



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Towards balancing the benefits of pharmaceutical care and minimizing its environmental harm

Identification of potential levers in the
medicinal product chain

RIVM Report 2015-0145

E. van der Grinten et al.



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and the Environment
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Colophon

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Naar een balans tussen de voordelen van medicijngebruik voor humane gezondheid en milieuschade als gevolg daarvan Mogelijke handelingsperspectieven in de medicijnketen.

In toenemende mate worden medicijnresten in oppervlaktewater en drinkwater aangetroffen, zoals pijnstillers, hormonen en antidepressiva. Van een aantal is bekend dat ze negatieve effecten hebben op het milieu. Als eerste stap voor een aanpak om deze effecten te beperken heeft het RIVM de relatie tussen medicijngebruik en het milieu in beeld gebracht. Hiertoe is tot in detail het proces beschreven dat medicijnen doorlopen, van hun ontwikkeling, de markttoelating, de productie, de inkoop door apotheken, het voorschrijfgedrag van artsen en het gebruik door patiënten, de inzameling van medicijnafval, tot waar ze daarna in het milieu terechtkomen (de medicijnketen).

Daaruit blijkt dat in elke fase van de keten veel handelingsperspectieven zitten om negatieve gevolgen voor het milieu van medicijngebruik door mensen te beperken, zonder de positieve effecten van medicijnen teniet te doen. Welke van deze suggesties een optimale balans opleveren én haalbaar zijn, moet nog worden onderzocht. Door een geïntegreerde benadering hoopt het RIVM de gezondheidszorg en milieusector bewuster te maken van de relaties die ze met elkaar hebben.

Momenteel zien drinkwaterzuiveringsbedrijven zich genoodzaakt nieuwe, kostbare technieken in te zetten om medicijnresten zoveel mogelijk te verwijderen zodat ze niet in drinkwater terechtkomen. Bij de huishoudelijke afvalwaterzuivering (RWZI) lopen ook allerlei initiatieven voor het oppervlaktewater. De kosten liggen daardoor vooral aan het eind van de keten.

De geboden handelingsperspectieven zijn onderverdeeld in twee categorieën: informatie-uitwisseling door de hele medicijnketen heen en financiële maatregelen. Informatie over milieuschade zou bijvoorbeeld meegenomen kunnen worden bij de ontwikkeling van nieuwe medicijnen. (Drink)waterzuiveraars zouden op hun beurt medicijnresten effectiever kunnen verwijderen als zij weten welke eigenschappen deze stoffen hebben. Zorgverleners en patiënten kunnen informatie over de schadelijkheid voor het milieu betrekken bij hun keuze voor medicijnen. Een mogelijke financiële maatregel is om de kosten om medicijnresten uit het milieu te verwijderen, te verrekenen ergens in de keten. Ook zou met financiële prikkels kunnen worden gestimuleerd dat ongebruikte middelen worden teruggebracht naar de apotheek.

Bekende milieueffecten zijn weefselschade en geslachtsverandering bij vissen door resten van respectievelijk pijnstillers en anticonceptiemiddelen in oppervlaktewater. Op dit moment zijn de concentraties geneesmiddelenrestanten in het drinkwater dermate laag dat ze niet schadelijk zijn voor de volksgezondheid. Voor de toekomst is de drinkwaterkwaliteit wel een aandachtspunt, vanwege de klimaatverandering en de verwachte toename van medicijngebruik door de vergrijzing.

Kernwoorden: medicijnresten, geneesmiddelen, milieu, ketenanalyse, speler, maatregelen, oppervlaktewater, waterzuivering, gedragsdeskundigen, burger, wetgeving

Synopsis

Towards balancing the benefits of pharmaceutical care and minimizing its environmental harm

Identification of potential levers in the medicinal product chain.

Residues of medicinal products are increasingly detected in surface water and drinking water, such as painkillers, hormones and antidepressants. Some residues are known to have environmental effects. As a first step towards an approach to limit these effects, RIVM has mapped the relationship between medicinal product use and the environment. To this end, the processes that medicinal products go through are described in detail, from development, market authorisation, production, buying and selling by pharmacies, prescription by physicians, and use by patients, collection of waste, until discharge and their fate in to the environment (the medicinal product chain).

In each phase of the chain potential levers were identified, that could limit the negative consequences of human medicinal product use to the environment, while maintaining the benefits of human pharmaceutical care. Which (combination) of levers results in an optimal balance and is feasible, is yet to be investigated. Through an integrated approach, RIVM aims to create awareness on the relationship between the human health sector and the environmental sector.

Currently, drinking water companies are compelled to use new and costly treatment techniques to remove medicinal product residues from drinking water sources. Such initiatives are also explored at water treatment sites for domestic wastewater. Therefore, the costs are concentrated at the end of the chain. The suggested potential levers are divided in two categories: information exchange through the medicinal product chain, and financial feedback mechanisms. For example, information on environmental toxicity could be incorporated in the developmental process of new medicinal products. (Drinking)water companies, in turn, could use information on properties of compounds when optimising their treatment facilities. Information on environmental fate and impact could be taken into account by health care workers and patients in their choice for specific medicinal products. A possible financial feedback mechanism is to balance the cost for removal of medicinal product residues higher up in the chain. Financial incentives could also be used to stimulate returning unused or out of date medicinal products to the pharmacy.

Known environmental effects are tissue damage and change of sex in fish due to residues of painkillers or contraceptives respectively. Currently, concentrations of medicinal product residues are below concentrations that could harm public health. For the future, drinking water quality is a matter of concern, because of climate change and the expected increased use of medicinal products by the ageing population.

Keywords: Pharmaceutical residues, medicines, environment, medicinal product chain analysis, stakeholder, reduction measures, surface water, wastewater treatment, behavioural experts, citizen, legislation

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Summary

Medicinal product residues are increasingly detected in the environment, which might cause ecological and human effects. This report describes the complete route of medicinal products for human use from their development until their fate and consequences in the environment after use. The aim of this medicinal product chain analysis is to describe in an integrated way the processes and actions that are usually considered separately in the pharmaceutical care sector and the environmental sector, thus creating an integrated view of the phases that all medicinal products for human use go through. With this view, we aim to create awareness and action perspectives to optimize the balance between costs and benefits of pharmaceutical care and environmental damage (health care benefits, biodiversity loss and threat to drinking water quality), entailing the whole life cycle of pharmaceutical products.

The advantages of the use of medicinal products to humanity are numerous. Advances in microbiological and pharmaceutical sciences have resulted in the development of many safe and effective medicinal products for the most prevalent diseases. Their use, along with increased societal and sanitary progress, has led to a healthier and longer living human population.

However, medicinal product residues are known to have environmental effects. For example, the oestrogen derivate ethinyl oestradiol (used in the birth control pill) is responsible for the feminization of male fish, most likely in combination with other hormones or hormone-mimicking substances. Residues of the anti-inflammatory drug diclofenac in freshwater have been shown to exceed in some cases the lowest observed effect concentration for aquatic organisms. Currently, the concentrations of individual medicinal residues in drinking water are well below the therapeutic dose to cause an effect on humans.

Medicinal product residues pass partly, either unchanged or as metabolites after use, through the sewer system and the wastewater treatment plant. Common sewage treatment plants are not designed to remove all medicinal product residues from the wastewater, resulting in emission of these residues to surface waters. The European Commission, who is currently developing a strategic approach to diminish the pollution of water by pharmaceutical residues, acknowledges this problem. On a national level, the Ministry of Environment coordinates activities to come to a chain agreement with all the players in the field, from pharmaceutical industry to drinking water companies and water authorities.

To contribute to these policies, this study presents a number of 'potential levers' along the medicinal product chain, from development, via use, to its environmental fate and consequences. The potential levers have been identified by comparing differences in processes on any level (international, national, regional or between individuals). For example, in some countries, oral diclofenac is exclusively available on prescription, whereas in other countries it is also available over the counter. This example and other different practices presented show that

the potential environmental impact of a particular process in the medicinal product chain depends on decisions made by actors in the chain, and thus can be changed, when there are good reasons to do so. Further discussions on achievable implementation of the potential levers may identify the barriers and subsequent solutions or may bring up other ideas to create possibilities to combine pharmaceutical care and reduction of the environmental burden from medicinal product residues.

This report was developed under the umbrella of the international “noPILLS in waters!”-project, which aims to provide – via a number of case studies – practical experience on the identification of potential and actually implemented technical and social interventions across the medicinal product chain.

Our analysis of the medicinal product chain provided potential levers throughout the whole chain. The next phase is to weigh the levers in order to assess their practical feasibility.

List of abbreviations

ACM	Authority for Consumers and Markets [Autoriteit Consument en Markt]
AIDS	Acquired Immune Deficiency Syndrome
API	active pharmaceutical ingredient
BIG Act	Dutch Individual Healthcare Professions Act [Wet op de Beroepen in de Individuele Gezondheidszorg]
CCMO	Central Committee on Research Involving Human Subjects [Centrale Commissie Mensgebonden Onderzoek]
CMD(h)	The Coordination group for Mutual Recognition and Decentralized procedures
CHMP	Committee for human medicinal products
COPD	Chronic Obstructive Pulmonary Disease
COX	cyclo-oxygenases
DBC	Diagnosis Treatment Combinations [Diagnose Behandel Combinatie]
DNB	The Dutch Bank [de Nederlandsche Bank]
E1	Estrone
E2	17-beta-estradiol
EC	European Commission
EE2	17-alpha-ethinylestradiol
EFPIA	European Federation of Pharmaceutical Industries and Associations
EG	Emschergenossenschaft
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	environmental risk assessment
EU	European Union
FIGON	Federation for Innovative Pharmaceutical Research [Federatie voor Innovatief Geneesmiddelenonderzoek Nederland]
FTC	Pharmaco-Therapeutic Consultation Group [Farmacotherapeutisch Overleg]
GCU	Glasgow Caledonian University
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GS	general sales [algemene verkoop]
GP	General Practitioner
GVS	Medicine Reimbursement System in The Netherlands [Geneesmiddelenvergoedingssysteem]
HKZ	Harmonisation of Quality Assessments in Health Care [Harmonisatie Kwaliteitsbeoordeling in de Zorgsector]
IGZ	Dutch Health Care Inspectorate [Inspectie voor de Gezondheidszorg]
IMI	Innovative Medicines Initiative of the EU and EFPIA
KNMP	The Royal Dutch Association for Pharmacy [Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie]
LAP	National Waste Management Plan [Landelijk Afvalbeheer Plan]
LAP2	National Waste Management Plan 2009-2021 [Landelijk Afvalbeheerplan 2009-2021]

