implementation of an effective take-back scheme in consequence has the potential of showing effectiveness within a short time span.

In the case of landfills, domestic waste that is not given an incineration pre-treatment can leach important amounts of pharmaceuticals over very long periods of time. The time for effectiveness of a take-back scheme for this PPs' disposal pathway is consequently much longer.

## **Environmental classification scheme of PPs (risk communication)**

### Impact/effectiveness

In theory, the possibilities of the information schemes such as the Swedish environmental classification for limiting the discharge of pharmaceuticals into environmental waters seem significant, in view of the 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 of the public regarding this issue.

In practice, there is no information available on the scheme's impact and effectiveness; no completed studies exist on its impact or effectiveness on prescription or consumption of human medicines. An evaluation of the scheme's effectiveness in practice is ongoing; results are expected in 2009. The developers of the scheme recognise the difficulty of measuring its impact, due to the multiple factors that influence prescription behaviour. It has not been possible to link the results of the evaluation attempts to the classification scheme directly. Changes in prescription practice can be strongly influenced by market changes for instance, e.g. new drugs appearing or old drugs disappearing, influencing the sales figures of their alternatives (pers.comm, Wennmalm, June 2008).

### Other environmental benefits (e.g. in terms of soil or other micropollutants)

Improved public information associated with the implementation of an information and classification scheme could be beneficial in other ways for the issue of PPs in the environment, due to a general higher awareness of the consequences of their presence in the environment. Synergy effects with other management approaches of PPs in the environment can be expected, for instance with take-back schemes.

### Environmental costs

Due to the scheme being based on the generation and distribution of information, it can be assumed that no noteworthy environmental costs are associated with it. The information is made available on the internet, but also published in hard form. There are also very minor environmental costs related to the logistics of the health personnel's training in the system.

### Costs

Concerning running the classification system, costs are shared by several partners. The different pharmaceutical producers' headquarters provide environmental data from their respective files and send them to the Swedish branch organisation. Possibly, each company's headquarter has to allocate 0.5 person for this job, and another 0.5 person in their Swedish agency. In the branch organisation about 1.0 person runs the coordination for all companies, and in the classification agency (independent from the producers) there is another person making all audits of the classifications. In approximate terms, this would end up with 1 person per company plus 2 who run coordination and classification (pers. comm. Wennmalm, June 2008).

### Limitations & obstacles to application

The implementation of a similar scheme to the Swedish one in the rest of Europe would have important data requirements. The risk assessment is carried out on the basis of the sales volumes for medications, so as to provide Predicted Environmental Concentrations (PECs). In Sweden, the Swedish Pharmacy (national pharmacy retail system with no private competitors) provides data for the current scheme, but in countries with a less centralized health system this data may not be available. At the KNAPPE York workshop, stakeholders raised these

doubts: it would be possible to acquire this information for patented drugs, perhaps for prescriptions, but not for OTC drugs.

This obstacle may be surmounted by an evaluation of the sensitivity of the Swedish classification scheme to conditions in other countries. If accurate data is not absolutely necessary for scheme implementation, but rather the orders of magnitude that are important, then these information requirements would cease to be hurdles for the scheme's implementation elsewhere.

The lack of available data on the effectiveness of the scheme could be a barrier to its further implementation. Some stakeholders see as prerequisite for its extension a thorough evaluation of the "pilot" Swedish experience.

Other doubts voiced by stakeholders in the KNAPPE workshop was related to the difference in environmental awareness of the general public: the scheme may not work in other countries where people are not as environmentally aware as in Sweden.

#### Time until effectiveness

In the case of Sweden, the complete implementation of the scheme has been a lengthy process, due to the compilation process of the necessary information and its evaluation: a total of 5 years to completion (beginning 2005 – expected end 2010). The scheme's effectiveness has to date not been clearly established (see above). The effectiveness of the process should be a function of the extent to which the information has been made available to the scheme (i.e. effectiveness increases with increasing amount of substances taken up in classification scheme). Once the information is made available for use, the environmental benefits should in theory begin directly (direct pathway from patient to environment) as well as increase progressively (increasing amount of patients start treatment with environmentally friendly option; increasing familiarity of the practitioners and public with the scheme).

### **Good prescription practices**

#### Impact/effectiveness

Reducing the consumption of pharmaceuticals through education of medical professionals in order to minimise over prescription was rated as the second most effective management option in a recent survey of expert stakeholder opinions (with 27 interviewees) on possibilities of management of human pharmaceuticals in the environment (Doerr MacEwen & Haight, 2006). Consumption of PPs is the main route through which PPs enter the environment and reducing consumption addresses the problem in a proactive way.

The exact impacts and effectiveness of adopting good prescription practices still need to be assessed in detail.

