Management Strategies for
start Pharmaceutical Residues
in Drinking Water

Pharmaceuticals for Human Use: Options of Action for Reducing the Contamination of Water Bodies

A Practical Guide

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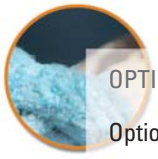
Contents

STATE OF KNOWLEDGE



OPTIONS OF ACTION

IMPLEMENTATION PROSPECTS

Foreword

Pharmaceuticals are in many cases an indispensable element of a comfortable and healthy life. Nevertheless, there is also a downside to the extensive use of medicinal products: their impact on the environment. Since the early 1990s, research findings have confirmed the occurrence of a wide range of human and veterinary active pharmaceutical ingredients in surface waters, in groundwater, and occasionally even in drinking water. Moreover, an increasing volume of data shows that specific substances can also trigger negative effects in animals and plants.

It remains scientifically uncertain which risks to humans and the environment actually exist. It must be expected, however, that the problem will be aggravated in coming years, since the demographic development in Germany and in Europe towards increasingly aging societies will bring with it an increase in consumption of medicinal products. Precautionary action is therefore more and more indicated. Long-lasting strengthening of drinking water protection should receive particular attention in this respect. From a sustainability perspective this means already reducing contamination exposure of water bodies. This is the only way that the drinking water sources can be conserved also for the benefit of future generations and at the same time environmental risks be minimised.

Systematic studies on corresponding options of action are, however, so far largely lacking. This brochure presents a premier practical study that should contribute to filling this gap as regards pharmaceuticals for human use. Starting with the life cycle of a medicinal product, three spheres of activity are considered in which solutions to the problem addressed can be implemented: drug development, handling of drugs and technical emissions control in urban water management. The results presented were developed in the framework of the *start* ("Management Strategies for Pharmaceutical Residues in Drinking Water") transdisciplinary research project funded by the German Federal Ministry of Education and Research. Although *start* focused on the situation in Germany most of its results can be transferred either directly or conceptually to other countries of the European Union as well.

This brochure is addressed to decision-makers in politics, administration, companies, and organisations. It provides information and concrete recommendations on where options of action can apply and which aspects should be observed when implementing individual measures. The goal is to stimulate the broadest possible discourse on solution perspectives and to provide a stimulus for the inception of an approach that includes actors from all three spheres of activity in collaborative problem-solving.

In order to ensure the practical relevance of the research results a dialogue process with experts from medical associations, official bodies, pharmacy associations, pharmaceutical industry, public health funds and water management was carried out in *start*. Special thanks go to the following contributors for their constructive commitment over more than two years:

Prof. Dr. Thomas Beck (Drug Commission of the German Pharmacists, Eschborn), Dirk Betting (badenova AG & Co. KG, Freiburg), Dr. Peter Diehl (Rheingütestation Worms), Dr. Paul Eckert (Public Services Düsseldorf AG), Dr. Karin Gerhardy (German Technical and Scientific Association for Gas and Water, DVGW, Bonn), Dr. Klaus Heuck (Bayer HealthCare AG, Wuppertal), Silke Hickmann (German Federal Environment Agency, Dessau), Peter Jagemann (Emschergenossenschaft, Essen), Ute Kerschensteiner (Barmer Ersatzkasse, Landesgeschäftsstelle Hessen, Frankfurt/Main), Prof. Dr. Gottfried Kreutz (Drug Commission of the German Medical Association, Berlin), Dr. MD Peter Ohnsorge (European Academy for Environmental Medicine, Würzburg), Dr. Jürg Oliver Straub (F. Hoffmann-La Roche AG, Basel, Switzerland), Dr. Jochen Türk (Institute of Energy and Environmental Technology, Duisburg), Prof. Dr. Åke Wennmalm (Stockholm Läns Landsting, Stockholm, Sweden)

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Dr. Florian Keil
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Contamination of Water Bodies and Drinking Water by Pharmaceuticals

In the early 1990s, an active ingredient for reducing blood lipids was found in Berlin drinking water sources – it was clofibric acid, a substance that is rarely used today. Since that time, in numerous scientific publications, the widespread occurrence of far more than 100 different substances in almost all surface waters in Germany, in groundwater affected by surface water and even rarely in drinking water has meanwhile been demonstrated – a finding that also applies to other countries worldwide. In addition, more and more data are documenting that specific pharmaceuticals have harmful effects on animal and plant life. Based on the current state of knowledge, this chapter will answer the central questions on the topic of "Contamination of Water Bodies and Drinking Water by Pharmaceuticals for Human Use".

How do the substances reach the water bodies?

The occurrence of active pharmaceutical ingredients in water bodies is an undesired side effect of their normal use. In order for the substances to develop their intended effects in the human body, sufficient intact molecules must reach the diseased cell before they are degraded into a multitude of metabolites by the body's biochemical processes. In order to achieve this goal, pharmaceuticals are optimised for stability. This has two consequences: On the one hand, the active ingredients are not metabolised completely in the human body but excreted primarily via urine and thus reach domestic wastewater. On the other hand, the desired stability of the molecules hinders their biological degradation in conventional sewage treatment plants. Many of the active ingredients studied so far become only partially removed, others not at all. On reaching the rivers and lakes in the effluent of the sewage treatment plants, the stable molecules can then make their way into the groundwater and finally – via drinking water – back to humans.

The main entry of active pharmaceutical ingredients into water bodies occurs through excretion via domestic wastewater.

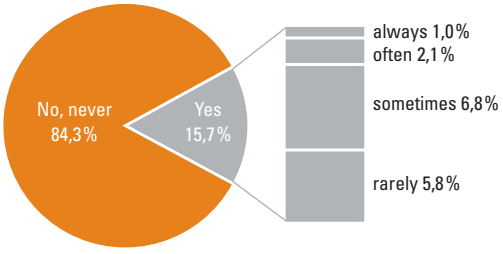
Domestic wastewater is the main source of occurrence of active pharmaceutical ingredients in the environment. Alongside, pharmaceutical production sites and hospitals or other medical facilities play a lesser role. Whereas – at least in Europe – residues are generally largely removed from contaminated production wastewaters by means of costly technology on-site, the contribution of hospitals is maximum 10 to 20 per cent of the total quantity of pharmaceuticals released into the environment each year.

Are unused medicinal products improperly disposed of through drains and toilets?

A representative *start* survey showed that in 2006 one out of seven German citizens at least occasionally dispose of unused or expired tablets in the toilet. Liquid medicinal product remnants are dumped down the drain or the toilet by even one out of two – 10 per cent of the population does this consistently. The significance of these figures depends on the annual amount of medicinal product waste that occurs, in that not all of the drugs purchased or prescribed are also taken, or some quantity remains after completion of therapy.* Corresponding reliable data that are differentiated according to active ingredients are unavailable, however. Based on different sources, it must be assumed that several thousand tons of medicinal product wastes annually accumulate in Germany. By means of the data acquired in *start*, it can be estimated that several hundred tons thereof are improperly disposed of down the drain or the toilet. In proportion to the quantity of active pharmaceutical ingredients that reach the environment via excretory routes, this is indeed only a fraction of a few per cent. However, it must be considered that for such active ingredients that are almost completely metabolised in the body, improper disposal may be the main route of entry.

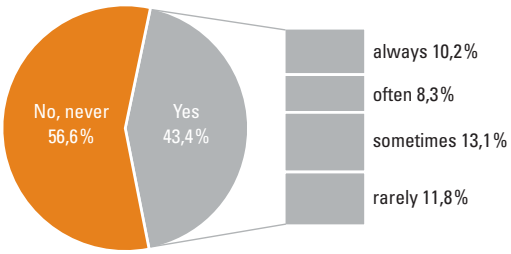
*The extent to which patients observe a medical recommendation on taking a particular pharmaceutical – the so-called "medication compliance" – depends strongly on the indication. While contraceptives are generally fully consumed, compliance with anti-epileptic medication is only 50 to 70 per cent.

Disposal of tablets via the toilet



Sample: 1,306 interviewees; numbers apply to Germany only

Disposal of liquid medicinal products via drain/toilet



Sample: 1,306 interviewees; numbers apply to Germany only

In what quantities are pharmaceuticals used?

In Germany only limited data are available on the consumption of medicinal products because to date manufacturers of medicinal products have not been required to disclose their production volumes. Although the statutory health funds have public-access data on annual prescriptions, these data, however, neither reflect the growing market of over-the-counter medicines increasingly traded via the Internet nor the portion of prescriptions dispensed to patients of private insurers. The most up-to-date available data were published by the German Federal Environment Agency based on figures from the Institute for Medical Statistics (IMS Health AG, Frankfurt/Main). They show that in 2001 pharmacies and hospitals dispensed a total of around 38,000 tons of pharmaceuticals shared out over 2,671 different active ingredients. According to these data some 2,500 tons of analgesics and antirheumatics, followed by antibiotics (500 tons), anti-epileptics (200 tons) and blood pressure reducing agents (antihypertensives, beta-receptor blockers, 150 tons) were among the largest-selling pharmaceutical substances. However, these figures don't reveal anything about actual consumption, because part of the drugs dispensed (sometimes contrary to medical instructions) is not taken at all.

In Germany, more than 30,000 tons of medicinal products are consumed annually distributed over more than 2,500 different active ingredients.

In what concentrations do pharmaceuticals occur in water bodies?

A high consumption volume is an indication for the widespread occurrence of an active ingredient in water bodies. Accordingly, analgesic and anti-inflammatory substances like diclofenac and ibuprofen, antibiotics like roxythromycin and sulphamethoxazole, anti-epileptics like carbamazepine and primidone, and anti-hypertensives like metoprolol and sotalol are found particularly common in almost all surface waters in Germany. Add to these another group of substances that, strictly speaking, are not medicinal products, but are so-called diagnostic products: x-ray contrast media like iopromide or amidotrizoic acid. The concentrations measured in water bodies are on average in the range of a few millionth to some billionth of a gram per litre ("nanograms" and "micrograms" per litre, respectively). To illustrate this point: If a sugar cube is dissolved in the Berlin Wannsee, a sugar concentration in the order of one nanogram per litre would result.

In surface and ground waters far more than 100 different active pharmaceutical ingredients are nowadays detected.

In Germany, more than 100 different active pharmaceutical ingredients have been detected in water bodies so far. This figure, however, does not immediately mean that the rest of the around 3,000 active ingredients available on the German market do not occur in the environment. Rather, it can either be that for a particular active ingredient the technical options for detecting it do not exist, or that it is degraded in the human body to such an extent that primarily only its metabolites are excreted. The metabolites' structure, however, is generally not known such that they can elude environmental ana-

lytical surveillance. Due to different natural degradation processes (biologically through microorganisms and photo chemically through solar radiation), or by adsorption to suspended substances and sediment particles the concentrations of active ingredients in rivers and lakes is generally higher than in groundwater.* Groundwater resources can be particularly affected when they are located near surface waters.

Active Ingredient	Indication Group	Consumption Quantity (2001) in kg	Maximum concentration in µg/L surface water bodies	groundwater	drinking water
Aminotrizoic acid	X-ray contrast agent	60,700	0.950	0.650	0.085
Carbamazepine	Anti-epileptic	87,600	1.810	0.110	0.030
Cyclophosphamide	Cytostatic	385	0.100	**	0.008
Diclofenac	Anti-inflammatory	85,800	2.000	0.030	0.006
Ethinylestradiol	Hormone	50	0.005	0.002	0.001
Ibuprofen	Anti-inflammatory	344,880	1.500	0.510	0.003
Iphosphamide	Cytostatic	170	0.180	**	No evidence
Iopromide	X-raycontrast agent	64,100	0.450	0.040	0.086
Metoprolol	Anti-hypertensive	93,000	1.800	0.030	No evidence
Primidone	Anti-epileptic	10,000	0.560	No evidence	No evidence
Roxythromycin	Antibiotic	9,550	0.060	0.026	No evidence
Sotalol	Anti-hypertensive	26,600	0.850	0.560	No evidence
Sulphamethoxazole	Antibiotic	53,600	0.380	0.030	No evidence

** Below detection limit; µg/L : microgram per litre. Source: BLAC, LANUV NRW

What are the hazards for the environment?