LHV	National Association of General Practitioners [Landelijke Huisartsen Vereniging]
LIST	Luxembourg Institute of Science and Technology
LOEC	lowest observed effect concentration
LV	Lippeverband
MEB	Medicines Evaluation Board in The Netherlands [College ter Beoordeling van Geneesmiddelen, CBG]
NHG	The Dutch College of General Practitioners [Nederlands Huisartsen Genootschap]
NHS	National Health Service
NRWF	North Rhine – Westphalia
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NVPF	Dutch Association for Outpatient Pharmacy [Nederlandse Associatie voor Poliklinische Farmacie]
NVZA	Dutch Association of Hospital Pharmacists [Nederlandse Vereniging van Ziekenhuis Apothekers]
NZa	The Dutch Health Care Authority [Nederlands Zorgautoriteit]
OTC	Over-the-Counter
PAR	public assessment report
PDO	pharmacy and drugstore only [uitsluitend apotheek en drogist]
PEC	predicted environmental concentration
PH	pharmacy only [uitsluitend apotheek]
PO	prescription only [uitsluitend op recept]
R&D	Research and development
REACH	Registration, Evaluation, Authorisation and restriction of Chemical substances
RIVM	Dutch National Institute for Public Health and the Environment [Rijksinstituut voor Volksgezondheid en Milieu]
RMS	Reference member state
SmPC	summary of product characteristics
SOR	Strategic Research RIVM [strategisch onderzoek RIVM]
STP	sewage treatment plant
SWP	Safety Working Party
UK	United Kingdom
UniLim	Université de Limoges
US(A)	United States (of America)
UV	Ultraviolet
WFD	Water Framework Directive
WGS	Water Authority Groot Salland [Waterschap Groot Salland]
ZiN	National Health Care Institute [Zorginstituut Nederland]

1 General introduction

1.1 Background

Medicinal product residues are increasingly detected in the environment, which might cause ecological and human effects. After use, the active pharmaceutical ingredients (APIs) in human medicinal products are excreted by the body in urine or faeces, either unchanged or as metabolites. Unused medicinal products may end up in the sewer system by incorrect disposal. Medicinal product residues pass partly, either unchanged or as metabolites after use, through the sewer system and the wastewater treatment plant. Common sewage treatment plants are not designed to remove all medicinal product residues from the wastewater, resulting in emission of these residues to surface waters. Consequently, human pharmaceutical residues are found everywhere in the aquatic environment: in surface waters, sediments and in groundwater.

Since the late nineties, numerous studies have reported concentrations of medicinal products in the aqueous environment in the ng/L to µg/L range (Halling-Sorensen et al., 1998, Daughton and Ternes, 1999). So far, the knowledge gathered on the presence and concentration of medicinal products in water bodies mostly comes from (incidental) monitoring campaigns. There is limited regular monitoring of these compounds in the environment. One example is the monthly monitoring along the Rhine from 2002-2008 which showed the presence of 128 pharmaceuticals, including X-ray contrast mediums, and endocrine disrupting chemicals of which 20 pharmaceuticals were observed regularly, with median concentrations of X-ray contrast mediums above 0,1 µg/L and Carbamazepine around 0,1 µg/L (ter Laak et al., 2010). Observed concentrations are generally in line with concentrations found in various Dutch surface waters (Derksen et al., 2007, Versteegh et al., 2003, Walraven and Laane, 2009).

The advantages of the use of medicinal products to humanity are numerous. Advances in microbiological and pharmaceutical sciences have resulted in the development of many safe and effective medicinal products for the most prevalent diseases. Their use, along with increased social and sanitary progress, has led to a healthier and longer living human population (van der Aa et al., 2011a, Hut et al., 2013).

However, exposure of non-target organisms in the environment may have negative consequences. For some pharmaceutical substances, clear ecological effects have been reported (EEA, 2010). Ecotoxicological research has revealed that the effects of pharmaceutical compounds on organisms are observed at concentrations in the same order of magnitude as determined in the environment (e.g. Brooks et al., 2003). A number of studies for example, report that the oestrogen derivate ethinyl oestradiol (used in the birth control pill) is responsible for the feminization of male fish, most likely in combination with other hormones or hormone-mimicking substances (Blanchfield et al., 2015, Vethaak et al., 2002). Residues of the anti-inflammatory drug diclofenac

in freshwater have been shown to exceed the lowest observed effect concentration for aquatic organisms in some cases (Acuña et al., 2015). Adverse effects of diclofenac were reported in the liver, kidney, and gills of rainbow trout, resulting in pathological effects on renal and gill functionality (Schwaiger et al., 2004, Triebkorn et al., 2004, Hoeger et al., 2005). Both substances were recently put on the 'watchlist' of the EU priority substances Directive because of concerns for the aquatic environment (Directive 2013/39/EU, 2013, paragraph 1.2).

In the Netherlands, surface water and groundwater are the resources for drinking water, in the ratio 1:2. The current purification steps in the preparation of drinking water from both resources are insufficient to remove all pharmaceutical residues (WHO, 2012). Fortunately this concerns very low concentrations, possible effects on public health are not expected (Houtman et al., 2014).

This report focusses on medicinal products for human use only, although it is known medicinal products used in veterinary medicine are also found in the environment (e.g. Henderson and Coats, 2009).

1.2 Policy background

The European Commission, who is currently developing a strategic approach to reduce the pollution of water by pharmaceutical residues, acknowledges the problem of medicinal products in the environment. To obtain specific monitoring data on the presence of pharmaceutical residues in the aquatic environment, the European Commission has legally established a "Watch List" for three pharmaceutical substances in EU water bodies under the Water Framework Directive (WFD). The objective of the implementation of the European watch list is to update the available information on the fate of the listed substances in the aquatic environment and, consequently, to support a more detailed environmental risk assessment.

Commission Implementing Decision 2015/495 (2015) lists the three pharmaceutical substances diclofenac, 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) for inclusion on this initial watch list, as well as Estrone (E1), a degradation product of E2. This necessitates Member States to making a series of measurements for these substances across a wide range of water bodies in order to ascertain if there is a potential problem. In 2015, some additional compounds were added to the watch list, amongst which three macrolide antibiotics (Commission Implementing Decision 2015/495, 2015).

According to article 8c of Directive 2013/39/EU on priority substances in the field of water policy, "the Commission shall [...until September 2015] develop a strategic approach to the pollution of water by pharmaceutical substances. That strategic approach shall, where appropriate, include proposals enabling, to the extent necessary, the environmental impacts of medicinal products to be taken into account more effectively in the procedure for placing medicinal products on the market. Within the framework of that strategic approach, the Commission shall, by 14 September 2017 and where appropriate, propose measures to be taken at Union and/or Member State level, as appropriate, to address the possible environmental impact of pharmaceutical substances [...] with a view to reducing discharges, emissions and releases of such substances

into the aquatic environment, taking into account public health needs and the cost-effectiveness of the measures proposed.” (Directive 2013/39/EU, 2013).

On national level, the Ministry of Environment coordinates activities to come to a chain agreement with all the players in the field, from pharmaceutical industry to drinking water companies and water authorities.

1.3 NoPILLS in waters!- project

This report was developed under the umbrella of the international “noPILLS in waters!”-project (www.no-pills.eu), which aims to provide – via a number of case studies – practical experience on the identification of potential and actually implemented technical and social interventions across the medicinal product chain.

The noPILLS in waters!-project is a European cooperation project with the Emschergerossenschaft (EG) and Lippeverband (LV), which are two German water authorities, the French Université de Limoges (UniLim), associated with SIPIBEL (a site of experimentation and an observatory), the Luxembourg Institute of Science and Technology (LIST), Glasgow Caledonian University (GCU) in the UK and the Dutch National Institute for Public Health and the Environment (RIVM) as partners.

The focus of this project is on the question how to reduce the pollution in waters by human pharmaceutical residues. Medicinal products for veterinary use have not been studied in detail in this project, although they form part of the observed pharmaceutical load in the environment. The project started in 2012 with EU funding from the INTERREG IVb programme and ended in 2015.

The noPILLS in waters!-project was based on the results of the previous PILLS project (2008-2012, www.pills-project.eu), which dealt with the efficiency of and requirement for treatment technologies at pharmaceutical pollution point sources. The PILLS project dealt mainly with the human medicinal product residues in wastewater originating from hospitals. The results of the PILLS project indicated that engineering and technical solutions alone would not be sufficient to result in a comprehensive reduction of all potentially toxic pharmaceutical residues, especially not at acceptable monetary and energy / CO₂ cost (PILLS, 2012). This triggered the recognition that successful measures will have to address all parts of the route, which ends with the end-of-pipe emission into the environment, and that society should be involved in reducing human pharmaceutical input into the environment.

Via a number of case study approaches throughout the project partnership, the noPILLS in waters!-project aimed to provide practical experience on the identification and implementation of technical and social interventions across the medicinal product chain, with a focus on consumer behaviour, wastewater treatment and multi-stakeholder engagement. In essence, the main aim of the noPILLS partnership was to contribute to the European discussions and decision-making process regarding the increasingly recognized problem of medicinal product residues in the environment. A summary of each of the partners’ work is

published in the international noPILLS report (Pahl, 2015) available at www.no-pills.eu.

1.4 RIVMs contribution

RIVM's role within the noPILLS in waters!-project was to provide a conceptual framework of factors that affect the discharge of medicinal product residues in the water cycle, using RIVMs environmental and sociological expertise fields.

This report describes the complete route of medicinal products for human use from their development until their fate and consequences in the environment after use: the medicinal product chain. The aim of this medicinal product chain analysis is to describe in an integrated way the processes and actions that are usually considered separately in the pharmaceutical care sector and the environmental sector, thus creating an integrated view of the phases that all medicinal products for human use go through. With this view, we aim to create awareness and action perspectives to optimize the balance between costs and benefits of pharmaceutical care and environmental damage (health care benefits, biodiversity loss and threat to drinking water quality), entailing the whole life cycle of pharmaceutical products.

The term medicinal product chain is not to be confused with the term "Dutch medicines chain", which is used for the national governmental organizations responsible for the availability of safe and effective medicinal products in The Netherlands (see 3.1.2).

This study presents a number of 'potential levers' along the medicinal product chain, from development, via use, to its environmental fate and consequences. The potential levers have been identified by comparing differences in processes on any level (international, national, regional or between individuals). For example, in some countries, a specific medicinal product is exclusively available on prescription, whereas in other countries it is also available over the counter. These differences show that the potential environmental impact of a particular process in the medicinal product chain depends on decisions made by actors in the chain, and thus could be changed, when there are good reasons to do so. Further discussions on achievable implementation of the potential levers may identify the barriers and subsequent solutions or may bring up other ideas to create possibilities to combine pharmaceutical care and reduction of the environmental burden from medicinal product residues. It is, however, not the topic of this report to determine which levers may be most effective in maintaining the benefits of pharmaceutical care, while reducing the environmental harm, or to weigh policy alternatives. Therefore, the term potential lever is used in this report, instead of the terms concrete actions, measures or interventions.