#### Limitations & obstacles to application

Limiting the over prescription of medicines could presumably be against market interests (the market is in favour of highest possible sales), therefore, market and industry support may be limited for this instrument. The interviewees of Doerr MacEwen & Haight (2006) were uncertain of the feasibility of convincing doctors to reduce prescription rates when they are subject to much advertising on the part of the pharmaceutical industry. An interviewee from the industrial sector also suggested that the pharmaceutical industry is unlikely to see a need to reduce rates of drug consumption.

Issues related to this instrument that require further assessment are its *costs* and *time until effectiveness*.

## **Ecolabels**

### Impact/effectiveness

Ecolabels seem to be more suited to provide an evaluation of the production process of a particular product, than for the end-of-life behaviour in the environment of its. This fact is also reflected in the stakeholder discussion of ecolabels in the KNAPPE Workshop in York (Summerton et al. 2008), where the information to be provided by an ecolabel was defined as a stamp certifying that the product is produced in a green/sustainable manner. The focus on the production process, except for having other significant environmental benefits, would have some effect on the presence of pharmaceutical ingredients in the environment by addressing the issue of the release of ingredients in the production processes via discharge of industrial waters.

In general, it is argued that ecolabels would mainly be applicable for OTCs rather than drugs based on prescriptions. Market consumers only choose themselves medication sold over the counter, but not drugs prescribed by the doctor. However, some argue that even a possible ecolabel for OTCs may not be very effective, considering that most consumers have their ‘favourite’ drugs and there are doubts whether buying behaviour could change on the basis of an ecolabel.

In the case of an ecolabel system that would include prescription medicine, the process of prescription and the different drivers that affect it would limit the possibilities of its application. In most cases, it can be assumed that, in their decisions, doctors would put cost over the environment first, due to budgeting limitations imposed for instance by health insurers.

### Other environmental benefits (e.g. in terms of soil or other micropollutants)

Other environmental benefits that could be achieved by an ecolabel scheme on pharmaceutical products mainly relate to an improvement of the sustainability or “greenness” of pharmaceutical production processes.

### Limitations & obstacles to application

The labelling of pharmaceutical products is a highly regulated field. The introduction of a labelling system would have to pass significant administrative hurdles.

Furthermore, a possible drawback of ecolabels is that voluntary participation is limited to reaching only part of the manufacturers. In the same time, ecolabels appeal only to a limited part of market consumers. Experience with ecolabels applied in other sectors shows that there is a possibility of a larger number of consumers participating, if labelled products are priced competitively compared to non-labelled ones. In the case of pharmaceuticals, however, price is not considered to be as influential on consumption as in other sectors (e.g. food).

### Time until effectiveness

The time until effectiveness of this instrument is not clear; further assessment is considered necessary. On a theoretical level, the time span for first effects of an ecolabel scheme on consumer behaviour can be considered comparatively short. The level of effectiveness would progressively increase with the growing public awareness of the scheme. Public awareness and overall instrument success would be strongly dependent on the labelling characteristics and on the characteristics of a possible information campaign to back this ecolabel scheme.

Issues related to this instrument that require further assessment are mainly its *costs* and its *time until effectiveness*.

## **Consideration of environmental risk criteria in hospital procurement**

### Impact/effectiveness

The impact/effectiveness of this instrument is not clear; further assessment is required. As mentioned in chapter 2, the Swedish environmental classification system is in a way connected to pharmaceutical procurement to hospitals in Stockholm, since producers have to be loyal in delivering environmental data to the classification system in order to sell drugs to hospitals. In reality, hospitals can order whichever pharmaceuticals they want, as long as the producers are delivering environmental data to the system. It is not quite easy to evaluate how much the classification system requirements to procurement impacts hospital purchasing choice. The market changes all the time; new drugs appear and old ones disappear, while new clinical trials may also favour the choice of one drug instead of another. This means that even if a market shift is observed in a positive direction from an environmental point of view, it cannot be sure that this is due to classification; other factors may have had an influence as well (pers.comm, A. Wennmalm, Stockholm County Council, 4.8.2008).

### Limitations & obstacles to application

There are arguments suggesting that “greener” PP hospital procurement may not be appropriate and goes beyond advising physicians on the environmental risk of the drugs they prescribe. It is pointed out that there is a great difference between educating prescribers as to the relative environmental profiles of various drugs available in a therapeutic class using a classification system, and denying them the choice by eliminating drugs from the formulary on environmental grounds. Many therapeutic classes contain drugs that approach the same condition by different mechanisms and patients respond differently even to different drugs having the same mechanism. Limiting the choice may put patients at risk (post-York-workshop comments, F.Mastrocco/Pfizer).

It is also argued that the primary choice for users of PPs (e.g. hospitals) is efficacy and that, only at the second level, greener drugs may have a preference, mostly for OTC drugs (Summerton et al. 2008).