The state of knowledge with respect to possible hazards for animal and plant life due to the occurrence of active pharmaceutical ingredients in the environment is currently still scarce. Ecotoxicological studies are to date available only for a few substances. The reason for this is not only the huge variety in substances but primarily also the fact that meaningful results can be obtained only with long-term studies. The identification of such *chronic* effects is associated with increased costs in terms of time and financial resources, however. The majority of the active pharmaceutical ingredients investigated so far are directly – that is, *acutely* – toxic to aquatic organisms only at concentrations that are considerably above current measured values in water bodies.

The example of ethinylestradiol (EE2), the active ingredient used in most hormonal contraceptive agents, however, shows that even in concentrations commonly found in water bodies hazards do occur for animal life. EE2 occurs in surface waters at concentrations of a few nanogram per litre. It has been shown that because of its high estrogen potential EE2 at these concentrations is one substantial factor in the observed feminisation of male fish whose habitat is near sewage treatment plant outlets. According to the

* Because of the cleansing effect of the soil layers not every active ingredient that occurs in surface waters reaches the groundwater. On the other hand, pharmaceuticals for human use can enter the groundwater directly through leakages in sewer systems, leaky landfills, and the application of sewage sludge on agricultural land.

current state of knowledge, it can't be strictly ruled out that some animal and plant species react particularly sensitively to a specific active ingredient in concentrations commonly found in the environment. This is demonstrated by the widely discussed example of the anti-inflammatory agent diclofenac, which has led to the virtual extermination of three important vulture species in India and Pakistan. They fed on the carcasses of dead cattle that were treated with the substance.

A comprehensive hazard assessment for animal and plant life faces fundamental obstacles. The so-called "cocktail effect" is particularly important in this respect. As a rule, creatures living in the environment are exposed to a number of active pharmaceutical ingredients and other chemicals simultaneously; according to current research, the effects of the individual substances are adding, inasmuch as they demonstrate the same mechanism of action. It remains unclear how such cocktail effects can be appropriately taken into account in the hazard assessment of pharmaceuticals. The latter is further hampered by the numerous degradation products of active pharmaceutical ingredients that are generated in the human body, in the sewage treatment plant, or in the water bodies themselves. Almost nothing is known about their toxicological properties.

Do pharmaceutical residues occur in drinking water?

According to a current study that was conducted on behalf of the Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen ("Regional Authority for Nature, Environment, and Consumer Protection of North Rhine-Westphalia") 15 different active pharmaceutical ingredients were detected so far in German drinking water samples. At a few nanogram per litre, the measured concentrations are considerably lower than in surface waters and in groundwater. The corresponding measurements were carried out only at selected locations, however. Wider area contamination of German drinking water cannot be deduced from the available findings to date.

Pharmaceutical residues are measured sporadically also in drinking water samples. The concentrations are in the range of a few billionth of a gram per litre.

A good two-thirds of the drinking water in Germany is recovered from groundwater. The rest comes from surface water (rivers, lakes, or storage dams), bank filtrate, and enriched groundwater.* Bank filtrate is a mixture of groundwater and river water harvested from wells in the vicinity of the river bank. Enriched groundwater is – for example in the case of scarcity of natural groundwater – produced artificially by percolating surface water via appropriate wells or ponds. In both instances contaminants are at least partially eliminated by passage through the soil.

Because surface water and bank filtrate are generally more strongly contaminated with pharmaceutical residues than groundwater, water works that use these two types of raw water for abstracting drinking water, and do not employ advanced treatment technology such as activated carbon filtration, are at greater risk of breakthrough of active ingredients into drinking water. This finding caused the German Consortium on Chemical

* The current proportions fluctuate from Bundesland to Bundesland sometimes considerably: Whereas in 2004 Berlin, Bremen, and Hamburg harvested 100 per cent of their drinking water from groundwater, this proportion was only 42 per cent in North Rhine-Westphalia and only 24 per cent in Saxony.

Safety ("Bund/Länder-Arbeitsgemeinschaft Chemikaliensicherheit") to recommend in its 2003 study "Arzneimittel in der Umwelt" ("Pharmaceuticals in the Environment"), that for such water works special attention should be paid to the entry of active pharmaceutical ingredients.

Does contaminated drinking water represent a health hazard?

Active pharmaceutical ingredients belong to the best-studied substances in terms of human toxicology. In the context of the market authorisation process, an active ingredient is tested not only in terms of its therapeutic efficacy but also for a number of undesirable side effects. According to unanimous expert opinion acute health hazards in the sense of the occurrence of such side effects due to the consumption of contaminated drinking water can virtually be excluded. This is illustrated by a simple calculation example: The active ingredient carbamazepine used in anti-epileptics was sporadically detected in drinking water samples in concentrations of not more than 30 nanograms per litre; if two litres of water per day were consumed in a seventy-year lifespan, a person would thus ingest only a few thousandths of one recommended daily dose (about 600 milligrams) of the substance. But it remains largely to be ascertained if, even in the range of these extremely small doses, as yet unknown effects can occur. This applies particularly to chronic effects due to life-long uptake of substances and effects due to mixtures of substances with similar mechanisms of action ("cocktail effects"). A well-founded scientific risk assessment is therefore not yet possible.

Today, acute health hazards due to pharmaceutical residues in drinking water can be virtually ruled out. However, long-term effects have so far not been studied.

How is the problem perceived by the public?

The problem of drinking water contaminated with pharmaceutical residues so far has hardly had an impact on public perception. This was a finding of social-empirical studies carried out in the framework of *start*. In group discussions with German citizens it became initially clear that neither the fact of demonstrated drinking water contamination itself nor the corresponding causal relation was generally known. If the basic state of affairs was introduced in the sense of a bare headline "Pharmaceutical Residues in Drinking Water", strong reactions due to this absence of information such as spontaneous refusal to consume tap water or even fending off the problem were observed.

Feelings of alarm and threat are expressed particularly by women and the chronically ill. The topics of fertility and pregnancy have a far greater significance to women than to men. Together with catchwords like "hormonal effects" this triggers fears of being directly affected. For the chronically ill, there is a special dilemma: Because they depend on continuous and careful ingestion of pharmaceuticals, they fear that careless handling of medicines by others could have long-term negative consequences for themselves.

If additional information is provided in the course of the discussion – on the current state of knowledge and particularly as regards the meaning of the measured concentrations – and an opportunity for an opinion-forming process is offered, different processing patterns become identifiable. They open out into behaviours that range from sereneness and rejection of the need for action, to relativisation and the need for further research, to threat and the demand for a precautionary approach. It is generally true that citizens do not accept pharmaceutical residues in their drinking water even if it is not demonstrably associated with a health hazard.

What is the current legal situation?

In the course of the market authorisation of a human pharmaceutical in Europe an environmental risk assessment (ERA) is compulsory since 1993 (directive 93/39/EC) – a regulation that since 2004 also applies to generics (directive 2004/27/EC and 2001/83/EC, respectively). An ERA is not required for pharmaceuticals which were authorised before this regulation came into effect. A consistent technical standard for drug manufacturers on how to implement the ERA is, however, only available since December 1, 2006, in the form of a guideline provided by the European Medicines Agency (EMEA). This guideline is applied both in the pan-European and the national authorisation of a drug. In Germany the technical control of an ERA is enforced by the German Federal Environment Agency in accordance with the competent authorisation authority (German Federal Institute for Drugs and Medical Devices).

Active pharmaceutical ingredients must be tested for environmental risks at the time of authorisation. But authorisation cannot be denied even in the case of an assessed environmental risk.

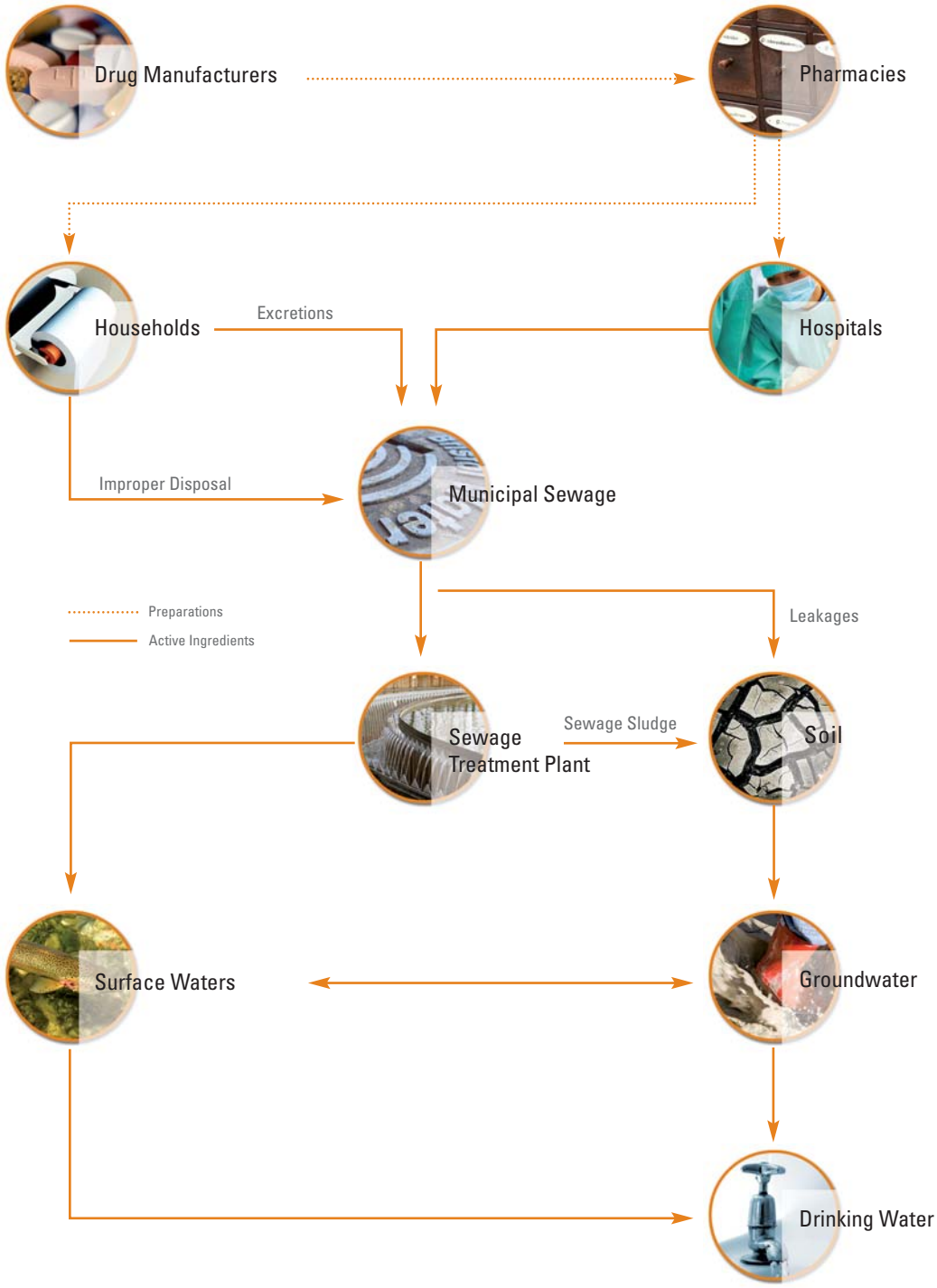
It is crucial to note that if, in the framework of the ERA, an environmental risk is identified, authorisation of the human medicinal product can explicitly not be denied. In this case only precautionary measures for mitigating the risk may be required. The actual options for the competent authorities to enforce such measures are currently strongly limited, however. In practice they are confined to information about the assessed environmental risks on package leaflets and product instructions for physicians and pharmacists. For veterinary pharmaceuticals the legal situation is different: Here authorisation may be denied or limited to certain application areas if evidence for an environmental risk exists (directive 2004/28/EC and 2001/82/EC respectively).