1.5 Reader's guide

In the following chapters 3 to 9, an extensive description of the different phases in the medicinal product chain is provided. Each description starts with the most important processes, and then lists the most important actors and their role. Potential levers are given in the text in **bold**, followed by a specification of the considerations that could play a role when weighing these levers, illustrated by the case of diclofenac (see paragraph 2.2). *All text specifically concerning the diclofenac case*

is given in italics. Furthermore, in some sections, transnational differences in the structure of the medicinal product chain are pointed out in a text box.

The report concludes with a general chapter containing conclusions, discussion and recommendations.

2 The medicinal product chain analysis and diclofenac case

2.1 Medicinal product chain

The medicinal product chain involves a sequence of numerous processes and actors, such as development and production of active pharmaceutical ingredients (APIs) by industry, marketing authorization, physicians' choices and prescribing practices, dispensing by e.g. pharmacies, health care insurance, patients' choices and expectations, consumption patterns, disposal behaviour and the emission and fate of medicinal product residues in the environment. The actors and processes in the chain are affected by social, organizational, financial, technological and/or policy factors. Figure 1 gives a simplified representation of the medicinal product chain.

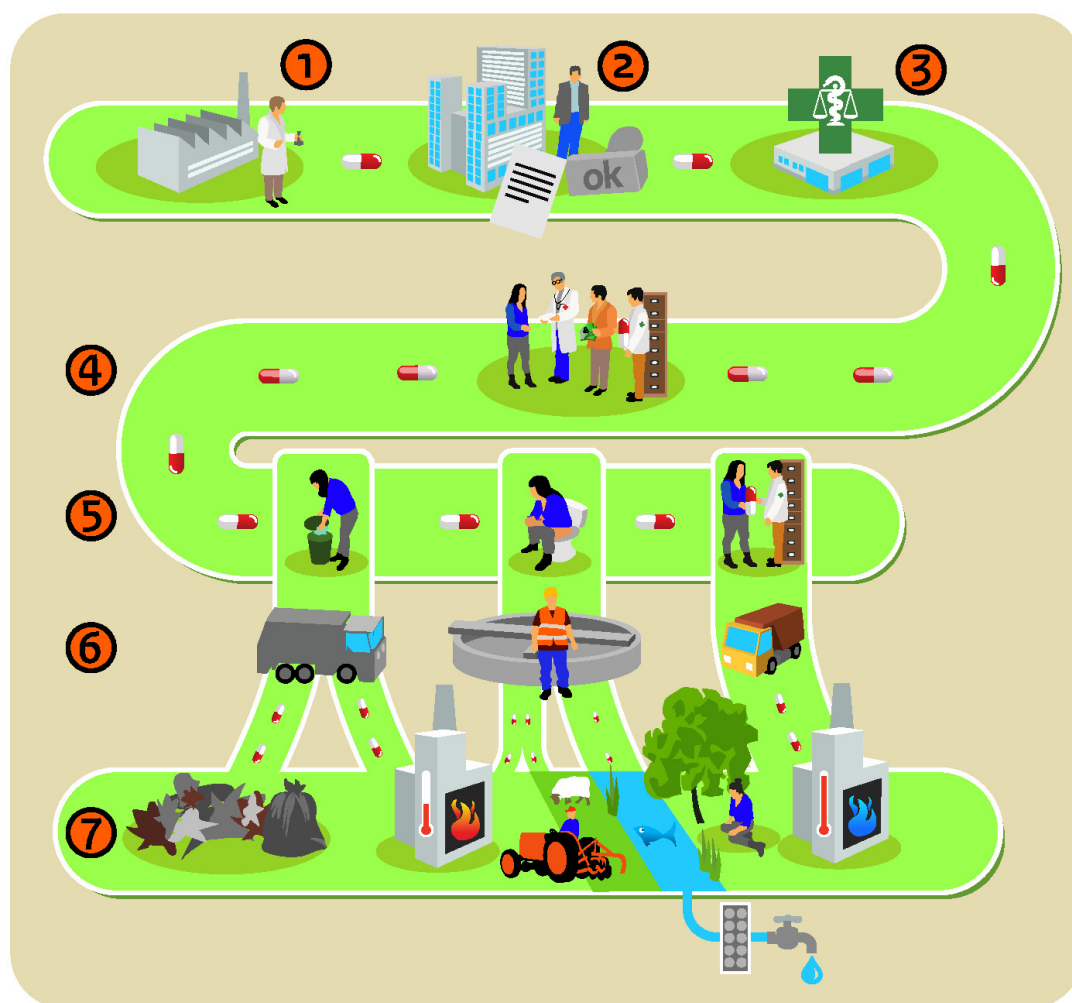


Figure 1: A simplified representation of the medicinal product chain. Numbers correspond with subsequent phases described in Chapters 3-9 in this report.

We identify processes and actors and deduce their drivers, which play a role in the entire medicinal product chain and thus may possibly

influence the flow of medicinal product residues into the environment. Furthermore, we identify differences in processes, for instance between countries or actors. These differences point to potential levers for change, where stakeholders (actors) may theoretically adapt their activities in order to reduce medicinal product residues in the environment.

It should be noted that we only aim to identify a capita selecta of *potential* levers for change; further research is necessary in order to make an integral assessment of the feasibility of interventions in these potential levers and of the effects these interventions may have on both health care and the environment. The potential levers described may be seen as input for discussions on their effectivity and do not reflect a prioritization.

We limited our analysis to medicinal products for human use. The chain for medicinal products for veterinary use has not been studied, although a large (substantial) part of the observed pharmaceutical load in the environment results from veterinary use.

Our medicinal product chain description is primarily based on the Dutch situation. In a preliminary comparison study between the situations in the UK (Scotland), Germany (North Rhine Westphalia) and the Netherlands, we identified important differences between these countries and geographical regions (see textboxes). Some relevant international comparisons are made in this part, which highlight the need for the regionalization of some potential levers for intervention.

In this report, we use the term medicinal product according to the definition in Directive 2001/83/EC art 1.2: "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" (Directive 2001/83/EC, 2001). After the use phase, the term medicinal product residues is used, which includes left over product, as well as metabolites formed either in the human body or in the environment.

2.2

Diclofenac case

To illustrate the applicability of the levers described in this report, the case diclofenac is presented. The outcome of the weighing of a specific lever for application with a specific compound may be different, depending on the type of medicinal product concerned. Specification of the considerations that could play a role when weighing these levers is given, as well as examples of the applicability for other types of medicinal products. This is done to illustrate the subtle nuances that determine the final applicability of a lever. All potential levers from the main text (Chapters 3 - 9) are described in more detail for this specific case. Attention is given to case-specific details and reasons of feasibility or non-feasibility of levers.

Background information on diclofenac

Diclofenac is not removed completely during wastewater treatment and is measured in environmental samples (surface water, wastewater).

There are indications that diclofenac has an effect on ecosystems (Acuña et al., 2015, Küster and Adler, 2014, Toxnet, 2015).

Diclofenac belongs to the category of non-selective Nonsteroidal Anti-inflammatory Drugs (NSAIDs). It is widely used for the relief of mild to moderate pain and inflammation in various conditions, such as rheumatic disorders, postoperative or post-traumatic pain, in particular when inflammation is also present.

NSAIDs cause suppression of the prostaglandin synthesis by inhibiting cyclo-oxygenases (COX), enzymes participating in the biosynthesis of prostaglandins in the human body. They convert arachidonic acid into prostaglandin H₂, a precursor for other prostaglandins, which play an important role in pain sensation, fever activation and inflammation. Consequently, the prostaglandin concentration decreases leading to relief of pain and suppression of fever and inflammation. NSAIDs differ in their analgesic, antipyretic and antiphlogistic effect (MedicinesComplete, 2016).

Diclofenac is available in oral, rectal, parental, ophthalmic and topical administration forms, such as tablets, suppositories, intra-muscular or intravenous injections, eye drops and gels. If application of paracetamol has an insufficient effect and gastro-intestinal complications are not to be expected, diclofenac is considered a first-choice medicinal product in clinical practice. In The Netherlands, several presentations are available without prescription.

Diclofenac is a phenylacetic acid derivative, mainly used as the sodium salt.

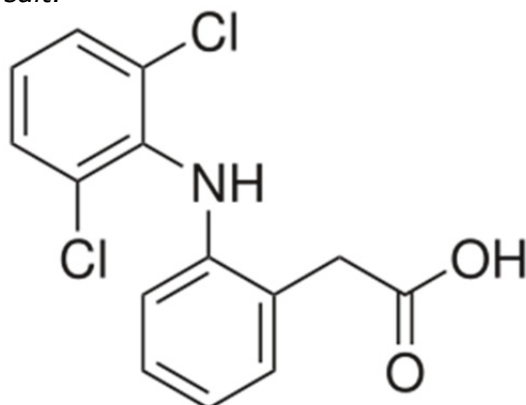


Figure 2: structural formula of diclofenac (Sallmann, 1986, Toxnet, 2015)

Diclofenac can be administered orally, by injection, rectally or by a gel on the skin (Zorginstituut Nederland, 2016). The smaller doses pills for oral use are available OTC, higher doses only on prescription. In 2014, the Dutch pharmacies handed out users 44 million defined daily dose to 1.2 million of the most used form (ATC code M01AB05) in the Netherlands (GIP, 2015). This was partly OTC and part by prescription. This number contains no information on the volume that was prescribed in hospitals, drugstores and supermarkets.

Based on the use in Germany (approx. 80 tons/year in 2012 (Küster and Adler, 2014), the amount used in the Netherlands is estimated to be about 16 tons/year. Van der Aa et al. (2008) report 2.4 mln

prescriptions in The Netherlands in 2007, good for 6227 kg. The amount of "over the counter" use is not known.

Ecotoxicological Effects

Besides the examples of effects on vultures already touched upon in the introduction, Acuña et al. (2015) identified 156 publications on the ecotoxicological effects of diclofenac regarding freshwater ecosystems. The reported LOEC values in this review range from 0.01–40,000 $\mu\text{g L}^{-1}$ (any species, any effect), and these values are partly overlapping with the observed concentrations in freshwater ecosystems. In fact, the median of the reported LOEC in the literature (3000 ng L^{-1}) is much higher than the median reported concentration (21 ng L^{-1}), but the 5th percentile of the reported LOEC in the literature (30 ng L^{-1}) was surpassed in 42% of the 1264 analysed samples (Fig. 3). The authors conclude that diclofenac might pose harmful effects on the environment, but that more research is needed before robust conclusions about the ecotoxicology of diclofenac can be made. Furthermore, besides the parent compound, some of the phototransformation products of diclofenac carry a higher toxicity than the parent compound, as was reported in studies on algae (Schulze et al., 2010).