In the Swedish system of procurement described above in section 2, hospitals and doctors are informed about the environmental data of different medicines, but are not obliged to exclude environmentally harmful medicines from the market. The reason for not doing so is that a voluntary selection system has a better chance of becoming accepted than a compulsory one (pers.comm, J.Page, HCWH, 5.8.2008).

Issues related to this instrument that require further assessment are its *environmental impact/effectiveness*, its *costs* and its *time until effectiveness*.

## **Partnerships**

### Limitations & obstacles to application

Even if set up solely to provide improved information to prescribers, partnerships between UWWTP operators and doctors/pharmacists may face obstacles (e.g. acceptance) in countries

where plant operators are mainly private companies. The pros and contras and the most suitable design of such partnerships need to be assessed in advance depending on the context conditions of such a possible partnership.

Issues related to this instrument that require further assessment are its *environmental impact/effectiveness*, its *costs* and its *time until effectiveness*.

## **Economic instruments**

### Impact/effectiveness

The possible impact and effectiveness of applying different economic instruments such as sewage fees and tax-systems still need to be assessed.

In terms of instrument feasibility, the application of a sewage treatment fee has been recently proposed as the less complex solution (see KNAPPE expert workshop conclusions in Kampa (2008)).

As far as taxes (directly on the industry) are concerned, these are seen by the pharmaceutical industry as a blunt instrument and if implemented they would have to be large enough to affect the company - if not they would be included as part of business cost. Increasing taxation is generally considered as a stick in relation to the stick-and-carrot analogy and could potentially send manufacturing outside of Europe (Summerton et al. 2008).

At the KNAPPE workshop in York, it was also commented that market stimulating instruments seem to work better than tax-systems due to the creation of advantages (cf. ecolabels, classification systems). For the way forward, the impacts of both approaches need to be assessed in a more detailed way (Kampa, 2008).

### Limitations & obstacles to application

For the application of any kind of economic instruments to limit water pollution from PP emissions, it is important to clarify the role of the polluter (industry or consumer) in order to develop an appropriate approach for implementing the polluter-pays principle.

The issues related to the different options for the polluter definition still need to be assessed in more detail. Nevertheless, at least at the KNAPPE workshop in York, there seemed to be agreement that PPs are a societal problem and the cost should be borne by all, not the supplier or the consumer only (see summary Kampa (2008)).

Issues related to this instrument that require further assessment are its *costs* and *time until effectiveness*.

## **Improving the implementation of the current policy framework**

### Impact/effectiveness

In the survey of stakeholders of Doerr MacEwen & Haight (2006), ERA regulations were given the lowest score in terms of effectiveness. The results of the 27 interviews of experts of PPs in the environment highlight that traditional risk assessments do not address the questions that they are asking regarding PPs in the environment, such as “What are the chronic, sublethal effects? What are the effects of mixtures?” Furthermore, interviewees involved in

management recognised that ERA regulations often exist without a clear purpose. The assessment process is not linked to any management outcomes. Risk assessment, as it exists now, was considered ineffective but as having potential as future management strategy (Doerr MacEwen & Haight, 2006).

All in all, the impact and effectiveness of better implementing the current policy framework on the PP occurrence in the water environment need to be assessed in more detail both concerning ERA regulations as well as water policies such as the WFD.

#### Limitations & obstacles to application

The present lack of knowledge on several aspects of PP occurrence in the environment, as well as the low quality of data used in environmental risk assessment, are possible limitations to the improvement of current policy implementation.

Issues related to this instrument that require further assessment are mainly the related *costs* and its *time until effectiveness*.

## 4 Conclusion

Despite our limited current understanding of the emerging issue of PP occurrence in the water environment and only few cases of confirmed environmental impacts of PPs, the scientific community tends to agree that, for the sake of the precautionary principle, we should explore ways to limit the input of PPs into the environment, thus anticipating action needed in the future. Indeed, there is no clear picture yet within the pharmaceutical industry of the potential PP risks for the environment but it cannot be denied that there might be risks unknown at present.

All in all, the future selection of instruments that should be applied for limiting PP discharge into water should be based on the following:

- New scientific knowledge on environmental risks & impacts of PPs.
- A balance between the appropriate level of scientific evidence on risk and the cost of management strategies and instruments.
- An assessment of the costs and benefits of optional instruments (e.g. benefits of take-back schemes for the environment; impact and effectiveness of environmental classification schemes of PPs).

Currently, information available is not enough for a full assessment of all options. To assist decision-making on this issue, more information should be collected and evaluated on the costs & benefits via targeted research projects as well as pilot projects on specific instruments.

Until more targeted information on PP occurrence and impacts as well as on instrument effectiveness and costs is available, it is wise to recommend actions that have broader benefits. For instance, optimizing existing wastewater treatment can improve the removal of many compounds other than PPs from wastewater and promoting drug take-back schemes can also reduce the risk of unintentional poisonings.