There are currently no compulsory threshold values for the occurrence of active pharmaceutical ingredients in surface waters and in groundwater on a European level or in Germany. However, their definition is in principle legally possible for example in the framework of the European Water Framework Directive. Medicinal products are explicitly excluded from the central provisions of the new European Community Regulation on chemicals, REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), because they are separately handled by the aforementioned directives.

On a European level (in the framework of the Drinking Water Directive 98/83/EC) there is to date no threshold value for pharmaceutical residues in drinking water (this applies both to human and to veterinary medicinal products). Analogously, there are currently no compulsory threshold values for active pharmaceutical ingredients defined in the framework of the German Directive on the Quality of Water for Human Consumption ("Trinkwasserverordnung"). Here only the non-toxicologically inferred and non-compulsory precautionary threshold value of 0.1 micrograms per litre recommended by the German Drinking Water Commission applies to drugs and other as yet unevaluated substances.

With the amendment of the EU directive on the creation of a Community Code Relating To Medicinal Products For Human Use (2004/27/EC), an article for establishing collection systems for unused or expired medicinal products was incorporated which should make possible proper disposal of the substances (Article 127b). All member states were required to provide such systems by October 2005. In Germany there has been a take-back system via pharmacies since 1995. This system was originally set up so that manufacturers of pharmaceuticals and other medicinal products could comply with their obligations under the "Verpackungsverordnung" (German Regulation on Packaging) with respect to the recovery of potential recyclables. At the present time about three quarters of all pharmacies in Germany are connected to a take-back system.

How do pharmaceuticals reach the environement?



Risk and the Precautionary Principle

In order to assess a risk to human beings or the environment it is necessary – in the classical approach – to establish a causal relationship between an agent and an observed harmful effect. In risk assessment of chemicals generally and particularly in the case of active pharmaceutical ingredients, this is manifestly possible only in rare cases, however. There are essentially two reasons for this. On the one hand, due to the great variety of substances: Negative effects such as the observed feminisation of male fish can be triggered by different substances acting on their endocrine system, or can also be the result of the combined and simultaneous action of several substances ("cocktail effect"). On the other hand, long periods of time can pass between the causation and the observed effect. The identification of causal relations for this type of chronic effects is scientifically markedly difficult. In such a situation of scientific uncertainty the precautionary principle as a legal instrument for dealing with a possible hazardous situation comes into play.

Since the Maastricht EU Treaties of 1992 (Treaty on the European Union, 92/C 191/01, Article 174), the precautionary principle is one of the most important legal policies in European environmental legislation. It legitimises decisions, and the conduct based thereon, even when possible effects harmful to humans and to the environment are known, but their risk cannot be determined with sufficient certainty through scientific evaluation. The incorporation of the precautionary principle is based on a normative claim that requires preventive creation of latitude and safety margins, even for risks that may be characterised as such only in the future. The regulations currently in force at EU level – particularly the obligatory performance of an ERA as part of the first time authorisation of a pharmaceutical – must be viewed in the context of an invocation of the precautionary principle.

Uncertainty predominates regarding type and extent of risks to humans and the environment. The precautionary principle thus plays a prominent role in problem solving.

In the *start* round of talks with experts from pharmaceutical industry, water management, medical and pharmacy associations, health funds and authorities, there was consensus that the precautionary principle should play a decisive role in dealing with drinking water contamination by active pharmaceutical ingredients. The central discussion points, however, were the question of the proportionality of concrete precautionary measures in view of the existing uncertainties in risk assessment and the avoidance of goal conflicts for individual actors. Both points are an expression of the high societal benefit that is connected with the development and the use of drugs. Precautionary measures for reducing water contamination should therefore neither hamper innovations in drug development nor impair the quality of medical care (for example in that particular measures cannot be integrated into the complex professional routine of physicians). In other words, a precautionary approach must be configured such that the individual actor's capacity to act and innovate is preserved or, if possible, even increased.

Options of Action for Reducing Contamination of Water Bodies

At the present time there are no progressive and harmonised strategies in Germany or on a European level for reducing contamination of drinking water and water bodies by active pharmaceutical ingredients. The existing legal provisions within the European authorisation process are limited to individual active ingredients and therein set a narrowly limited framework for measures of risk reduction (see page 12). Therefore there is an urgent need for the systematic identification of options of action that enable a precautionary handling of the impacts of the use of pharmaceuticals for the protection of drinking water and water bodies, while taking into account their high individual and societal benefits. This requirement was incorporated in *start* for human pharmaceuticals. Starting with the life cycle of a pharmaceutical, the project investigated three spheres of activity in which precautionary action can be applied: "Drug Development", "Handling of Drugs" and "Technical Emissions Control in Urban Water Management".

Drug Development	Handling of Drugs	Emissions Control
Development of active pharmaceutical ingredients that are optimised both for efficacy in humans and degradability in the environment	Change in current prescription practices, utilization, and disposal patterns towards a greater degree of environmental compatibility	Optimisation of wastewater disposal, wastewater treatment, and drinking water processing in the removal of pharmaceutical residues

The objective of precaution is a strengthening of drinking water protection. Sustainable solutions safeguard water bodies as drinking water sources and as habitat for animals and plants.

The approach developed addresses policy and administration, manufacturers of medicinal products, medical and pharmacy associations, water management, health funds and consumer councils. The results of the *start* study that are presented in more detail in the following should initially point out which options of action are available to the actors in the three spheres. In the case of the spheres of activity of "Drug Development" and "Handling of Drugs" these are measures that are strategically harmonised with each other. For the sphere of activity of "Technical Emissions Control in Urban Water Management", this type of strategy definition was impossible due to insufficient data (see page 36). Advice on what must be observed when implementing individual options, and on how a process can be launched that in the long term integrates all actors of the three spheres of activity in common problem solving, are provided in the last part of this brochure.

The starting point for determining options of action to reduce contamination of water bodies by active pharmaceutical ingredients in *start* was the precautionary and long-term strengthening of drinking water protection. In the spirit of the life cycle-oriented research approach, the principle of starting as much as possible at the source of entry of the active ingredients – that is already at the development and utilisation of the substances – was employed for this purpose. Because it is only with this principle that sustainable problem solutions can be developed – solutions that preserve our drinking water sources for the benefit of future generations and simultaneously reduce environmental risks.

Sphere of Activity "Drug Development"

Starting directly at the source of the problem means to initially examine the properties of the active ingredients critically. In general, contamination of water bodies and thus possible risks to humans and to the environment can be reduced if organic chemical compounds like active pharmaceutical ingredients are degraded completely and as quickly as possible, or are decomposed into ecologically innocuous components. Here, "quickly" means a degradation in the sewage treatment plant in a time horizon of a few hours or days, in surface waters of several days, and in the soil of several weeks. Up to now the rapid biological degradability in the environment hardly plays a role in drug development. The priority objective rather is to achieve optimal functionality of the active ingredient. At the heart, this means: High efficacy with simultaneously the fewest possible side effects. One consequence that emerges from this objective is that the active ingredient molecules are optimised for stability so that they can develop their desired efficacy in the human body before they are degraded. But stability in the human body generally also means stability in sewage treatment plants and in water bodies.*

Efficacy and good environmental properties do not represent a fundamental contradiction for a medicinal product. Both can be optimised by a specific molecular design.

There need not be a fundamental conflict of objectives between optimal functionality and rapid degradability in the environment, however. This becomes clear when the factor of stability is not viewed absolutely but is related to the different phases of the life cycle of the active pharmaceutical ingredient. Because whether an active ingredient molecule is rapidly or slowly degraded depends not only on its structure but also critically on the decisive conditions at the site of the event, such as incidence of light, pH-value, temperature or type and quantity of microorganisms present. These conditions do, however, differ considerably in the human body and in the environment. When developing pharmaceuticals such differences can be systematically exploited if it is known which chemical moieties are particularly advantageous for the desired application properties and which are particularly disadvantageous for rapid degradation in the environment. Given this knowledge, it is fundamentally possible to follow a new design principle: By targeted intervention in the molecular structure both the degradability of a "green" active pharmaceutical ingredient in the environment and its functionality are optimised.

Vision for the Future: "Green" Pharmaceuticals

The vision for the future thus is: Helping to prevent environmental and water contamination through the development of green active pharmaceutical ingredients. As a matter of course it is clear here that not every potential active ingredient for every application can be made "green" through molecular design – there will be a deliberation process among a number of factors in each individual case. The concrete action perspective rather is to think ahead and examine this option as one important criterion besides others as early

* The development of pharmaceuticals on the basis of close to nature molecules (for example proteins or nucleic acids) today is a growing market. In some cases it appeared that such 'Biopharmaceuticals' can also have better environmental properties.

as possible in the process of developing an active pharmaceutical ingredient. In this fashion, more and more successful examples for green active ingredients will appear over the long term and the structural-chemical knowledge base will be expanded. Computer-assisted molecular design is a promising method for building this knowledge base. Using this technique, first of all *known* active substances could be optimised for functionality and degradability. In doing so, already minor changes in the molecular structure can greatly influence the physical-chemical properties of the substances. Manufacturers of new active pharmaceutical ingredients are already utilizing this method to optimise the efficacy of a substance and to minimise its side effects. The optimisation of active ingredients also in terms of environmental aspects thus doesn't require a new approach, but merely the extension of the methodology by an additional objective.*

Two Examples of Green Active Ingredients

Two examples illustrate that the development of green pharmaceuticals is fundamentally possible. The cytostatic agent 5-fluorouracil (5-FU) has been shown in different standardised tests to be non-biodegradable. At the same time, it can be shown that the biological key component of 5-FU – the so-called uracil – is easily biodegradable. The 5-FU molecule differs from the uracil molecule only with respect to one fluorine atom in its ring structure, however. Obviously the fluorine atom has a negative influence on the biodegradability of 5-FU. This correlation is further confirmed by a comparison with the structurally similar but non-fluorinated cytostatic agents, gemcitabine and cytarabin. In the same tests both of these substances are much more biodegradable than 5-FU. But the decisive point is that at the same time gemcitabin and cytarabin have improved application properties compared to 5-FU.

The cytostatic agents ifosfamide and glufosfamide represent another example. Glufosfamide is clearly more biodegradable than ifosfamide. At the same time it has better application properties – it is better resorbed in the gut and it is more compatible. Glufosfamide was obtained from ifosfamide in a specific developmental process through a modification of the molecular structure of ifosfamide: The pharmaceutically active part was retained and the rest was modified by means of attaching sugar molecules. Interestingly, depending on the specific type of the sugar molecule used in the process both the efficacy and the biological degradability are different. Glufosfamide has optimal application properties and is at the same time degraded effectively in conventional sewage treatment plants. Even if the original aim was the improvement of the application properties, it appears here, too, that optimal functionality and good degradability does not have to be antipodes.

* In some cases suitable computer programmes were already successfully used in modifying active ingredients in terms of enhancing or attenuating specific effects. A well-known example is the AIDS preparation, agenerase.