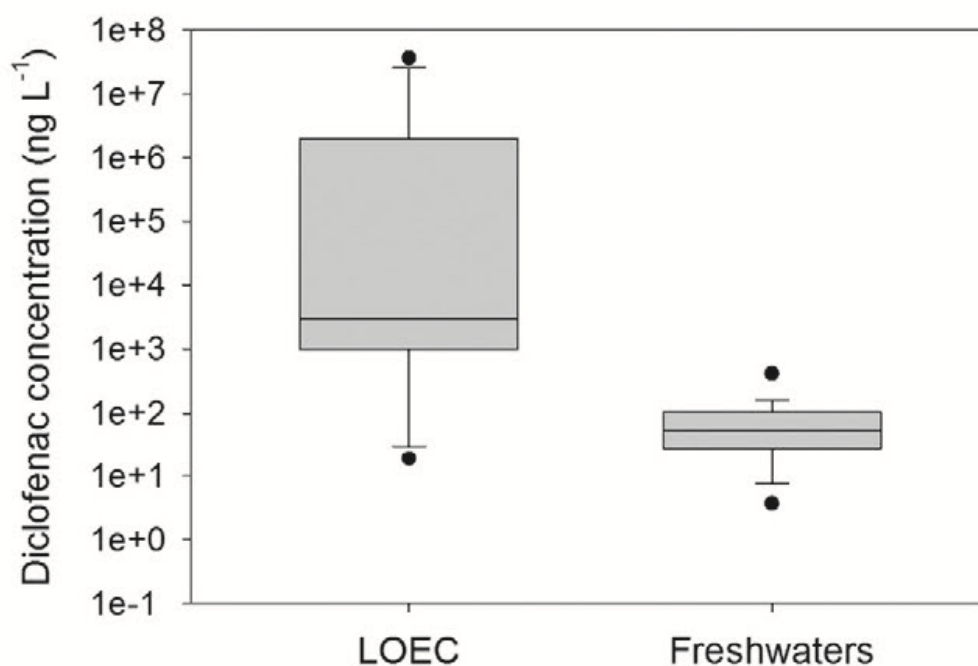


Figure 3. Box-plot with the reported lowest observed effect concentration (LOEC) and freshwater occurrence concentrations of diclofenac. Note that the error bars indicate the 5th and 95th percentiles. (Taken from Acuña et al., 2015).

3 Phase 1: Development of new medicinal products

3.1 Development of generic medicinal products

3.1.1 *Processes*

A generic medicinal product is a medicinal product which equals the innovator medicinal product with regards to qualitative and quantitative composition of active substances and pharmaceutical form, and for which bioavailability studies have demonstrated bioequivalence to the innovator medicinal product (CBG, 2015a). They are marketed under a non-proprietary name rather than a brand name, and are often much cheaper than brand-name medicinal products.

A generic medicinal product has active pharmaceutical ingredient(s) for which the intellectual property rights have expired. The European legislation does not allow the development process of a generic medicinal product to start before expiration of the data protection period. The development of a generic medicinal product takes 4 years on average, which includes an average marketing authorization period of a year and a half.

Whereas the active pharmaceutical ingredient in generic medicinal products is the same as the active substance in an innovative medicinal product, this is not the case for biosimilar medicinal products. Biological medicinal products have complex three-dimensional structures, which makes the production of an exact copy difficult. Variations in the production process lead to differences in this structure between the biological reference medicinal product and the biosimilar product, which can have major consequences for quality, effects and side effects of a biosimilar. Therefore, biosimilars are subject to more clinical trials before authorisation is possible compared to generic medicinal products (EMA, 2014).

3.1.2 *Actors*

Pharmaceutical companies

Pharmaceutical companies that develop generic medicinal products can be either independent companies or a division of a larger company that also has an innovative division. On average, generic companies spend 7.4% of their revenues on research and development (R&D) (BOGIN, 2015). In the Netherlands, the producers of generic medicinal products are represented by BOGIN.

In 2012, generics represented 11.8% of total market sales of medicinal products in the Netherlands (EFPIA, 2014). However, as these products are much cheaper than innovative products, they represent more than 70% of the market in volume in 2015 (SFK, 2015a).

Governmental organizations

National governmental organizations stimulate research and development for innovative medicinal products by providing funding for R&D in universities or research institutes.

At the European level, R&D projects are supported by funding from the European Framework Programmes. In 2008, the European Union (EU) and the EFPIA set up the Innovative Medicines Initiative (IMI), a large

initiative that funds collaborative research projects between industrial and academic experts in order to boost pharmaceutical innovation in Europe.

From a regulatory point of view, it is important to realize that the national legislation on medicinal products is based on EU legislation. The European Medicines Agency (EMA) is responsible for the scientific evaluation and supervision of medicinal products at the European Level, whereas the European Commission provides the marketing authorization.

At the national level, the so-called Dutch Medicines Chain, consisting of several national governmental organizations, is responsible for the availability of safe and effective medicinal products in The Netherlands. The Ministry of Health, Welfare and Sport provides permits for animal studies and for the production and import of medicinal products for research purposes. The Central Committee on Research Involving Human Subjects (CCMO) and Medical Ethical Committees assess study protocols involving human subjects, e.g. study protocols for clinical studies with medicinal products.

The Medicines Evaluation Board is responsible for the marketing authorization of medicinal products in the Netherlands. The independent organization Netherlands Pharmacovigilance Centre Lareb collects and analyses reports of adverse reactions of medicinal products and reports these to the Medicines Evaluation Board.

The Health Care Inspectorate supervises the conduct of clinical trials and the production and distribution of medicinal products, both for clinical trials and marketing.

3.2 Research and development of innovative medicinal products

3.2.1 Processes

Research and development (R&D) of innovative medicinal products requires considerable investments, both in terms of costs and time. Although these investments are made by universities and pharmaceutical companies, increasingly smaller biotech companies become important in the R&D process. On average, the process of developing an innovative medicinal product takes 12 years (Nefarma, 2013).

Pharmaceutical innovation is driven by various factors, such as medical need, scientific and technological advances, financial considerations, legislation (that affects R&D and the competitive setting) and market demand (Achilladelis and Antonakis, 2001). Possible environmental consequences of medicinal product residues are generally not taken into account in this phase.

For future medicinal products, developers could take ecotoxicological properties into account when choosing the best option for further development

The applicability of this lever for the example diclofenac is indirect, because diclofenac is already on the market. Diclofenac is a widely used, cheap medicinal product for which extensive clinical experience with respect to effectiveness and side effects exists. If application of the alternative paracetamol has an insufficient effect and gastro-intestinal complications are not to be expected, diclofenac is considered a first-choice medicinal product in clinical practice. It is highly unlikely that diclofenac will

be abandoned for ecotoxicological reasons only. There must be strong evidence that the impact on ecological systems is evident and severe and more environmental friendly alternatives are available.

However, development of environmentally friendly alternatives by the pharmaceutical industry (which is possible in principle, e.g. Kummerer, 2007) will only take place, if the new product is profitable, meaning that the use of the older product would need to be restricted by regulations.

Developers of new medicinal products could publicly provide environmental data on their products to enable other actors (e.g. researchers, water authorities or policy makers) to optimize removal of substances based on the potential adverse effects in the environment.

In the case of diclofenac, it is not known whether this information has been collected in the past. Diclofenac is on the market since 1973. For products licensed before 2006 the Market Authorisation (MA) File probably does not contain any ecotoxicological information, as in those days it was not required. Therefore, such information needs to be collected. MA-files for products licensed after 2006 should contain ecotoxicological data, but as these files are "closed" (between the MA-holder and the competent Authorities), this information is not available in the public domain.

Registration authorities could search for options to share environmental information publicly throughout the whole distribution chain. Furthermore, such data ought to be collected for compounds, of which such information is not available.

The development process of innovative medicinal products can be divided into the pre-clinical phase and the clinical phase.

Pre-clinical phase of medicinal product development

Most APIs are small, chemically produced, stable molecules. Many highly prevalent diseases are effectively treatable with these small molecule APIs, having well-established, safe use and no need for innovation from a medical point of view. R&D output from the big pharma companies has been decreasing (van Opstal, 2012, Horrobin, 2000, Nefarma, 2009) and has become increasingly expensive. Innovative research of pharmaceutical companies therefore focusses on new and complex pharmacological targets associated with less prevalent diseases. Since the nineteen-eighties, biotechnological processes have resulted in larger, more complicated and less stable protein molecules. Biotechnologically produced medicinal products are becoming increasingly important, when it comes to finding cures for complex diseases (Nefarma, 2012). In the Netherlands, many small and large companies are involved in research and development, with a primary focus on these biotechnologically produced medicinal products (van Opstal, 2012).

Innovative pharmaceutical companies often have their own R&D programmes, resulting in both original innovations and incremental innovations (Horrobin, 2000). Yet there is a trend among the 'big pharma' companies of retreating from the initial research aspect of R&D;

this initial research now takes place in an open innovation model, in which academic institutions and smaller pharmaceutical and biotechnological businesses join forces, often (partly) funded by governmental organizations. In these public-private partnerships, knowledge gathered from different disciplines is combined to develop innovative medicinal products. After this, the big pharma companies use their size and budgets to drive the clinical phase of medicinal product development and start production processes (Nefarma, 2009, Nefarma, 2012, van Opstal, 2012).

The design and synthesis of promising new medicinal products is followed by extensive pre-clinical testing (e.g. in vitro testing, animal testing) in order to gather initial information on safety and efficacy. The added value of many of the products that accessed the market has been disputed. In the last two decades, about 85-90% of the newly developed APIs provided little or no clinical advantages (Light and Lexchin, 2012, Pattikawa, 2007). However, some innovative developments in pharmaceutical research (such as the development of personalized medicinal products and the application of nanotechnology in medicinal products) could contribute to more targeted administration of medicinal products reducing the total amount of medicinal products needed in the future.

New technological developments in pharmaceutical science, such as the development of personalized medicinal products or the application of nanotechnology, could be assessed for their potential to enhance a more efficient use of active ingredients; a promising development in this respect could be specifically stimulated in the research funding system.

In the case of diclofenac, there is no specific technological development that has led to a more efficient alternative.

Diclofenac is a widely used painkiller for a general well-established use. However, investments necessary to improve a targeting use might lead to other therapeutic choices.

For other medicinal products a more efficient use of active ingredients may lead to reduced use and subsequent reduced discharge into the environment.