In a survey of expert stakeholders' views (based on 27 interviews) which included government, academia, pharmaceutical and consulting industries, it was suggested that a mixture of strategies addressing the various stages of the life cycles of PPs should be used in management (Doerr-MacEwen & Haight, 2006).

Within the KNAPPE project, the following instruments have been discussed and proposed as good management practice for preventing and limiting PP discharge into water:

- *Upgrading of wastewater treatment*, which is a cost-intensive strategy but could be financed via economic instruments, e.g. sewage fees or taxes. The upgrading of wastewater treatment can have a direct impact on the improvement of environmental quality as well as synergies with other environmental issues, especially the removal of other micro-pollutants from wastewater.

- *Wastewater collection & treatment at hospitals*

There are several projects testing this alternative, e.g. in the Netherlands and Germany, showing that this is seen in some countries as both a significant and viable approach.

- *Set up and/or improvement of the operation of drug take-back schemes*

Drug take-back schemes is one of the less cost-intensive management strategies accompanied by positive synergies with public safety (e.g. from accidental drug

poisoning) and increased public awareness on the issue of PP occurrence in the environment. It is recommended that the drafting of an EU guideline on take-back schemes could be helpful to further establish this management strategy in European countries.

- *Improving the implementation of the current policy framework*

The current policy framework is considered sufficient to deal with the issue of PPs in the water environment. No extra Directives are needed. Next to the quite complete framework provided by current guidelines for ERA, the WFD provides an overall framework for water protection from chemicals in Europe. Nevertheless, certain implementation gaps exist and, in order to close them, we need a better understanding, data & research on PPs in the water environment.

Recommendations to improve the current policy framework include improving ERA data quality & accessibility, continually improving ERA on the basis of newest scientific evidence, addressing the issue of “old medicine” in the ERA framework, e.g. by testing representatives of non-tested PP classes, as well as addressing PPs in the framework of the Water Framework Directive (WFD) implementation. PPs can be incorporated more consistently into the WFD scheme of identifying water pressures and impacts, once more data have become available on PP occurrence and ecological impacts in water bodies failing to reach the WFD objectives.

- *Environmental classification of PPs for communicating risk to doctors and public*

This strategy is being explored for possible application in other European countries beyond Sweden. The actual effectiveness of the scheme in practice is subject of ongoing research.

- *Good prescription practices for a wiser use of PPs and limiting over prescription*

- *Economic instruments* based on the polluter-pays-principle (e.g. sewage treatment fees to fund the upgrading of wastewater treatment) as well as economic incentives for the production/consumption of “greener” PPs.

Some additional instruments were also raised but these need to be further discussed with stakeholders and assessed before considering them for possible application: Partnerships between UWWTP operators & prescribers (doctors, pharmacists) in their catchment; the consideration of environmental risk criteria in hospital procurement; and, finally, the use of ecolabels for PPs (mainly OTC drugs).

## 5 Recommendations for further research and consultation

The identification of possible instruments to limit PP occurrence in the water environment and their preliminary assessment in terms of effectiveness and costs in this paper make clear that further research is still needed to support this type of work and to clarify several open issues.

Some of the key issues include:

- What are the costs and benefits of different options and management tools? This is also related to the need for detailed cost-benefit analysis of scenarios of options.
- How much time is needed after the adoption of different options and management practices for an effect to be measured in the water environment?
- More data are needed to allow proper comparison of the removal efficiency of several compounds with a variety of wastewater treatment technologies.
- More research is needed on the formation of by-products when using advanced treatment technologies for pharmaceuticals.
- Do take-back schemes bring benefits to the environment? Can this be assessed? Can we learn more about consumer behaviour and drug disposal behaviour on pharmaceuticals related to the issue of unused drugs? Can more information be collected on the estimated relation between sold drugs, the rate of these drugs that are potentially unused and the rate of unused drugs taken back to the pharmacy?
- What is the impact and effectiveness of the Swedish environmental classification scheme on prescription or consumption of human medicine?
- What are the pros and contras of different definitions of the “polluter” in the context of discussing economic instrument options to limit PP occurrence in the environment?
- Can we learn more about consumer buying behaviour, esp. on OTC drugs, in view of the possible introduction of a drug ecolabel?
- Can we learn more about the behavioural impact of different measures on doctors or vets?
- Can we learn more about public risk perception & public risk tolerance with respect to PP occurrence in the environment?

Not only is further research on possible instruments needed as well as a careful assessment of costs and benefits for any recommendations on policy and instrument options , but also the need for consultation should not be neglected. Prior to the binding selection of certain management instruments and to the introduction of new policies, a consultation phase and dialogue including public and private stakeholders should be carried out. .

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