How the Development of Green Pharmaceuticals can be Promoted

For pharmaceutical industry, this action perspective means no longer relating sustainable corporate management solely to the raw materials and production processes but, more emphatically, to the product itself. This type of corporate management corresponds to the model of Sustainable Pharmacy. Besides the question of their economic market potential, there are several factors that decide the chances of a green product policy in pharmaceutical industry. These include the further development of computer-assisted methods for molecular design, the implementation of the new design principle in research and development and pre-eminently the early availability of successful examples of green active ingredients from as many different areas of application as possible – wherein "success" means that the green pharmaceuticals are not only better for the environment but have equally good or even better application properties than conventional ones.

In the following a catalogue of options of action is presented by means of which the development of green active pharmaceutical ingredients can be promoted. They aim primarily at anchoring the new design principle as a fundamentally new mindset and approach in research and development practice. In addition, incentives are introduced that can make a green product policy attractive for medicinal product manufacturers.

Research and Development	
Research funding programmes	Independent research institutions and medicinal product manufacturers are supported in the development of green active pharmaceutical ingredients.
Evaluation of the programmes	The focus of the evaluation will be the significance of a green product policy for the innovative capacity of medicinal product manufacturers.
Examples of success	In order to promote a green product policy in pharmaceutical industry a list of successful examples for green active ingredients will be published.
Adjustment of University Education	
Research and education focuses	Their set-up should promote rapid implementation of the new design principles in chemistry and pharmacy.
Change of the Legal Frameworks	
Extension of patent duration	The privilege of green active ingredients creates stimuli for innovation and increases the economic security when pursuing this development strategy.
Change of authorisation	Green active ingredients become priviledged through tightened coupling of the environmental risk assessment and the medicinal product authorisation.
Communication Measures	
Awards and competitions	They should promote the issues of "Green Pharmaceuticals" and "Sustainable Pharmacy" in research, education, and in the general public.
Public relations campaign	Through campaigning for the sustainable pharmacy model and the advantages of green drugs, their acceptance and marketability is increased.

* In contrast to Sustainable Chemistry, the overall concept of Sustainable Pharmacy has not yet been established. Sustainable Chemistry today rather focuses on the alteration of the raw material base and the synthesis routes. Nevertheless, Sustainable Pharmacy can learn from the experiences gathered here. Both models are discussed internationally under the keywords "Green Chemistry" and "Green Pharmacy".

Research and Development

The pharmaceutical industry is highly knowledge-based. It is therefore necessary to address research outside of the branch itself. Public research funding should arrange special support programmes for the development of green active pharmaceutical ingredients that appeal particularly to universities and independent research institutions. Its focus could be further development of *known* active pharmaceutical ingredients with poor environmental properties into green products. A further element of such programs could be the establishment of a specialised institute for "Sustainable Pharmacy".

For medicinal product manufacturers to take up a green product policy, both their technical and their business feasibility must be ensured. An assessment of the support programmes must therefore primarily answer the question of to what extent the criterion "better environmental properties" excludes economically or therapeutically promising active ingredients from further development and thus curtails the industry's innovative capacity. An outcome of the programme evaluation should be a list of examples of successful cases. Using this demonstration of "Best Practice", a green product policy can be campaigned for with medicinal product manufacturers.

Implementation of the new design principles for green pharmaceuticals needs examples of success. Targeted research funding and education focuses can contribute here.

Rapid dissemination of the new design principles for green active ingredients in research and development requires a strong stimulus. The establishment of a main focus of "Sustainable Pharmacy" in university research could be such a stimulus. The main focus would network relevant disciplines like medical, pharmaceutical, and organic chemistry as well as environmental chemistry and environmental health, in order to move the importance of the overall life cycle of an active ingredient also structurally into focus. Its establishment could, for example, be achieved through national research foundations or by corresponding government departments.* Harmonisation with funding and support measures in the area of Sustainable Chemistry that aim for example at the optimisation of synthesis processes would be recommendable in this context.

The financial and practical participation of the pharmaceutical industry in the establishment, implementation, and evaluation of funding programmes and research focuses must be strived for, because here the practical knowledge relating to required substance properties with respect to a specific application, as well as to the defining factors in the selection of active ingredient candidates, is available. With direct involvement, green active ingredient structures that were developed in the framework of such programmes could directly be further developed by the companies up to readiness for marketing.

* In Germany this could be the Deutsche Forschungsgemeinschaft (German Research Foundation) or the Ministry of Education and Research. For the latter a current opportunity could be to promote Sustainable Pharmacy in the framework of the recent 'Pharmaceutical Initiative for Germany'.

Adjustment of University Education

Changes in research and development will contribute to a shifting of focuses in the education of chemists, pharmacists and physicians, and to the strengthening of a principle of active ingredient development, that integrates environmental aspects from the very start. Universities and faculties should actively support this process. Organic-chemical basic and advanced practical courses in the study of chemistry and pharmacy should be aligned with the notion of Sustainable Chemistry and Sustainable Pharmacy and should introduce computer-assisted molecular design methods early. Because the training curricula and methods will change over time anyway, the cost for such an adjustment of university education can be estimated to be rather low. Such adjustment can be promoted by the narration of a positive image. A pharmacist or chemist involved in substance synthesis would, in the sense of the new overall model, describe his- or herself as "molecular designer" or "molecular architect" who is not merely "cooking" a novel compound but develops it beforehand using to a highly intellectual standard, and in the process considers sustainability aspects like consequences for the environment and health.

Change of the Legal Frameworks

Along with the sometimes only indirect effect of measures in research funding, the introduction of directly effective incentive instruments would make sense in order to foster a green product policy in companies. One such instrument can be the extension of patent terms exclusively for green active ingredients from the current 20 years to for example 23 years. This would increase economic security when pursuing a green product policy and would support the development of environmentally compatible active ingredients up to readiness for marketing. In which case an active ingredient can be labelled as "green" must be defined by a transparent criterion. How strictly this criterion needs to be interpreted in the individual case should depend inter alia on the expected market penetration of the new active ingredient.

If the environmental properties of pharmaceuticals become relevant to authorisation, incentives for developing green active ingredients will result.

In parallel, the medicinal product authorisation process and the environmental risk assessment can be more strongly coupled (the determination of an environmental risk is not a grounds for rejection of market authorisation for a medicinal product according to current European legislation). If the environmental properties of an active ingredient become as relevant to authorisation over the long term as its efficacy properties, there will be a stimulus for developing green products. A possible model would be, in a first phase, to generally limit (for example to ten years) the authorisation term for active ingredients for which an environmental risk is determined.* In a second phase, the authorisation could then be rejected for environmental reasons if there is an already authorised, more environmentally compatible, and therapeutically equivalent alternative to the active ingredient in question. Only in a third phase will authorisation be denied if an active ingredient represents an environmental risk. Whether the favourable environmental properties exist only incidentally in the active ingredient or whether the attempt

* Pursuant to current European legislation, the authorisation of a medicinal product is valid initially for five years. The authorisation expires if an application for extension is not filed six months before expiry of the term. The extension then applies without time limitation, unless grounds for the safety of the medicinal product contravene.

was made to specifically integrate them would be irrelevant for the application of the instruments described. Ultimately it is solely a question of the properties of the active ingredients and not the path towards them. This would be left to the companies themselves.

Communications Measures

Agencies or interested manufacturers of medicinal products should, as soon as the first green active pharmaceutical ingredients are available, initiate a public relations campaign in order to draw early attention to the benefits of the newly developed pharmaceuticals. In this fashion, their market penetration is accelerated and, if applicable, prolonged exploitation of the patent term can be realised. Here, it makes sense to specifically address the target groups who will use the new pharmaceuticals: Physicians, pharmacists, and patients must be informed that the medical standard is not compromised by the new approach. In addition funding awards should be made and competitions organised in the topical areas of “Development of Green Active Pharmaceutical Ingredients” and “Sustainable Pharmacy” in Germany and Europe. They can contribute to move these themes forward in research and university education as well as to the general public.

Sphere of Activity „Handling of Drugs“

Contrary to other product areas, environmental aspects have previously hardly played a role in prescribing or purchasing, use or disposal of medicinal products. In the scenario of the substance life cycle, however, the phase of handling drugs also provides approaches for effective options of action for reducing the contamination of water bodies. In general, these can be implemented at two points: On the one hand in reducing the consumption of pharmaceuticals, and on the other hand in the avoidance of medicinal wastes that may be improperly disposed of via domestic wastewater (or in ensuring proper disposal of medicinal products, respectively).

Changes in the interaction with medicinal products are in the tug-of-war between safeguarding health and conserving the environment. This must be taken into consideration when designing procedures.

The use of medicinal products is associated with high and undisputed individual and social benefit. Moreover, a medical decision for a medicinal therapy generally depends on a number of factors that must be weighed against each other. Here, in each individual case, priority is given to the best possible strategy for curing or palliation of a disease. When in doubt, the rule is “health protection before environmental protection”. At the same time, it must also be assumed that further regulations in an already heavily regulated system that are aimed at an objective that is perceived to be secondary will encounter opposition particularly with physicians. Measures that are intended to make the handling of drugs more environmentally compatible must therefore satisfy three prerequisites:

- They must not result in a quality loss in prevention and therapy;
- The must be integrable into the complex professional routine of physicians and pharmacists;
- They should co-operate with already societal desirable plans for reform in the healthcare system.

Behavioural changes that should contribute to a reduction in contamination of water bodies, however, require a corresponding awareness of the problem, particularly if they are to be implemented voluntarily. Empirical studies in *start* have however shown that physicians and pharmacists have previously hardly confronted the consequences of consumption and disposal of medicinal products for water quality.

Awareness of the Problem in the Professional Routine of Physicians and Pharmacists

In in-depth interviews with physicians in Germany (non-representative selection) it became clear that they were largely unaware of the environmental aspects as regards consumption and disposal of medicinal products or it did not affect their professional routine. The paucity of reliable information on the occurrence of individual active ingredients in water bodies and their negative ramifications on animal and plant life was bemoaned. In order to achieve a change in the problem awareness, therefore, physicians must be given the opportunity to form an opinion that corresponds to their professional self-image as natural scientists; in other words, it should take the course of discussion and should not run in predetermined tracks. Moreover, in the interviews, reservations relating to measures aimed at problem solving surfaced. The fear was expressed that purposes other than healing would move into focus, or that additional regulation could further narrow the physician's freedom of action. Changes in professional behaviour that contribute to an environmentally compatible handling of drugs should therefore be based on the physicians' own decision-making.

To date the topic hardly plays a role in physicians' professional routine. Pharmacists, in contrast, see themselves closer to the topic.because of their competence as regards substances.

Pharmacists complain of an increasing loss of recognition as important actors within the healthcare system. The reasons for this are the growing commerce in medicinal products and the increasing medical advice offerings on the internet. At the same time, due to their training, they view themselves as the real specialists for substance assessment of medicinal products. Therefore, they take the contamination of water bodies by active pharmaceutical ingredients seriously as a topic that fundamentally approximates their area of competence and responsibility. This was a finding in corresponding group discussions carried out in the framework of *start*. They refer to figures relating to medicinal product wastes and their own experiences that only a fraction of the medicinal product wastes are returned to pharmacies. Pharmacists expressly recognise and share the requirement of precautionary action. But they see their room for manoeuvring in the case of pharmaceuticals only available on prescription essentially limited to the service of proper disposal. From their point of view, however, on the growing market of over the counter products, advisory services that include also more extensive environmental aspects could be of particular value.