Clinical phase of medicinal product development

After the initial development of a new medicinal product, it needs to undergo several clinical trials to study the safety and efficacy in humans. The clinical phase of medicinal product development consists of four phases. In phase 1, the medicinal product is evaluated for safety in small groups of healthy volunteers (20 to 80 people). Phase 2 aims to establish the efficacy and effective dose of the medicinal product for treating a specific disease. These trials involve groups of patients (100 to 300). In phase 3, the results of earlier trials are confirmed with respect to efficacy and safety in much larger groups of people (1,000 to 3,000). This phase provides the primary basis for the benefit-risk assessment for the marketing authorization by the competent authorities, such as the European Medicines Agency (EMA). In phase 4, the pharmaceutical company conducts post-marketing studies conducted after the medicinal product has received marketing authorization.

3.2.2

Actors

Academic institutions

In the Netherlands, most universities conduct research on aspects of medicine (design, development and use) and on many different diseases. Research by universities is financed from different sources, both public and private (e.g. governmental bodies, European Framework Programmes, pharmaceutical companies) (VSNU, 2015).

Pharmaceutical companies

In The Netherlands, innovative pharmaceutical companies are represented by their sector organization Nefarma, which is part of the European sector organisation European Federation of Pharmaceutical Industries and Associations (EFPIA). The Dutch biotechnological pharmaceutical sector has its own association, Biofarmind.

Small (biotechnological) research businesses

The number of small and medium sized high-tech pharmaceutical businesses is increasing in the Netherlands. These businesses often specialize in niche markets. In 2012, there were approximately 300 of these start-up businesses active in the Netherlands (van Opstal, 2012, Nefarma, 2009).

Governmental organizations

For innovative medicinal products, the same governmental organizations are involved as for generic medicinal products (please refer to 3.1.2).

Sector organizations

In the Netherlands, several sector organizations are active with regard to pharmaceutical innovation. For example, the Federation for Innovative Pharmaceutical Research (FIGON) is an integrative platform for innovative drug research in the Netherlands. Another example is Top Institute (TI) Pharma, which sets up and manages collaboration between public and private partners in pharmaceutical research and facilitates open innovation (van Opstal, 2012).

3.3

Developmental phase of diclofenac or possible alternatives

The substance diclofenac was developed in the seventies of the 20th century. Diclofenac was first synthesized by Alfred Sallmann and Rudolf Pfister and introduced as Voltaren by Ciba-Geigy (now Novartis) in 1973 (Sallmann, 1986). At that time, the marketing authorization procedures were still at a national level in the member states of the European Union and did not entail an environmental risk assessment (ERA). The submitted registration dossiers did not include ecological data and licensing authorities were not responsible for assessing the environmental risk. At present, diclofenac is a widely used medicinal product. Obviously, levers in the developmental phase are not relevant anymore for diclofenac, but they can be relevant for newly developed analgesics and NSAIDs (Kummerer, 2007, Rastogi et al., 2015). Knowledge on the ecotoxicity of diclofenac and other relevant data could be taken into account in the ERA of newly developed NSAIDs.

4 Phase 2: Registration and market access of medicinal products

In Europe, a medicinal product has to be authorized before it can be marketed and becomes available to patients for which various authorization procedures exist. After receiving marketing authorization, the legal status governing the supply of the medicinal product (over the counter or prescription only) is decided on at a national level. Furthermore, reimbursement of the medicinal product by health insurers may determine its accessibility.

4.1 Marketing authorization of a medicinal product

4.1.1 Processes

Registration procedures

Pharmaceutical companies can apply for marketing authorization for a medicinal product at the national level or at the European level (Weda and Hegger, 2006, Hoeber et al., 2014). The different procedures take a maximum of 210 days; this period may be extended to allow the applicant to answer questions (CBG, 2015c).

When the medicinal product is already authorized in one member state of the European Union, a Mutual Recognition Procedure (MRP) can be followed to apply for authorization in other member states. If a pharmaceutical company wants to apply for authorization in several member states simultaneously, a Decentralized Procedure can be used. For certain innovative medicinal products, it is mandatory to apply for marketing authorization through the Centralized Procedure at the European Medicines Agency (EMA). This is the case for medicinal products that have been developed using biotechnology and for new medicinal products intended to treat cancer, AIDS, neurodegenerative diseases and diabetes (CBG, 2015c). In the case of other innovative products, companies are free to opt for either centralized or national registration. The main advantage of the Centralized Procedure is that new, innovative medicinal products can be made available to all European residents at the same time once marketing authorization has been granted.

To obtain a national marketing authorization in the Netherlands, a national procedure is followed at the Medicines Evaluation Board (MEB). In order to get access to the EU market, producers can choose to start a mutual recognition procedure or a decentralized procedure. The Coordination group for Mutual Recognition and Decentralized procedures (CMD(h)) is the European consultative body with the responsibility for the proper functioning of the mutual recognition and decentralized procedures. Each member state has one representative in the group, who may be accompanied by experts if necessary (CBG, 2015c). Applicants following the Centralized Procedure must submit a dossier to the EMA. Essentially, the dossier contains the same information as described for the national procedures.

Once a positive decision on the medicinal product in the mutual recognition or decentralized procedures has been made, translations of the summary of product characteristics (SmPC), patient information leaflet and labelling texts are submitted and a national marketing

authorization is issued in all member states involved. The reference member state (RMS) makes the PAR available, which contains a summary of the information in the dossier, including endpoints from the environmental risk assessment, if available.

Marketing authorisation

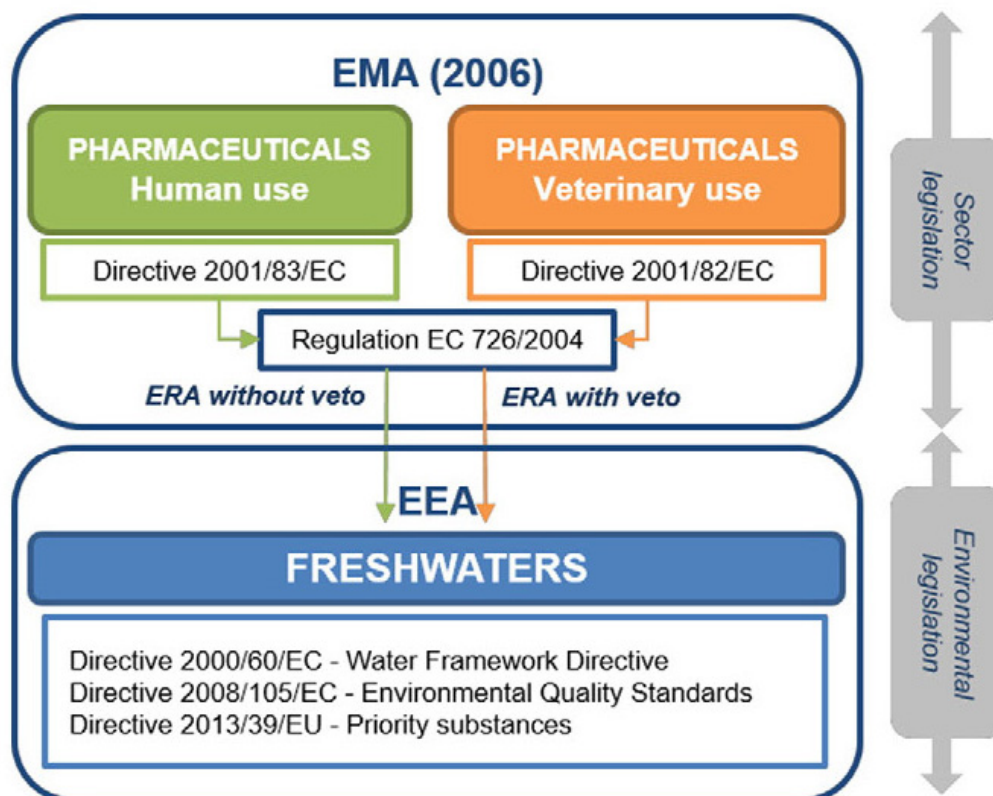


Figure 4: European Union legislation scheme on pharmaceuticals (Acuña et al., 2015).

Applicants for a marketing authorization of a medicinal product must submit a marketing authorization dossier, which contains administrative data (i.e. labelling, package leaflet and the SmPC) and all scientific data regarding the technical quality, efficacy and safety of the product gathered during pre-clinical and clinical development. Furthermore, an environmental risk assessment should be provided in this dossier (EMA, 2006).

The evaluating organization, e.g. EMA or MEB, examines the efficacy, safety and quality of the medicinal product and determines whether the advantages of using the medicinal product have been proven to outweigh the risks (i.e. the benefit/risk balance). If the benefits outweigh the risks, the medicinal product receives marketing authorization. According to the regulations this decision is solely based on the efficacy and safety for the patient. Other aspects, such as costs, therapeutic need and environmental risk assessment (ERA) are not taken into account during this process. The latter is in contrast with the legislation for pharmaceuticals for veterinary use, where ERA has a veto role in marketing authorization (Fig. 4).

In the benefit/risk analysis for human medicinal products, only part of the societal costs and benefits are taken into account. EU member states could agree on amending the human pharmaceutical legislation to take the results of the environmental risk assessment into account. There are different options to do so, for example:

- **as veto criterion in the marketing authorization**
One of the possibilities is that a re-evaluation of compounds can be done, taking new information into account. See also Küster and Adler (2014). In the specific case of diclofenac, which is also being used as a veterinary pharmaceutical, ERA may already be taken into account for the access to the market.
- **By giving environmentally friendly medicinal products easier access to the market than their environmentally unfriendly alternatives.**
*In principle, it is possible to develop environmentally friendly alternatives for medicinal products (e.g. Kummerer, 2007). One of the design criteria for new pharmaceutical products may be the environmental fate and effect. However, it must be made profitable for the pharmaceutical industry to bring such a new product to the market.
The impact of diclofenac and its alternatives on the ecosystems has to be evaluated to make such choices possible. If this information is not available, it must be collected.
If there would be an environmentally friendly alternative, the old product may be made less accessible by changing the prescription advices, by restriction of "over the counter" availability, by taking financial measures, or by taking the old product from the market.*
- **By requiring to prove increased efficacy and safety for specified health problems and/or reduced environmental costs.**
Such a lever provides the possibility to develop a "green pharmaceutical" as an alternative for diclofenac. (see also comment under the former lever).
- **By introducing a registration time limit for environmentally unfriendly medicinal products.**
- *When access to the market of diclofenac would be reconsidered, and would result in a limited time registration, this could promote the development of environmentally friendlier alternatives.*
- **By providing a label of environmental friendliness on packages (similar to the 'energy label').**
Provision of approved environmental information may raise awareness of the environmental impact of the product, leading to careful disposal of waste, and possible use of environmentally friendly alternatives.