How the Handling of Drugs can Become more Environmentally Compatible

In the following a catalogue of options of action is presented, by means of which the handling of drugs can be structured to be more environmentally compatible. Official bodies, health funds, the different organisational levels of the medical and pharmacy associations, practicing physicians and pharmacists themselves, patients and the manufacturers of medicinal products are addressed. It must be considered that options of action that can contribute directly to a reduction of contamination of water bodies can be realised only if appropriate foundations are laid beforehand. Policy frameworks that highlight contamination of water bodies by active pharmaceutical ingredients as a societal problem to be reckoned with, as well as dissemination of knowledge and information on the subject are part of this. In this sense, the options of action presented strategically build upon each other.

Policy Frameworks	
Environmental objective: Protection of water bodies	Safeguarding surface and groundwater from contamination with pharmaceutical residues is defined as an environmental objective.
Increasing Problem Awareness	
Discussion opportunities	Targeted information opportunities promote opinion-formation in physicians and pharmacists on the topic of contamination of water bodies by active pharmaceutical ingredients.
Professional retraining	The topic of contamination of water bodies by active pharmaceutical ingredients will become an integral part of the retraining of physicians and pharmacists.
Change in Prescription Practices	
Environmental classification	An environmental classification for human pharmaceuticals allows physicians to prescribe environmentally compatible active ingredient alternatives.
Drug consumption	Reduction of drug consumption by the possibility to increasingly prescribe non-medicinal forms of therapy that generally promote health
Avoidance of Medicinal Product Wastes	
Information on drug consumption	Control of patient demand through creating cost and quantity transparency for insurants in statutory health insurance
Package sizes	Offer of variable package sizes, starter packs for chronic diseases and dispensing of partial quantities (for example tablet blisters)
Disposal of Unused or Expired Medicinal Products	
Disposal standard	Creation of a consistent and compulsory disposal standard through pharmacies and simplification of the take-back system for pharmacies
Education and labelling	Sweeping information campaigns relating to proper disposal as well as disposal instructions on medicinal product packaging and package leaflets

Policy Frameworks

Safeguarding surface waters and groundwater resources from the entry of active pharmaceutical ingredients should become an environmental objective in Germany and Europe on different levels. As the Swedish example shows, such authoritative commitment decisively contributes to that the general public and the actors in the healthcare system recognise the consequences of consumption and disposal of pharmaceuticals as a problem and that they proactively undertake precautionary action.* In Germany such change in political framework conditions can, for example, be stimulated by the National/Regional Consortium on Water ("Bund/Länder-Arbeitsgemeinschaft Wasser") in the context of the current implementation of the European Water Framework Directive (WFD). When setting up the management plans for the respective river basin districts,

*The provincial government of Stockholm primarily engages in the solution of environmental problems that result from the activities of the regional government (for example as the task manager for public health). Here, the reduction of water, air, and soil contamination by active pharmaceutical ingredients is one of the especially recognised objectives.

the Bundesländer should be urged to relate environmental objectives for water bodies explicitly to active pharmaceutical ingredients. Corresponding recommendations on defining water quality objectives for index substances like the anti-epileptic agent carbamazepine or the anti-inflammatory agent diclofenac are already being discussed in the current phase of establishing the management plans (to be concluded by the end of 2009). An impetus for including selected pharmaceuticals in the list of priority substances of the WFD could emerge from such an initiative – with a corresponding signal effect.

Increasing Problem Awareness

Physicians and pharmacists are key players in the implementation of options of action that directly influence the entry of active pharmaceutical ingredients in water bodies. Therefore, they must be provided with special offers for information and opinion forming on the subject. Suitable instruments for doing this are targeted publications in print and online media that are recognised by these professional groups to be credible (for example specialist medical media, and medical association information platforms) as well as contributions at relevant congresses, meetings, and specialised journalist seminars. In the medium term, such discussion offerings can contribute to an increase of awareness of the problem in both professional groups. In their design it must be noted that there are quite different reaction patterns to the subject. This was demonstrated by the empirical investigations in *start*. They range from spontaneous rejection in the sense of incompetence for an environmental issue on up to great openness to and interest in the problem.

Another instrument for supporting the opinion-forming process and for heightening problem awareness is the incorporation of the topic in the mandatory retraining of physicians and pharmacists. The subject-matter of retraining is generally the motivation of and confrontation with behaviours for professional routine. In the context of retraining, the consequences of consumption of medicinal products on water quality should thus be immediately associated with questions related to prescribing practices – for example: "Is there an equivalent non-medicinal treatment option or an alternative active ingredient that has less impact on water bodies?" If appropriate, these questions should be linked with a general discussion on measures for cost reduction in healthcare.

Change in Prescription Practices

The provision of measures that can be integrated into the complex professional routine is an essential pre-requisite for physicians and pharmacists to engage in problem solving with individual contributions. Environmental classification for human pharmaceuticals is an effective instrument for this purpose whose introduction in Germany is recommended. By means of a simple procedure it allows to compare the environmental risks and hazards of active pharmaceutical ingredients. If there are equivalent therapeutic alternatives, the more environmentally compatible active ingredient can be prescribed using this decision-making tool. A pan-European introduction of the environmental classification is principally advisable, even though presently not conceivable. Its introduction in Germany could yet generate a strong stimulus in this direction.

An environmental classification for human pharmaceuticals should be introduced in Germany. It can easily be integrated into the professional routine and allows physicians a practical contribution to problem solving.

The classification scheme should be geared to the guidelines in force for environmental risk assessment in the framework of the European medicinal product market authorisation process. In addition, the drinking water relevance of the active ingredients should be taken into account as a special evaluation criterion. The long-term goal would be to classify all active ingredients traded on the German market. When setting up this list, it would be recommendable to start with the active ingredients so far detected in water bodies. A list of recommendations that includes active ingredients with particularly good environmental properties, can reasonably supplement the classification. The environmental classification should be set up and maintained in collaboration with the medicinal product manufacturers through an independent institution. Imitation of the already established Swedish system is recommended. In order to ensure that the environmental classification meets with the acceptance of physicians and pharmacists, it must be ready to be easily integrated into the daily professional routine. Therefore, efforts must be made to incorporate the environmental classification into relevant reference and recommendation works and information systems (in Germany for example the Rote Liste® or in existing software for selecting medicinal products). The introduction of the classification should be accompanied by appropriate information material and consultancy services.

A majority of medicinal product consumption traces back to illnesses that are associated directly with an unhealthy lifestyle. A contribution to reducing medicinal product consumption and simultaneously to an enhancement of preventive healthcare is the encouragement and support of physicians in prescribing non-medicinal, generally health promoting forms of therapy. The prerequisite for this is that such a "prescription for a healthy lifestyle" be accepted and recompensed by the healthcare funds. Examples of such therapies are movement training, back training, or professional support in changing dietary habits. The Swedish experiences have documented that patients accept these types of prescriptions, because providing a prescription creates a greater obligation than the mere recommendation of behavioural change in the physician-patient dialogue. In addition, the widespread expectation of patients vis-à-vis the physician of prescribing "something" (the "prescription wish") can be accounted for. Corresponding pilot trials are already being conducted in Germany such as the Hessen Medical Association's "Fit and healthy with the prescription for movement" campaign. Current initiatives of health funds are aligned more with prevention and are based on bonus programme: They offer incentives if certain healthy offers are taken advantage of.

A direct contribution to reducing the consumption of pharmaceuticals will be pssoible, if non-medicinal forms of therapy become more and more eligible for prescription.

Another possibility for reducing therapeutically unnecessary medicinal product consumption is the increase of co-payments in the case of prescription drugs. For some time now this option has been discussed again and again as a suitable tool for increasing cost-efficiency in the healthcare system. The new argument of an increasing contamination of water bodies by active pharmaceutical ingredients could be used supportively at its implementation. Naturally, different societal groups would have to be

addressed in different ways for this type of "demand-side management". In any case, special hardship case arrangements for the chronically ill and socially weak patients would have to be considered. An increase in co-payments could ultimately also represent a contribution to preventing "hoarding" of medicinal products in private households and consequently to a reduction of medicinal product waste.

Avoidance of Medicinal Product Waste

People insured by the statutory health funds are scarcely aware of the annual cost of their medicinal product consumption. The absence of cost transparency leads – according to general findings in a government organised care system – to the phenomenon of the so-called "Moral Hazard". In the case of providing medicinal products this phenomenon means: Patients collect drugs through double prescriptions "in stock" without actually needing them. Some of these pharmaceuticals are then at some time no longer needed and must be disposed of as waste. As representative studies in *start* have shown, a significant portion of the German citizens then choose the drain or the toilet to this end. Measures that lead to avoidance of medicinal product waste thus contribute indirectly to the prevention of contamination of water bodies.

Voluntary measures in Germany that are intended to result in better cost awareness like the so-called "patient receipt" (service and cost information) have scarcely been accepted by patients to date. The anticipated introduction of the electronic health card in Germany might be more effective here. By recording prescribed and actually dispensed medicinal products by specific active ingredient, it is possible for the physician to inform the patient of multiple prescriptions for the same indication. This type of feedback has, in conjunction with quarterly medicinal cost information for the insurant, the potential of bringing about behavioural changes and thus of reducing therapeutically unnecessary prescriptions. The prerequisite for implementation of such a measure is an accord between the medical associations and the health insurance funds, as well as a modification of the organisational processes in surgeries.

By establishing cost and quantity transparency the introduction of the health card can be an effective contribution to reducing medicinal product wastes.

The expanded offering of medicines in variable package sizes can likewise help to avoid medicinal product waste. As the physician interviews in *start* have also confirmed, the problem of package sizes not adapted to therapy has eased in recent years. Especially in the case of chronic disorders there is, however, still no small starter pack that can be prescribed for the purpose of determining compatibility. An unpackaged individual portioning of for example tablets – as is possible in the US – is deemed both by physicians and pharmacists as not expedient from hygienic and economic points of view. Individual mark-up can, however, make good sense, particularly for hospitals. For example, by allocating to each tablet on the blister, name, batch number, expiry date, and a code for fast and simple print-out of the package leaflet, residual stocks can continue to be used safely or dispensed by the physician to needy patients – in Germany today a common, although as yet unauthorised practice.

Disposal of Unused or Expired Medicinal Products

Improper disposal of unused or expired medicinal products via the drain and the toilet occurs in Germany to a relevant degree. This was the result of population-representative survey in the framework of *start* (see page 7). The main reason for this disposal misconduct is: In Germany there is no uniform disposal standard and no uniform, active communication strategy for proper disposal of unused or expired medicinal products. The recommendations of waste-disposal operators, municipalities, and the Bundesländer sometimes differ considerably. They range from return to hazardous or problematic collection stations to disposal in domestic waste and return to the pharmacy. The uncertainty that thus arises in the population on the proper way of disposal gains significance in view of the high willingness to recycle among Germans: Obviously the structured routines in separating waste are transferred indiscriminately to medicinal product waste. This means, for example: In order to be able to dispose of liquid medicinal products in glass containers, they must first be emptied – and to do this only the drain or the toilet stands ready. This behaviour is reinforced by the low level of knowledge among the population regarding the possible consequences of contamination of water bodies by active pharmaceutical ingredients.

The introduction of a nationwide – and possibly an EU-wide – consistent and binding disposal standard for unused or expired medicinal products is therefore necessary. The return of medicinal products that are no longer needed to the pharmacy – an already well-established system in Germany – is recommended here. The prerequisite for this is that pharmacies continue to accept the remaining supplies voluntarily and at no charge. As the empirical studies in *start* have shown, pharmacies are in principle ready to continue to offer acceptance of unused or expired medicinal products as an additional customer service. In order to further increase acceptance in the pharmacies, however, simplification of the return system for the pharmacy personnel is advisable. At the present time, pharmacists take on the task of recyclables separation.* In the future, this should be provided by the operator of the return system. A practical option would be to distribute free special bags at the pharmacies in which the customer can return his or her unused or expired medicinal products. If the containers – that are emptied by the operator of the return system – can be set up in the customer area, the customer can even deposit its filled bags by him- or herself.

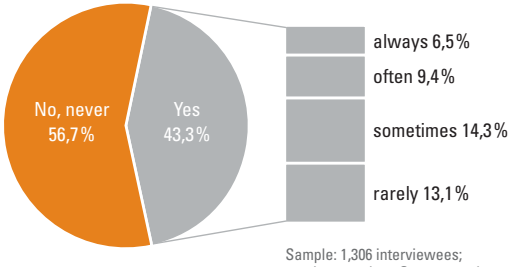
A uniform disposal standard for unused or expired medicinal products is needed, in order to promote their proper disposal. In Germany the take-back system via pharmacies is suitable for this prurpose.

* In Germany today, pharmacy staff must distribute the returned medicinal products according to primary packaging (e.g. tubes and blisters), packaging parts made out of cardboard or paper, and the actual medicinal product, to three different bags. These are then regularly collected by the operator of the return system.

According to current legislation, medicinal products – with a few exceptions like cytostatics – are not hazardous waste and can therefore, in principle, be disposed of with household waste. In addition, because today almost 100 per cent of household waste in Germany is incinerated, this way of disposal is unproblematic also from the environmental point of view. Even if this solution is obviously more convenient for citizens, it must be critically reflected. On the one hand, in terms of precautionary aspects possible risks to

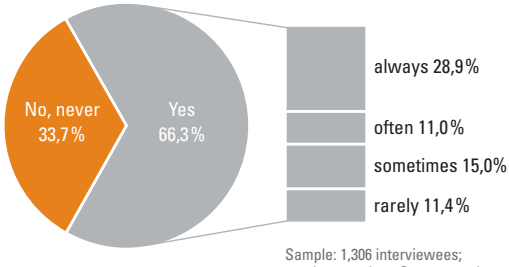
third parties – playing children, for example – must be taken seriously. Today only about 7 per cent of the Germans consistently throw away their unused medicinal products in household waste. If in the future this figure should increase considerably, the risk will also increase that this hazardous waste could some day lapse into the wrong hands. Information on how this can be prevented – for example by wrapping the old tablets in newspaper – is difficult to communicate and actual compliance can hardly be ensured. On the other hand, in recent years collection systems have been set up in the majority of the member states of the European Union – in part because of the applicable legal regulation (see page 13). Favouring disposal via household waste in Germany would counteract an EU-wide uniform solution.

Disposal of unused drugs via household waste



Sample: 1,306 interviewees;
numbers apply to Germany only

Return of unused drugs in pharmacies



Sample: 1,306 interviewees;
numbers apply to Germany only

Today, only about one third of Germans return their unused or expired medicinal products consistently to the pharmacy. In order to increase this number and to counteract improper disposal, a wide-range, professionally planned and organised campaign for educating the public should be implemented. Because return to the pharmacies has already been in place as a disposal option for some time in Germany, a communications link can be easily established here. Water body protection should be allocated emphatic significance in such a campaign. Here the individual options of action should be communicated as positive experiences without reinforcing possibly existing fears. In addition, patients should be explicitly informed that generally all unused or expired medicinal products – prescription and over-the-counter – should be returned to the pharmacy.

Supportively, an appropriate statement on the proper disposal of medicinal products should be printed by default on the medicinal product packaging and on the package leaflet. This measure is already incorporated in corresponding EU legislation but so far not consequently implemented. Here also pharmaceutical industry is called on to go ahead pro-actively.

Even if green pharmaceuticals become more and more available and the use of drugs becomes more environmentally compatible, environmental technology for reducing the occurrence of active ingredients in water bodies will remain indispensable in the foreseeable future. Active pharmaceutical ingredients, however, represent only part of the spectrum of organic trace contaminants that present urban water management with technical problems as regards their removal from waste and raw waters. Investments in specific upgrades and improvements of the existing systems and processes of wastewater disposal, wastewater treatment, and drinking water processing must therefore always be viewed in connection with the solution of more extensive substance problems. Options of action for reducing water body contamination with trace contaminants can be approached basically at three levels:

- Reduction of substance emissions into municipal wastewater;
- Wastewater treatment in sewage treatment plants;
- Drinking water processing in water works.

How do sewage treatment plants and water works operate today?

In order to remove trace contaminants and other problematic substances from wastewater, sewage treatment plants generally have a mechanical and a biological treatment step. Larger plants are additionally equipped with a step for removing nitrates and phosphates. The biological treatment step is based on the so-called activated sludge process. Here, the wastewater is collected in a settling tank or clarifier, mixed thoroughly, and aerated. As a result of the metabolic processes of the microorganisms present in the wastewater, sludge fluffs occur in which the actual purification process takes place; in other words, organic compounds are biologically degraded therein by microorganisms. An additional retention occurs, depending on the physical-chemical properties of the substances, by deposition to suspended particles in the sludge. In a secondary clarifier the activated sludge is settled out of the treated wastewater and led back in part into the aeration tank. The excess sludge is thermally exploited or used as agricultural fertiliser, for example. Research results have shown that active pharmaceutical ingredients, because of their specific properties, can be removed only partially or in some cases not at all from the wastewater using this process.

Today's sewage treatment plants can hardly remove active pharmaceutical ingredients from wastewater. For water works these substances sometimes represent a special challenge.

The aim of drinking water providers in Germany is the close to natural treatment of their raw water; this means that drinking water should be abstracted as much as possible without the use of complex environmental techniques. The prerequisite for this is a correspondingly good raw water quality. In recent decades this goal has yet become a greater and greater challenge due to, among other things, the increasing use of chemicals. Water works that convey groundwater meet this challenge through measures for

safeguarding their catchment areas (for example the establishment of protected zones and accords with agriculture). Where this is not possible, a minimum degree of treatment technology is used. However, coping with active pharmaceutical ingredients presents these water works with special problems not only due to the specific substance properties but also because as for physical reasons it is principally more difficult to further reduce already small concentrations by means of technical procedures. Water works whose raw water originates from surface water are particularly affected by this (see page 10). Therefore these water works most often supplementary use activated carbon filtration (often coupled with ozonation), in order to remove organic trace contaminants from the raw water as much as possible. It must be assumed that in Germany at least the water works along the Rhine River generally have this technique available. Exact figures on the spread of the procedure in all of Germany are not publicly available.

Advanced sewage treatment technologies: What can they achieve?

In the framework of *start*, a comprehensive evaluation of innovative technologies that come under consideration for advanced sewage treatment was carried out on the basis of the current state of research. This includes membrane bioreactors, adsorption processes with powdered activated carbon, ozonation, and photo oxidation. The overall result of the evaluation is that none of the technologies considered is capable on its own of completely removing the known spectrum of active pharmaceutical ingredients from municipal sewage.

Sewage treatment plants that were equipped with membrane bioreactors on a trial basis, only rarely produced better performances in removing active pharmaceutical ingredients than conventional facilities. Depending on the active ingredient investigated, generally not more than an additional 50 per cent of a substance was removed from the sewage. Initial studies using pilot plants produced these results. In contrast, powdered activated carbon that is added to the wastewater after the biological treatment step, was shown to be clearly more effective. In experimental facilities, active pharmaceutical ingredients in wastewater were reduced overall by up to 80 per cent using this method. To date no reliable data are available on the performance of photo oxidation. Initial experiments with highly contaminated industrial wastewater have shown promising results. More research is required in this technology, however. Ozonation has likewise been shown to be an effective process for removing active pharmaceutical ingredients. But a number of complex reaction products are generated in this process. About their toxicity generally nothing is known – a problem that deserves special consideration when using this technology.

To date, none of the currently discussed technologies of advanced sewage treatment is able on its own to completely remove all active pharmaceutical ingredients.

One possibility for initially avoiding or substantially reducing the contamination of municipal sewage is provided by sustainable sanitation systems. They are based on the separation of wastewater component flows at the site of their origin. In households, these component flows are utility or service water (for example for cleaning and body care) and toilet wastewater, which is further separated into yellow water (referring to the urine fraction) and brown water (referring to the fecal fraction). Because concentrations of active pharmaceutical ingredients in unmixed toilet wastewater are higher, the available treatment technologies – such as membrane bioreactors, but also fermentation processes – can be more effectively used here. After an accordingly optimised treatment of the component flows at the site of their origin, they can then be either discharged into the municipal sewage network or reused directly (closing of local water circuits). Such systems are of particular importance because they can be combined with sustainable technologies. These include energy production from the fermentation processes in brown water and the recovery of finite and already scarce resources like phosphorus from urine.

How Water Body Contamination can be Reduced by Environmental Technology

The basic principle of a sustainable technical strategy for reducing water body contamination by active pharmaceutical ingredients and other organic trace contaminants should preferably be to tackle it at the source of entry of the substances. By reducing the pollution of rivers, lakes, and groundwater reservoirs in this way, not only can drinking water contamination be prevented in the future, but through the improvement of water body quality, risks for the aquatic animal and plant life will also be reduced. In this sense, methods for reducing the emission of active ingredients into municipal wastewaters attain special significance. Here, however, a temporal aspect must be taken into account: For an effective contribution in this area the changes necessary in urban water management can be realised only over the long-term. As the entry of active pharmaceutical ingredients is yet likely to increase in the future, measures of an advanced wastewater treatment at the sewage treatment plants that can be implemented also over the medium term as well as individual case solutions realisable over the short-term in drinking water abstraction must be considered.

Sustainable technical solutions must apply at the source of entry of pharmaceuticals. This means first of all preventing the substances from reaching municipal wastewater.

Reduction of Emissions of Active Ingredients into Municipal Sewage	
Separation of sewage component flows	Through separation of sewage component flows and their optimised treatment at the point of origin, municipal wastewaters can be disburdened.
Hospital wastewaters	In case of a strong contamination with problematic substances, a separate collection and treatment should be effected before discharge into the municipal sewage system.
Wastewater Treatment in Sewage Treatment Plants	
Assessment of advanced technologies	As soon as data from large-scale experiments with powdered activated carbon in sewage treatment plants are available, a comprehensive assessment should be carried out.
Increase of activated sludge age	By an increase to about 10 days, an improvement of the biological degradation of some active pharmaceutical ingredients is possible at low cost.
Drinking Water Processing in Water Works	
Activated carbon filtration	Water works that directly or indirectly use contaminated surface water and do not yet use activated carbon filtration, should upgrade accordingly.

In the following, options of action based on environmental technology are presented, by means of which water body contamination by active pharmaceutical ingredients can be reduced according to the current state of research and technology. Because information in the case of several technological options – such as the use of powdered activated carbon in sewage treatment plants – is still insufficient in order to make a reliable recommendation it is referred to the implementation of corresponding research and investigation as an appropriate option of action.

Reduction of Emissions of Pharmaceuticals into Municipal Sewage

The introduction of sustainable sanitation systems lends itself in the medium to long term to new-housing projects, industrial and commercial zones, office buildings, buildings with public toilets, thruway rest areas, and airports. In these types of building complexes, storage capacities for the wastewater volumes can be jointly constructed, whereby management concepts for their controlled emptying and a corresponding infrastructure for treatment of the wastewater flows would have to be set up. Ideally, these systems would be coupled with a recycling system for nutrients like phosphorus and potassium and techniques for energy abstraction from the wastewater component flows. In this manner, their acceptance and assertiveness is increased with investors. According to today's state of technology, the systems can be set up so that the wastewater purified at its point of origin can directly be reused right there (decentralised solution) or subsequently discharged into the municipal sewage system (semi-centralised solution). With a long-term, wide-area realisation, this will substantially reduce the entry of active pharmaceutical ingredients and other trace contaminants in municipal wastewater.

On the long term, sustainable sanitation systems can contribute to disburden municipal wastewaters. For hospitals such systems are also suitable in individual cases.