When marketing authorization is granted, the SmPC, the patient information leaflet and the labelling text will become public. The SmPC contains all important scientific information about the medicinal product (such as composition, indication, dosage, contra-indications, pharmacological properties and pharmaceutical data) and is meant for

healthcare professionals. The patient information leaflet is meant to inform patients and contains information with regard to what the medicinal product is intended for, usage instructions, possible adverse events, and the ingredients of the product (van der Giessen and Hekster, 2005). The other parts of the registration dossier remain closed, although the evaluating body should make available a public assessment report (PAR) that contains a summary of the information in the dossier, including endpoints from the environmental risk assessment.

Pharmacovigilance

Once a medicinal product has been marketed, the medicinal product will be monitored by a process called pharmacovigilance. According to EU (Directive 2001/83/EC, 2001), both the producer of a medicinal product as well as the registration authority need to have a system for the reception and processing of reports of (uncommon) side effects after registration. Furthermore, The Netherlands Pharmacovigilance Centre Lareb collects notifications of side effects from both health care professionals and patients in The Netherlands. If necessary, the competent authorities, such as EMA and MEB, may take measures such as requirements to modify the patient information leaflet text or - in extreme cases - suspend sales or even withdraw the medicinal product from the market entirely (CBG, 2015e).

Environmental risk assessment within the marketing authorization procedures

Since 2006, an environmental risk assessment (ERA) is required to be part of the dossier for all medicinal products for which a manufacturer applies for marketing authorization. For all medicinal products that were admitted to the market before 2006 no such requirement exists. For most generics, when an increase in use of the specific AI is not to be expected, a new ERA is not necessary. The ERA is product-based, which means that it is performed for each specific medicinal product with an API and its specific indications. Thus, it is not substance-based, where one ERA would be made per API with all its possible indications.

The ERA in the dossier for marketing authorisation could be based on substances, instead of products. Or the information could be reused, if considered identical.

In the case of diclofenac, and generally, this would mean a reduction in effort, because this ERA, or at least the information in it, can be reused for different products/indications. However, certain parameters will not be the same for each product/indication. For example emission to the environment of applying a gel may not be the same as emission of using an oral product.

When performing the ERA, the 'Guideline on the environmental risk assessment of medicinal products for human use' and an accompanying Q&A document should be followed (EMA, 2006, CHMP, 2011). These guidelines are written by expert groups for the Safety Working Party (SWP), one of the working parties of the EMA's CHMP. The ERA starts with a phase I assessment, in which a first estimate of the predicted environmental concentration (PEC) is calculated based on the maximum daily dose. When a certain trigger value (as defined in the ERA

guideline) is met, a Phase II assessment is necessary, in which the applicant has to provide environmental fate and toxicity tests to show that the product is safe for the environment.

A possible environmental risk cannot constitute grounds for the refusal of a substance's approval, because of the major importance of medicinal products to public health (Derksen et al., 2007, Derksen and ter Laak, 2013a). Nor is there any obligation to monitor a substance's presence and effects on the environment after it has received approval (Montforts et al., 2006). There has been a call to make the information from the environmental assessment public upon the pharmaceutical's registration (Montforts and Keessen, 2008). The European Medicines Agency (EMA) has recently agreed that, following a pharmaceutical's EU-wide registration and approval, a table containing all the results (endpoints) of the environmental component of the registration dossier should be included in the European Public Assessment Report (EPAR) that is posted on the EMA website (www.ema.europa.eu). For medicinal products registered and authorised in the Netherlands, the Medicines Evaluation Board can post a summary of the environmental studies in the Medicines Data Bank on www.cbgmeb.nl. However, for a selection of medicinal products, in 2012, no environmental information had yet been made available on either site (van der Aa et al., 2011b).

Registration authorities could maintain a public database with data on the environmental effects of all approved products (i.e. an easy way to find the public assessment reports and the environmental risk assessment data in these reports).

When such information for diclofenac is not available with the registration authorities, this information needs to be collected. This lever would help to raise awareness among professionals and the general public. Furthermore, public availability of ERA data might help in risk assessment of new products, based on approved APIs.

4.1.2

Actors

Medicines Evaluation Board (MEB)

The MEB is the competent authority with regard to decision-making within the scope of the Dutch Medicines Act and related ministerial regulations. It consists, amongst others, of doctors, pharmacists and scientists. The MEB agency is an independent administrative body residing under the Ministry of Health, Welfare and Sports, which is accountable to both the Ministry and the MEB. It supports the MEB in its tasks.

European Medicines Evaluation Agency and the European Commission

For the centralized procedure, formally the European Commission grants the authorization. This decision is based on advice from the Committee on Human Medicinal products (CHMP) and EMA. The CHMP is responsible for preparing the opinions on all questions concerning medicinal products for human use. The committee is composed of a chair (selected by the serving CHMP members) and one member per member state, plus Norway and Iceland. The nominated members and their alternates serve the Committee for a renewable period of three years and they

have a bridging role between the European system and the national systems.

Applicant

The applicant is the pharmaceutical company that applies for the marketing authorization of a medicinal product.

4.2 Legal status governing the supply of a medicinal product

4.2.1 Process

After a medicinal product has gained marketing authorization, the legal status governing the supply of the medicinal product is determined at the national level. This legal status determines whether the medicinal product should be dispensed only on prescription by a physician or whether it can be dispensed without prescription.

Medicinal products can be categorized as prescription only (PO) or as Over-the-Counter (OTC). In the Netherlands, three OTC categories exist: 1) pharmacy only (PH); 2) pharmacy and drugstore only (PDO); and 3) general sales (GS) (CBG, 2015b).

If the Medicines Act would be amended, the results of the environmental risk assessment could be taken into account, when deciding on the legal status governing the supply; higher environmental risks could lead to a more restrictive status.

In The Netherlands, some diclofenac containing products are available with, and others without prescription. The latter type could be reconsidered, introducing more control on the use of the products that contain diclofenac. Decisions to give an OTC status are generally based on assessments of health risks and reducing reliance on healthcare.

4.2.2 Actor

The Medicines Evaluation Board

Besides the activities described in Chapter 4.1.2, the MEB is also concerned with determining the legal status governing the supply of medicinal products in the Netherlands

4.3 Reimbursement of a medicinal product

4.3.1 Processes

In the Netherlands, private health care insurance companies offer the compulsory health care insurance for every inhabitant. They are legally obliged to offer a basic package of coverage (i.e. the statutory insured package) and are not allowed to refuse people for this basic package. The Minister of Health, Welfare and Sports (based on advice from the National Health Care Institute) determines the contents of this statutory insured package on a yearly basis (Schafer et al., 2010). The majority of medicinal products are covered by the statutory insured package. However, individual health care insurers may put further specific conditions for reimbursement of medicinal products, for example reimbursement only of certain (generic) brands of a medicinal product (see Chapter 6.1.1.7.).

Reimbursement differs for medicinal products prescribed in extramural care (i.e. general practice or treatment of outpatients by specialist

doctors in the hospital) and medicinal products provided as part of intramural care. Reimbursement of extramural pharmaceutical care is based on a reference pricing system called the Medicines Reimbursement System (GVS). The Ministry of Health, Welfare and Sports ultimately decides on the uptake of medicinal products in the GVS and is advised in the decision by the National Health Care Institute (ZiN) (Schafer et al., 2010, Zorginstituut Nederland, 2015a). In intramural medical care, all medicinal products are considered part of the hospital care and become immediately available in the statutory insured package from the moment they receive a marketing authorization from the European or national regulatory authority (EMA and MEB respectively). Furthermore, several expensive medicinal products used extramurally have been transferred to intramural care. Hospitals receive add-on reimbursement for these medicinal products.

Reimbursement of the costs of extramural medicinal products

The GVS is set up in two categories: category 1A consists of clusters of medicinal products that are interchangeable in terms of therapeutic value (i.e. therapeutic equivalents) with a reimbursement limit, and category 1B consists of unique or innovative medicinal products having no reimbursement limit.

A marketing authorization holder can apply for uptake of his product in the GVS by an official request to the Ministry of Health, Welfare and Sports. The Ministry of Health, Welfare and Sports may decide, after receiving advice from the ZiN, to explicitly exclude certain medicinal products from the statutory insured package because they are not cost-effective, a decision which should be based on objective and verifiable criteria. Furthermore, the ZiN can provide a non-binding statement that, upon evaluation, a certain medicinal product was found not to befit the current state of science and practice. This may also exclude a medicinal product from the statutory insured package.

The reimbursement system could be amended to promote reimbursement of the most effective, safe and environmentally friendly medicinal products available. This can be done either by putting a premium on environmentally unfriendly medication and using those revenues to lower the price of environmental friendly medicinal products, or by putting a reimbursement limit on environmentally unfriendly medicinal product , i.e. green pricing with 'disposal fee'.

This may lead to a different pricing of diclofenac containing products, leading to reconsideration of the choice for specific medicinal products, based on a cost benefit assessment.

Currently, comparable information on the environmental effects of diclofenac and its medical alternatives is not available. For this lever to become effective, more knowledge on medical substitutability of diclofenac and its alternatives and on their subsequent environmental effects is needed to quantify the required and possible change needed for effective change in pharmaceutical care. Based on this information, the subsequent price differentiation can be determined.

The assessment system for uptake of a medicinal product in the package of insured medicinal product could be

amended to make environmental risk a criterion in the decision for inclusion or exclusion in the package.

This may lead to adaptation of the availability of diclofenac containing products, or to adaptation of prescriptions schemes of NSIAD medicinal products. Making results of ERA a criterion for uptake in an insurance package might make the development of "green medicinal products" more favourable. For this lever, similar to the previous lever, medical alternatives need to be studied for their environmental effects. If multiple medicinal products with similar pharmaceutical effects differ in their environmental effects, the substitutes that cause fewer or less severe environmental effects can be given preference when deciding on inclusion in the insurance.

Reimbursement of the costs of medicinal products in intramural specialist medical care

The Dutch Health Care Authority establishes performance directions and maximum tariffs for intramural specialist medical care, including medicinal products. The costs of intramural specialist medical care are reimbursed through Diagnosis Treatment Combinations (DTC), and medicinal products are thus reimbursed as an integral part of these DTC's.

4.3.2

Actors

Ministry of Health, Welfare and Sports

The Ministry of Health, Welfare and Sports ultimately decides on the contents of the statutory insured package and establishes maximum prices for medicinal products (see Chapter 5.2) and the reimbursement limits in the GVS.

National Health Care Institute

The ZiN is a governmental body subsidized by the Ministry of Health, Welfare and Sports and it has an important role to play in maintaining the quality, accessibility and affordability of health care in the Netherlands. It advises the Ministry of Health, Welfare and Sports on the content of the statutory insured package. It assesses most applications for the uptake of medicinal products in the GVS and advises the Ministry of Health, Welfare and Sports with its decision. The ZiN also advises the Dutch Health Care Authority (NZa) on (the extension of) the inclusion of medicinal products in special policies on expensive medicinal products or orphan medicinal products (Zorginstituut Nederland, 2015a).