A separate collection and treatment of wastewater component flows lends itself also for hospitals and other medical facilities. Since these sources of entry contribute a maximum of only 10 to 20 per cent of the total volume of pharmaceuticals discharged annually into municipal sewage, the equipping of hospitals with appropriate systems should not be required generally due to cost considerations. For facilities in which particularly high concentrations of problematic active substances such as cytostatics or antibiotics are measured in their sewage, separate collection and treatment of toilet wastewater before discharge into the municipal sewage system is advisable, however. By this means, municipal sewage can be selectively disburdened in a timely fashion over the short to medium term. Pilot studies have shown that these types of system are practicable and allow effective removal of active pharmaceutical ingredients. Here, a treatment technology was used, that consists of a sedimentation stage and subsequent ozonation. It must be examined on a case-by-case basis how such a measure – particularly in the case of old buildings – would be implementable without unacceptable impairment of hospital operation. In new buildings this measure is fundamentally recommendable – corresponding guidelines were already drafted in a bulletin of the German Association for Water, Wastewater and Waste in 2001.

Wastewater Treatment in Sewage Treatment Plants

Wide-ranging use of sustainable sanitation systems is feasible only in long time horizons. In addition, it must be taken into account that with these procedures – even in the ideal scenario – complete decontamination of municipal wastewater cannot be achieved. The reason is that despite the possibility of more effectively utilizing the available treatment technologies because of the higher substance concentrations in the wastewater component flows, even they cannot guarantee 100 per cent removal of active pharmaceutical ingredients. Therefore, advanced technologies for wastewater treatment in sewage treatment plants must be included complementarily in the deliberations. As the investigations in the framework of *start* have shown, in this area, too, there is insufficient directional certainty, which of the technologies currently being discussed should be implemented in practice. Although the strengths and weaknesses of the individual technologies are becoming increasingly clear, a reliable recommendation for a concrete technology or a combination of technologies, however, cannot be articulated based on the available data. Performance data from pilot plants that are operated on an industrial scale are required for this. As soon as corresponding expertise is available – such as from the German Zweckverband Klärwerk Steinhäule pilot project that has been running since 2004, wherein powdered activated carbon is added to the biologically pre-treated wastewater – a comparative assessment according to different criteria like efficacy and cost-effectiveness should be carried out.

To date, it cannot be resolved which technology of an advanced wastewater treatment is practically suitable for the treatment plants. Corresponding investigation is of prior importance.

In the field of wastewater treatment in sewage treatment plants the only sound recommendation that can be made on the basis of the current state of knowledge is to increase the sludge age in the aeration tank to about ten days. For sewage treatment plants that currently operate with shorter holding times, this represents a simple and comparatively low-cost measure for the improved biological degradation of some active pharmaceutical ingredients.

Drinking Water Processing in Water Works

The use of activated carbon filtration (partly coupled with ozonation) in water works that abstract their drinking water from bank filtrate, river water, or enriched groundwater is widespread in Germany. Here water management keeps ready a potential for drinking water protection that helps in many places to prevent breakthrough of active pharmaceutical ingredients and other trace contaminants. In order to further increase this potential, water works that do not possess this technology should – if necessary after a case-by-case assessment – upgrade their facilities accordingly, unless the precautionary threshold value of 0.1 microgram per litre defined by the German Drinking Water Commission cannot otherwise not be respected for selected index substances. In virtue of this step, additional latitude for the implementation of closer-to-the-source-measures

for reducing water body contamination with pharmaceuticals can be acquired. Moreover, the occurrence of a situation can be counteracted in which future detection of pharmaceutical residues in drinking water – even if they are negligible in terms of impact on health – will result in the possibility of a difficult-to-control dynamic in public risk perception. A situation in which sustainable approaches to a solution will give way to short-term stopgaps under the pressure to act.

The Implementation of Options of Action

In the three spheres of activity "Drug Development", "Handling of Drugs", and "Technical Emissions Control in Urban Water Management" there is a broad spectrum of options of action that can contribute to a reduction in water body contamination. But what can actually be accomplished with implementation of these options of action and what would be the consequences of concentrating only on one sphere of activity in the problem solution? These questions were examined in the framework of *start* using a formal assessment process wherein different criteria like efficacy, cost, and acceptance of a measure were evaluated. Because of the complexity of the individual spheres of activity and the data situation – which in many parts is insufficient – work had to be done generally only with orientation values and qualitative information. The central finding was: A sustainable contribution to solving the problem cannot reside in one of the three spheres of activity alone – a finding that was confirmed by the participants in the *start* practice dialogue. The most important aspects of this study are summarised below for each sphere of activity.

The results of a comparative assessment show: A sustainable contribution to solving the problem cannot reside in one sphere of activity alone.

Sphere of Activity "Drug Development"

The fact that "greening" of molecules is fundamentally applicable to all chemicals – whereby those that reach water bodies when used as intended or because of their open application (cleaning agents, pesticides, personal-care products, for example) are of particular interest here – is of special importance to the implementation of the new design principles. Up to now an orientation towards green product innovations was hardly a core element of sustainable corporate management in chemical industry. It was, however, emphasised from different parties that such an approach is future oriented. In 1994, the committee of inquiry of the 12th German Bundestag "Protection of Humans and the Environment" developed perspectives for a sustainable handling of chemical substances, in that the significance of the environmentally compatible design of chemicals for a sustainable development was emphasised. In the Sixth Environmental Action Program, the European Parliament and the European Commission formulated inter alia the partial objective of producing and using chemicals within one generation only so that they have no negative effects on the environment. The German Advisory Council on the Environment of the German Federal Government anticipates arise in innovation and increasing competitive advantages over the medium to long term on markets for environmentally and health-friendly products.

When estimating the costs of setting up and implementing the new design principles it must be taken into account that the development of new active ingredients is urgently imminent in different indication groups. Investment in drug development is therefore necessary anyway. Consideration of green options is yet hardly associated with relevant additional costs compared to the overall outlay.* In terms of the options of action presented, the main costs are attributed to funding of research. But these pay off in the reinforcement of top-shelf technology in pharmaceutical research and its sustainable orientation. The programs to be established – that are equally aimed at university and industrial research – would have to be jointly borne by the economy and the public. In order to achieve convincing results, such a phase of intensive research funding would have to extend over a period of from 10 to 15 years, according to expert opinion.

The promotion of sustainable design principles and the use of new technologies associated with them will create an essentially different understanding for innovations in pharmaceutical industry. Here, the concept of "Sustainable Pharmacy" should be established as a long-term research strategy or as a model in exploratory pharmaceutical industry. This represents a big challenge. Because on the one hand – in contrast with today – a clear longer-term action orientation in the field of research and development is necessary for achieving this. On the other hand, there is currently an innovation crisis in pharmaceutical industry. In this situation there is the risk that long-term development perspectives will regress vis-à-vis measures for fulfilling short-term expectations of returns. Although it is – both for the chemical and for the pharmaceutical industry – this very strategy that aims at sustainable design principles which provides a forward-looking way out of this crisis. Because in this way a worldwide product accountability is possible, since the green active ingredients and chemicals with less consequences for humans and the environment can also be used in regions in which there is no technically sophisticated wastewater purification or none at all.

The overall concept of "sustainable pharmacy" can be trend-setting for industry: It enables the adoption assumption of a worldwide product accountability.

* In this argument it must be noted that generally the costs of a new medicinal product up to wider market launch are incurred up to two thirds by marketing and only to one third by the development of the active ingredient itself.

Sphere of Activity „Handling of Drugs"

An essential part of the identified options of action aims at generating problem awareness, the provision of information, and stimulating motivation for bringing about behaviour change in handling of drugs. Along with its importance to the implementation of very practical measures such as the use of an environmental classification in the professional routine, these activities also have a superordinate meaning: They can have a positive effect on the overall perception of the problem and thus promote implementation of measures in other spheres of activity. It is very difficult to estimate the degree and the timeframe in which practical effective behaviour changes with physicians is possible. Experiences in Sweden show that the environmental classification introduced there in 2004 is adapted by a majority of physicians. This experience can be transferred only conditionally to Germany. One should be concerned that in view of the bemoaned over-regulation of professional routine, this type of instrument will be perceived as yet another burden. The upcoming "generation turnover" in surgeries – which in view of the age structure of the medical community will probably take place in the next ten years – provides one perspective, however. If the subject is already intensively integrated in university education, acceptance of an environmental classification and other options of action will be additionally increased in practice.

An increase of problem awareness among physicians is a prerequisite for targeted change in prescription practices. The quantities of pharmaceuticals which can be saved by these means can yet hardly be estimated today.

The discussed options of action relating to changing prescription practices and for avoiding medicinal product waste can, in cooperation with overlapping reform measures in the healthcare system, contribute to a more rational use of medicinal products. Here, too, it's hardly possible to reliably estimate using available data what volume of medicinal products can be saved by replacing them with equally satisfactory care – such as by prescribing non-medicinal forms of therapy.* It must be considered that the instruments presented do not apply equally to all indication groups. The consumption volumes of cytostatics but also of diagnostics (x-ray contrast media, for example), will probably remain virtually unaffected. A rough estimate of how strongly the entry of active pharmaceutical ingredients into domestic wastewater due to improper disposal can be reduced, is, in contrast, feasible. Estimates regarding the annual quantity of medicinal product waste in Germany are between 10 and 20 per cent of the total volume consumed – which at 38,000 tons per year (in 2001) is equivalent to 6,000 tons. If the figures from the *start* survey on the disposal behaviour of the Germans are used as basis, it follows that probably around 1,000 tons go directly into domestic wastewater via the drain and toilet – a number that can be clearly reduced over the medium term by the identified options of action for improving disposal.

The direct costs arising in the case of implementation of the discussed options of action will be contained in comparatively manageable limits, because communicative measures and the capacity building are in the foreground: Realisation of discussion opportunities and supplementation of professional retraining for physicians and pharmacists as

* In this context it must be considered that the prescription of non-medicinal forms of therapy does not necessarily initially contribute to directly relieving financial burdening of the healthcare system because even spa cures and physiotherapies incur costs. Through their long-term contribution to preventive healthcare, any additional costs would presumably have to be evaluated as economically neutral, however.

well as the implementation of information campaigns relating to proper disposal of unused or expired medicinal products, are clearly less than ten million Euros annually according to initial estimates – whereby investment periods of different lengths must be considered.

Sphere of Activity "Emissions Control in Urban Water Management"

Prospects for implementation of options of action in this area depend essentially on the answer to the question of how technical options of advanced wastewater treatment at municipal sewage treatment plants score in a comprehensive assessment. Emphasis should be placed on working out an appropriate clarification. Regardless of the outcome of this evaluation, however, there are aspects that should be considered critically in the discussion about solutions in the area of municipal wastewater. In cities with combined sewage systems, domestic and industrial wastewater is mixed with rain water. In the event of overloading the sewage system or the retention ponds due to heavy rains, the wastewater is discharged untreated into water bodies – an event that could increase in some regions in the future due to climate change. The relevance of this source of entry should be specifically examined and, if necessary, solutions worked out for its resolution, before an expensive upgrading of the sewage system is carried out.

In addition, in the decision-making process for advanced sewage treatment, it should be considered that limitation to the use of a single technology may critically limit the effectively treatable range of substances. Focusing on, for example, powdered activated carbon would preferentially solve the problem of active pharmaceutical ingredients that deposit easily on the carbon particles due to their physical-chemical properties. There are, however, other active substances such as the x-ray contrast agent amidotrizoic acid that is difficult to remove from water using this process. The acceptance of cost-intensive upgrading of sewage treatment plants would suffer considerably in the population if despite the increased expense active pharmaceutical ingredients and other trace contaminants were to reach water bodies. Moreover, it cannot be ruled out that new substances that reach wastewater only in the future will have properties that render them "insensitive" to the selected treatment technology. This problem would probably be confronted only with a combination of technologies, which would then come along with a further cost increase. Summarising, this means: Precautionary measures for drinking water protection through water works remain at least on the mid-term indispensable.