Dutch Health Care Authority

The NZa supervises the compliance of actors with the Health Insurance Act. Furthermore, the NZa establishes tariffs and performance directions for those health services that are not subject to free negotiations. Lastly, the NZa monitors the health care market and promotes its transparent operation, both in terms of price and quality (Schafer et al., 2010).

Registration holder

The registration holder of a medicinal product (i.e. a pharmaceutical company) needs to apply for inclusion in the GVS.

International comparison

The process for marketing authorization is comparable in the Netherlands, Germany and Scotland (countries also involved in the No-Pills project). However, there is a difference in the number of authorized medicinal product; in the Netherlands, approximately 14,000 medicinal products are authorized (CBG, 2015d), compared with 100,000 in Germany (BFARM, 2016) and 15,600 in the UK (MHRA, 2016).

Slight differences between the countries can also be found with regard to the legal status governing the supply of medicinal products. Differences exist with regard to where over-the-counter (OTC) medicinal products may be sold; in the Netherlands, this may be pharmacy only (under the supervision of a pharmacist), or pharmacy and drugstore only (under supervision of a pharmacist/druggist), or general sale (without supervision in retail outlets), compared with pharmacy only (under the supervision of a pharmacist) and general sale (without supervision in retail outlets) in the UK and Germany. In all three countries, the costs of OTC medicinal products are paid by the patient. However, both in Scotland and in Germany, the costs may be reimbursed by the health care insurer if the OTC medicinal product is prescribed by a physician.

Prescribed medicinal products are reimbursed by the third party payer in all three countries (i.e. statutory health insurance in both the Netherlands and Germany and the National Health Service (NHS) in Scotland). However, in Germany, reimbursement is only applicable if the medicinal product is prescribed for indications given in the guidelines.

5 Phase 3: Production and distribution of medicinal products

For patients to have access to medicinal products, they need to be produced and distributed to pharmacies. Pharmaceutical companies compete for attention of the pharmacies, physicians and potential users by marketing activities.

5.1 Manufacturing

5.1.1 Process

Manufacturing of medicinal products

Pharmaceutical manufacturing includes the production of APIs, complete medicinal products or semi-finished products, which are processed further by other factories or pharmacies. Furthermore, import from outside the EU and repackaging/relabelling medicinal products is also considered to be pharmaceutical manufacturing. For all manufacturing processes, a manufacturing license issued by the Minister of Health is required. In the EU, medicinal products have to be manufactured according to the guidelines for Good Manufacturing Practice (GMP) to warrant their quality. The European Pharmacopoeia contains legally binding quality standards for all medicinal products in its member states. The Dutch Health Care Inspectorate supervises pharmaceutical manufacturing and provides GMP certificates to manufacturers who meet the requirements set in the GMP guidelines (IGZ, 2015a). On the authority of the EMA and the MEB, manufacturers based in countries outside of the EU may also be subject to inspection.

The active pharmaceutical ingredient (API) (bulk substance) for diclofenac is not produced in the Netherlands, nor in the neighbouring countries. Therefore, changes in the synthesis route in the production of the bulk substance have no direct impact on the environmental quality in the Netherlands. The known production sites are located in Ireland, Italy, Spain, India and China.

Manufacturers can take measures to reduce environmental pollution by the active ingredient during the production process (in addition to Green Chemistry: sustainable production process, less solvent use, sustainable raw materials, etc.)

It is in the interest of producers to use raw materials as efficiently as possible. This decreases production price, and environmental pollution. If producers would decide to adapt the production process, the quality criteria for the API may change and have to be accepted by the registration authority. Furthermore, under such circumstances the monograph of the European Pharmacopoeia has to be adapted as well.

The GMP guideline could be amended by adding requirements for environmental care assurance.

It is in the interest of producers to use raw materials as efficiently as possible. This decreases production price, and environmental pollution.

The information on the environmental effects of new medicinal products could be used to specify the costs of removal from wastewater. Based on this information, a tax on the product could be imposed to finance measures further in the medicinal product chain that will reduce environmental pressure.

This may result in a change of the price of diclofenac containing products. The information on environmental effects can be made available in the public database as described in the levers in chapter 4.1.1.

This could lead to increased prices of medicinal products and therewith reduced availability. It might also lead to adaptation of prescription schemes and reduced use.

5.1.2

Actors

Manufacturers

Companies and organizations such as hospitals performing pharmaceutical manufacturing (including import of medicinal products from outside of the EU and repackaging and relabelling of medicinal products) need to be licensed, which means they must hold a Manufacturing License issued by the Ministry of Health, Welfare and Sports.

Ministry of Health Welfare and Sports

The Ministry of Health Welfare and Sports issues licenses for pharmaceutical manufacturing.

The Health Care Inspectorate

The Health Care Inspectorate in the Netherlands is a governmental organization that is responsible for enforcing the quality of health services, prevention measures and medical products. With regard to the manufacturing licenses for pharmaceutical manufacturers, the Health Care Inspectorate is the organization that enforces the EU legal obligation to supervise the production of medicinal products in accordance with the requirements of GMP in the Netherlands.

5.2

Distribution of medicinal products

5.2.1

Processes

Manufacturers can distribute medicinal products to pharmacies, drugstores and other retail outlets either directly or via wholesalers. Wholesalers are mainly involved in the distribution to community pharmacists and drugstores/retailers; they have large storage capacities and a high turnover, and may provide pharmacists with quick access to medicinal products when they need it. Distribution to hospital pharmacists often occurs directly from the manufacturer (Suykerbuyk and Tjoeng, 2005).

The Medicines Act dictates that the distribution of medicinal products is a 'reserved act' and the trading process is strictly channelled. Wholesalers need to be in possession of a Wholesaler's license issued by the Ministry of Health, Welfare and Sports. They receive this license after inspection by the Dutch Health Care Inspectorate to control whether they meet the requirements of the EU guidelines on Good Distribution Practices (GDP). The GDP warrants the quality and safety of

the distribution and requires that distribution should be restricted to authorized medicinal products, that storage and transport conditions should be adequate, that contamination should be avoided and that medicinal products should be stored safely without affecting shelf life, quality and safety.

Generally, manufacturers determine the prices of their medicinal products. However, the reference pricing system of the GVS dictates that prices cannot exceed the average price level in Belgium, France, Germany and the UK (Art 2.2 Pricing Act).

Volume/Amount of medicinal product per package could be tailored to the actual need of the patient to reduce waste of unused medicinal products.

This may lead to changes in volume/amount of diclofenac containing products per package. Deliverance of smaller amounts/volumes of products might lead to increased prices per unit and possibly increased use of package material. Under specific circumstances, it may lead to extra visits to drugstore or pharmacist. This personalisation of medicinal products may require a more flexible distribution system.

5.2.2

Actors

Pharmaceutical company

A pharmaceutical company can have different roles to play in the distribution process. It may operate as a supplier, as an importer or as a distributor directly to (hospital) pharmacists. Pharmaceutical companies often operate on an international level. Manufacturers make arrangements with other actors in the distribution chain, such as wholesalers, the brokers in active pharmaceutical ingredients and pharmacies, in order to optimize the accessibility of their products (Suykerbuyk and Tjoeng, 2005).

Wholesaler

The wholesaler is an intermediary actor in the distribution chain. Wholesalers purchase products on conditions that match the producer and sell products on conditions that match the pharmacist. Thus, the wholesaler has two roles: a logistical role (reception of goods, stock keeping and inventory control, order taking, order picking, transport and delivery) and a commercial role (buying and selling).

There are two kinds of wholesalers: 1) full-line wholesalers, which have a broad range of products and a short turnaround, and 2) short-liners, which have a limited assortment of several, much wanted medicinal products and a longer turnaround (Suykerbuyk and Tjoeng, 2005).

Pharmacy

Pharmacies in the Netherlands can be divided into community pharmacists (covering 92% of the population), dispensing General Practitioners (GPs) (covering 8% of the population, mainly in rural areas), hospital pharmacies (for in-patients) and outpatient pharmacies (for discharged patients and patients receiving outpatient specialist medical care).

Community pharmacies work under free market conditions and are involved with wholesalers, manufacturers and health care insurers when purchasing medicinal products. Hospital pharmacies are specifically responsible for buying, distributing and dispensing medicinal products in

the hospital and are often directly involved with manufacturers. The assortment of medicinal products in the hospital (i.e. the hospital formulary, see chapter 6.1.1, Delivery of medicinal products to patients) is directly influenced by hospital pharmacies.

Pharmacies are required to warrant the reliability of their suppliers. The Royal Dutch Pharmacists Association (KNMP) supports pharmacies by auditing all suppliers and their quality management systems. When suppliers have positive audit results, the KNMP provides them with the title 'reliable', which lasts for 2-3 years.

Drugstore and retail outlets

Drugstores, supermarkets and other authorized retail outlets (e.g. petrol stations) may sell over-the-counter medicinal products. Yet, according to the Medicines Act, not all employees are allowed to give advice on the use of medicinal products. This task is reserved exclusively to the (assistant-) chemist, who is specifically educated and has knowledge about the medicinal products.

5.3 Marketing

5.3.1

Processes and actors

Pharmaceutical companies are commercial companies, which leads to competition between them. Their competitive success relies not only on their R&D activities, but also on advertising and product differentiation. Since the 1990s, the return of advertising has become three times larger than that of R&D.

Pharmaceutical companies are allowed to promote medicinal products to health professionals under strict conditions (IFPMA, 2012); doctors get acquainted with new medicinal products through promotion techniques such as visits by pharmaceutical sales representatives to doctors (also called 'detailing') and advertisements in professional journals (Donohue et al., 2007, IGZ, 2015b). Furthermore, pharmaceutical companies also try to influence patients, institutions and opinion leaders, since they may indirectly influence the doctor's prescribing behaviour as well (Denig and Haaijer-Ruskamp, 2005).

6 Phase 4: Consumption of medicinal products

For the consumption of medicinal products, this report makes a distinction between two types of medicinal products. Patients can either consume medicinal products prescribed by a physician or patients can self-medicate with medicinal products they bought over the counter. There are indications that the overuse, underuse or misuse of medicinal products result in wastage of resources and health hazards (WHO, 2012). Different countries have attempted to improve the rational use of medicinal products, but so far, it has not been possible to determine the efficacy of those measures (Austvoll-Dahlgren et al., 2008).

6.1 Prescribed medicinal products

This chapter describes the actors and processes involved in the consumption of prescribed medicinal products. Two steps precede the consumption of prescribed medicinal products: (1) prescription of the medicinal product by a physician and (2) dispensing of the medicinal product by a pharmacy. In the Netherlands, the prescription of medicinal products is a process in which the patient, the prescriber and the insurer all interact with each other. Furthermore, physicians and hospital pharmacies interact to determine the hospital formulary, which influences the prescriptions of medical specialists for intramural patients.