When deciding on measures at the sewage treatment plants, provisions should especially be made that developmental routes for sustainable sanitation systems are not inhibited.

Concentration on sewage treatment plants and centralised wastewater disposal also raises other fundamental questions, however. Because in the view of many scientists, urban water management is facing a paradigm change that is leads away from the central system towards substance flow separation and compartmental wastewater treatment. Even if an effective and at the same time economic solution were to be identified for sewage treatment plants, stepwise implementation of options of action in the area of

sustainable sanitation systems is therefore trendsetting. It corresponds to the principle of retaining the contaminants at the source and furthermore provides latitude for sustainable development (energy abstraction from wastewater and recycling of scarce resources like phosphorous from urine). In the area of emissions management a locally dependent combination of measures for reducing water body contamination presents itself as the most realistic perspective. In implementing measures water bodies relevant for drinking water abstraction should receive priority.

An appraisal of the costs accruing in this area is virtually impossible today because with respect to the set-up of sustainable sanitation systems there is no basis for computations (how many new buildings, in which period of time and at which locations). At best, reliable guidance can be provided for furnishing hospitals with a plant for treating the separately collected toilet wastewater: For set-up and operation, annual costs in the order of 10,000 Euros would have to be assumed, whereby locally dependent investment for the conversion of pipelines for separation of the wastewater flows have to be considered additionally.

Shared Responsibility Instead of the Polluter Pays Principle

The previous considerations already indicate that a comprehensive solution of the problem cannot reside in one sphere of activity alone. Even if all courses of action were exhausted in one sphere, not all substances and all entries would be reached. This appraisal becomes even more concrete when questions of causation and responsibility are discussed. Formally considered, the cause of the problem is the healthcare system: Here the pharmaceuticals are used for treating diseases and for prevention and ultimately are released into the environment by one route or another. In the sense of the polluter pays principle, it could be argued: The costs of reducing water body contamination by active pharmaceutical ingredients must be borne by the healthcare system. In fact, it can be assumed that precisely if it were a question of the implementation of environment-technology problem solving strategies, the associated transfer of the environmental costs from the healthcare system to urban water management would be viewed as a violation of the polluter pays principle – an attitude which would at least hamper acceptance also for legally bound measures in this area.

An application of the "polluter pays principle" results in loss of acceptance. In contrast, assumption of responsibility in all three spheres of activity creates latitude for a sustainable problem solution.

Increased acceptance can instead be achieved if the healthcare system is integrated into a comprehensive solution right from the start and thus would bear a portion of the costs. The previously discussed options of action relating to the handling of drugs are designed such that this effect would probably be achieved, without concomitantly imposing unbearable burdens on a system that has reached its financial limit anyway. Even if at the same time the pharmaceutical industry were to undertake visible efforts at reducing the undesirable consequences of its products on water bodies by developing environmentally compatible active ingredients, latitude emerges for a joint effort towards a sustainably effective reduction of water body contamination and the risks to humans and the environment that possibly come along with it. Because ultimately all citizens and professionals in the different areas benefit from pharmaceuticals and are concomitantly co-causing the problem through their behaviours. Its solution should therefore follow in shared responsibility on the basis of precautionary thinking.

The Start of Collaborative Problem Solving

A joint effort generally requires a strong actor who encourages the process and ensures continuity and cohesion through his conduct. But it must be assumed that there is no such actor in the case of the problem of contamination of water bodies and drinking water by pharmaceuticals who has a correspondingly strong self-interest in a solution. In the framework of *start* a selection of options of action was therefore found whose implementation represents a comparatively low overhead for the actors concerned. The selection was arranged such that by implementing the corresponding measures the basis for an autonomous and self-reinforcing process could be created, that would lead to the realisation of further options of actions in the future – options like the ones presented in previous part of this brochure.

Research Funding Programs for Green Pharmaceuticals

This measure is intended to demonstrate the feasibility and economy of green active pharmaceutical ingredients and to promote the implementation of the new molecular design principles in research and development. It should be accompanied by a gradual change in the university education of chemists, pharmacists and physicians. Overall, a new, forward-looking way of thinking will be strengthened that would drive a sustainable development of pharmacy and chemistry. → page 21

Adjustment of University Education

Chemists and pharmacists should be familiarised with the principles of sustainable chemistry and pharmacy and the methods of computer-assisted molecular design through the gradual adjustment of university curricula. Physicians should be instructed in their education particularly on the consequences of consumption and disposal of medicinal products for the environment. This measure contributes to the dissemination and anchoring of a sustainability and environmental perspective in the concerned professional groups and so forms the prerequisite for acceptance and realisation of progressive options of action. → page 22

Increasing Problem Awareness of Physicians and Pharmacists

Discussion opportunities through publications in relevant professional media and supplementation of professional retraining enable physicians and pharmacists to form opinions on the topic of “Drinking water and water body contamination by active pharmaceutical ingredients” and thus enhance their problem awareness. In this fashion, the basis is created for also realising directly effective options of action – such as the use of an environmental classification for human pharmaceuticals – in the professional routine. → page 27

Introduction of an Environmental Classification for Human Pharmaceuticals

An environmental classification for human pharmaceuticals should be introduced in Germany in a joint initiative by official bodies, manufacturers of medicinal products, medical and pharmacy associations, and the research community. Here, imitation of the Swedish system is explicitly recommended. An independent institution should be entrusted with maintenance of the classification and with carrying out consultancy measures with physicians and pharmacists. Its timely introduction heightens professional and public perception and thus can provide stimuli for implementation of options of action also in other areas. → page 27

Creation of a Uniform Disposal Standard for Medicinal Products

Disposal of medicinal products in Germany should be uniformly controlled via the existing take-back system in pharmacies. To achieve this, the establishment of a binding disposal standard in the framework of the German Life-Cycle Resource Management Act is necessary. Here, pharmacy staff should be exempt in the future from the requirement of separating recyclables. The measure creates directional certainty in the population regarding the proper way of disposal of unused or expired medicinal products and thus contributes to the reduction of incorrect disposal via household wastewater. → page 30

Awareness Campaign on Proper Disposal

The population should be provided with information in widely applied awareness campaigns on the proper disposal of unused or expired medicinal products. The subject of water body pollution by active pharmaceutical ingredients should be emphasised in such a way that the correct disposal behaviour is conveyed as a positive experience, without reinforcing possibly existing anxieties. In complement, medicinal product manufacturers should consequently implement the existing EU regulations on placing corresponding disposal instructions on product packaging and in the package leaflet. These measures will reduce improper disposal of unused or expired medicinal products via drains and toilets and will contribute to a sensitisation of the public. → page 31

Special Enactment of Standards for Sustainable Sanitation Systems

Technical standards relating to the installation and operation of sustainable sanitation systems should be enacted, initially in selected sectors of the building industry (new housing projects, commercial and industrial complexes, and hospitals). This measure can contribute to advancing sustainable development of the state of technology for the area of wastewater disposal and treatment from buildings and adapt them to technological developments. By this means, dissemination of environmental innovations for reducing water body contamination will be accelerated in the regulated areas. → page 35

Outlook

With implementation of the selected options of action, an effective start can be made for a joint precautionary approach to reducing water body contamination by active pharmaceutical ingredients. Its potential resides in the fact that in many cases no extensive interdisciplinary and cross-sector agreements are required. For example, an adaptation of university education can be done at individual locations. An innovative university could, with the sponsorship of national research foundations, establish a research focus on the further development of methods of green molecular design and so be a trigger for corresponding developmental processes at other institutions. Standards enactment for sustainable sanitation systems can also be initiated by the competent technical associations alone. It is also conceivable that individual actors in the healthcare system – regional medical and pharmacy associations, or hospitals – develop specific discourse and information opportunities for their members. Direct action is thus possible in many situations. But the effect will depend decisively on as many activities as possible kicking off at the same time. Only then are mutual motivation and enhancement effects possible that will result in perpetuation of the process.

Certainly, some of the selected measures will require a more in-depth accord between several actors and corresponding patience, until successes grow. Introduction of an environmental classification for human pharmaceuticals is a special part of this. It can probably be achieved only in the context of a perennial stakeholder dialogue process and through the support of a strong driver like national environmental authorities (in Germany for example the Federal Environment Agency). For this reason, it is decisive for the success of a cooperative approach that different departmental polices at the national and regional level participate proactively in the implementation of the recommended measures. Here, "proactive" may not necessarily mean that the government policy generally provides the stimulus. Rather, it should support the relevant actors in the realisation of options of action, in that it more emphatically takes up the theme of "drinking water and water body contamination by pharmaceuticals" in a solution perspective.

Water is a special life resource that deserves our particular attention. Past experiences in interacting with the risks posed by substances have shown that remedial problem solving is generally more expensive for society than pre-emptive, precautionary action. If precaution is driven by all participating actors in the sense of shared responsibilities, not only can the "costs of error" be minimised, but potentials for social and technical innovation can even be opened up. The perspectives for action developed in *start* point in this direction. Finally, it is essential: The latitude in coping with water contamination by active pharmaceutical ingredients looms large enough today that we can learn from old mistakes.

Project Information

The transdisciplinary research project *start* ("Management Strategies for Pharmaceutical Residues in Drinking Water') was a cooperative project between the Institute for Social-Ecological Research (ISOE), the Department of Environmental Health Sciences at the University Hospital Freiburg, the Goethe-University Frankfurt/Main, and the Institute for Technology Assessment and System Analysis (ITAS) at the Forschungszentrum Karlsruhe. The project was funded from October 1, 2005 to May 31, 2008 by the Federal Ministry of Education and Research within the "Socio-Ecological Research" special funding programme (Grant No. 07VPS16). The following scientists participated in the realisation of the project:

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Further Information on the Topic

Detailed information on *start* are available on the project's web pages under www.start-project.de. Besides additional project publications the present brochure can be downloaded (PDF) or displayed (HTML).

Online Information

- The Swedish environmental classification for human pharmaceuticals is available at the internet: http://www.janusinfo.se (proceed via the link to the English pages) or www.fass.se/environment.

International Research Projects

- ERAPharm – Environmental Risk Assessment of Pharmaceuticals: Extension of the knowledge base and the existing methods for the environmental risk assessment of human and veterinary pharmaceuticals; project funded under the sixth EU framework programme; more information at www.erapharm.org
- KNAPPE – Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters: Identification of priority measures for reduction of the occurrence, impacts and risks of pharmaceuticals in waters; project funded under the sixth EU framework programme; more information at www.knappe-eu.org
- MistraPharma – Identification and Reduction of Environmental Risks Caused by the Use of Human Pharmaceuticals: Identification of human pharmaceuticals in use that pose a potential hazard to specific species in aquatic ecosystems as well as recommendations for new risk management strategies; project funded by the Swedish Foundation for Strategic Environmental Research, Mistra; more information at www.mistrapharma.se
- NEPTUNE – New Sustainable Concepts and Processes for Optimization and Upgrading Municipal Wastewater and Sludge Treatment: (among other things) Development of technological solutions for the elimination of trace contaminants in municipal sewage treatment; project funded under the sixth EU framework programme; more information at www.eu-neptune.org
- POSEIDON – Assessment of Technologies for the Removal of Pharmaceuticals and Personal Care Products in Sewage and Drinking Water Facilities to Improve the Indirect Potable Water Reuse; project funded under the fifth EU framework programme; more information at http://poseidon.bafg.de

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