The Dutch College of General Practitioners makes guidelines for health care professionals in the Netherlands. Their guideline on pain management consists of five steps. In the first step, the health care professional is advised to advise paracetamol to the patient, and in step five a strong opiate is administered.

Diclofenac is advised in step 2. In step 2 the health care professional is advised to choose between naproxen, ibuprofen and diclofenac. On a patient by patient base, health care professionals are advised to weigh the benefits to known side effects of all medicinal products when administering pain medication (NHG, 2016).

6.1.1 Processes

Physician – patient interaction

The physician-patient interaction can be summarized as follows: when a patient has a health problem and decides to take action, he or she can decide to go to a physician. The patient presents his symptoms, the physician makes a diagnosis and, based on this diagnosis, the physician decides on a treatment. This treatment may involve the prescription of medicinal products. The prescription of medicinal products is therefore primarily determined by morbidity, disease and the problems presented by the patient. However, similar problems and diseases do not always lead to similar medical decisions (Denig and Haaijer-Ruskamp, 2005), since the prescribing behaviour of physicians is influenced by many factors.

Physician and practice-related factors

In health care research, practice variation is well-known (e.g. SFK, 2015c). A number of factors that affect practice variation are known.

However, even though this is an indication that other factors than medical rationality affect the use of medication, in practice it is difficult to assess which patient is given too much or too little medication. Doctor's individual traits are known to influence this decision-making process. For example, female physicians tend to be more patient-centred instead of task-oriented, which leads to lower prescription rates. Age and working experience do not necessarily influence prescription volume, but they do influence the choice of medicinal products (Denig and Haaijer-Ruskamp, 2005).

The choices that physicians make are largely determined by their education, as doctors copy a large part of the arsenal of medicinal products they work with from the doctors that educated them. Over the course of time, their set of known options to choose from is adapted under the influence of factors such as marketing, continuing education, consultation with colleagues and pharmacies, professional literature and guidelines (Denig and Haaijer-Ruskamp, 2005, Coleman et al., 1957). Strategies to influence doctors' prescribing behaviour are used both by professionals (e.g. continuing education by the Royal Dutch Society for Medicine) as well as by pharmaceutical companies. Professional education aims to update the doctor's knowledge and it assumes that a change in behaviour is a rational process. Pharmaceutical companies try to influence doctors in order to create interest in their new product. Pharmaceutical companies often also try to influence patients, institutions and opinion leaders, as they may indirectly influence the doctor's prescribing behaviour as well (Denig and Haaijer-Ruskamp, 2005).

Guidelines

The Pharmacotherapeutic Compass provides an overview of all medicinal products registered in the Netherlands and was developed to aid professionals in decision-making with regard to the appropriate use of pharmacotherapy. Furthermore, for many conditions, professional guidelines have been developed in order to minimize mistakes and legitimize physicians' medical behaviour. These guidelines may legitimize off-label prescription, which is the prescription of a medicinal product for something other than the indication(s) for which it is registered. In principle, physicians in the Netherlands have prescription freedom, which means they are able to prescribe any (registered) medicinal product based on their expertise and professional responsibility. Since 2007, however, the Dutch Medicines Act sets stricter conditions for off-label prescription: it is only legitimate when the professional association has agreed on a guideline. If no guideline is available yet, off-label prescription must be discussed with the pharmacist (Zorginstituut Nederland, 2015b). This means that individual case to case deliberation takes place in the prescription process. Besides guidelines for specific conditions, guidelines and toolkits have been developed which focus specifically on appropriate prescribing. Primarily, these guidelines focus on therapeutic value and the safety of medicinal products/active ingredients. After that, other factors, such as costs, can be considered as well (OMS, 2011, LHV, 2015). If all physicians would adhere to the guidelines, little variation between physicians would exist. However research shows that, in the Netherlands, conformation to guidelines is not optimal (van den Berg et al., 2014). Guidelines that require less time-investment by the physician

are generally better adhered to than guidelines that require more time-investment (van den Berg, 2010). Other research shows it is no exception that patients with a chronic disease who are treated by multiple health care providers, receive contradicting advice (Lekkerkerk, 2010).

The environmental consequences of pharmaceutical use could be included in the training of physicians and/or their guidelines.

This may enhance awareness among professionals and may lead to other choices for medicinal product prescription. In every decision physicians make to prescribe medicinal products, they need to balance the expected benefits (reduction of pain in the case of diclofenac), versus known side effects (e.g. problems in the abdomens and cardiovascular risks) for the particular patient. When prescribing a pain killer, mostly the physicians only weigh costs and benefits for the patient. If knowledge of environmental effects of diclofenac and its possible alternatives is included in the guideline of the The Dutch College of General Practitioners (NHG, 2016), physicians may include environmental consequences in choice of medication, if there is no preference in choice based on medical reasons. Then, similar to prescription of antibiotics, physicians would also weigh effects of prescription after use by the patient.

The pharmacotherapy for the individual patient could be more targeted.

This may lead to adaptation of the provision quantities, or different choices for medicinal products. In the case of diclofenac, side effects and its clinical substitutes are known. Physicians will take the risks of the side effects into account and may therefore be expected to subscribe conservatively. It is therefore not likely that when no known environmental friendly substitute is available, knowledge of the environmental effects of diclofenac will lead to a substantial reduction in prescription by physicians. However, it is known that patients who use more than five types of medication and are treated by several health care professionals take too many medicinal products. Regular monitoring of the complete list of medicinal products, is expected to lead to a reduction in overuse of medication (Lemmens and Weda, 2013).

Practice-related factors

At the medical practice level, there is much variation in the volume and costs of prescribed medicinal products. Differences seem to be related to variations in practice size, location and organization. Being part of a larger organization seems to influence prescribing behaviour, since it is then regulated by internal guidelines, agreements and mutual interests within the organization (Denig and Haaijer-Ruskamp, 2005).

The composition of the patient population also influences the prescribing behaviour of a GP practice. A Prescribing Monitor in the Netherlands showed, for example, that GPs who have many elderly patients tend to prescribe more medication to their patients, even after correction for age (Lambooy et al., 2014).

The physician-patient relationship

The physician-patient relationship is another factor of influence. When patients decide to see a doctor, they expect the doctor to be able to solve their health problem. Research suggests that patients' expectations with regard to the management of their health problem influence the doctor's decision to prescribe medication (Webb and Lloyd, 1994). Perceived patient pressure has been found to influence the doctor's behaviour (Little et al., 2004), because it is important to doctors to maintain the therapeutic value of a good doctor-patient relationship (Butler et al., 1998). It has been suggested, however, that doctors misconstrue these patient expectations and actually overestimate them (Lado et al., 2008).

Market demand could be influenced by creating citizen awareness on the environmental impact of specific pharmaceutical care.

Patients could ask for environmentally friendly alternative medicinal products if available. In the case of diclofenac, media attention on the environmental effects could be the start of this process. Market demand is influenced by marketing activities. Restriction of such activities may lead to reduced medicinal product use. This is especially true in the chronic, preventive use of medicinal products, e.g. statins against high cholesterol levels.

Nowadays, many health problems are dealt with by prescribing medicinal products. Some health problems, especially chronic conditions such as type II Diabetes, high blood pressure and high cholesterol, can be managed by lifestyle changes as well (Dickinson et al., 2006, Gillies et al., 2007, Mannu et al., 2013, Ornish et al., 1990). In these cases, medicinal product prescriptions may be reduced.

Validated interventions to support patients to adapt their lifestyle or diet, could result in a reduced need for medicinal products and could be promoted.

In these cases, medicinal product prescriptions may be reduced. For diclofenac however, a change in lifestyle will not likely lead to fewer prescriptions, since it is a painkiller, often used when pain is acute or is inflicted by an external source such as a medical intervention or an accident.

For other medicinal products, especially when used chronically, this will be an effective measure to reduce medicinal product use and subsequent medicinal waste discharge. However, this will conflict with the business interests of the pharmaceutical industries.

Insurer – physician interaction

Health care insurers have two tools they can use for their negotiations with health care providers. These are 1) negotiations based on volume, quality and prices, and 2) the selective contracting of some care providers, e.g. some care providers are included in a preferred list and others are not. This has consequences for the way the costs of the patient's treatment are reimbursed. Thus, while purchasing care, insurers influence what care is delivered by whom.

GP's are financed according to a mix of a fee per registered patient and a fee-for-service. This fee-for-service consists of several components: a consultation fee for GPs and a consultation fee for nurse practitioners (if any) (Schafer et al., 2010).

Hospital care is financed through Diagnosis Treatment Combinations (DBC). This system aims to promote price and quality negotiations between insurers and hospitals during the contracting process. Average tariffs for DBC's include the costs of medical specialist care, nursing care, the use of medical equipment and diagnostic (Schafer et al., 2010). NZa also determines maximum tariffs for medicinal products placed on the add-on list (see Chapter 4.3); the health care insurer and hospital negotiate on the handling of potential purchasing discounts (NZa, 2015).

Patient – insurer interaction

All health insurers are legally obliged to offer a statutory insured package, the content of which is regulated by the Ministry of Health, Welfare and Sports. For the statutory insured package, Dutch citizens pay a nominal premium to the health insurer of their choice, which is community rated. This means that, for each product, an insurer must charge the same amount to each individual, independent of the individual's risk characteristics. Health insurers may only compete on service, price and quality of care, and citizens are free to switch insurers yearly (Schafer et al., 2010). Besides the compulsory basic health insurance, any individual may opt for complementary voluntary health insurance to cover a greater range of medical aids and treatment options. In the case of complementary voluntary health insurance, health insurers are allowed to determine for themselves which insurances they offer for which premiums, and under which conditions they accept clients (Zorgverzekeraars Nederland, 2014).

The reimbursement of most medicinal products is covered by basic insurance, but the reimbursement mechanism differs slightly between medicinal products prescribed in primary care and medicinal products prescribed in hospitals.

Dispensing of medicinal products to patients

In community pharmacies, prescriptions for medicinal products are processed, prepared and dispensed to the patient. During this process, pharmacies check the relevant patient information (name, age, health care insurer, medication history) and the dose and quantity of the medicinal products prescribed in order to make sure that the right medicinal products are dispensed to the right patient in the appropriate amount (Buurma et al., 2005, KNMP, 2013). During the dispensing of medicinal products, an exchange of information takes place between the pharmacist and patient.

Diclofenac is available OTC in tablets that include smaller doses. The stronger dosed medication that is submitted other than orally is available on prescription only and in the clinical setting.

Pharmacists could include information about environmental aspects and appropriate methods of disposal in the user information they provide to the patient.

There is no systematic publicly available database with environmental information of medicinal products. If pharmacists do not have the knowledge to provide proper information, such a provisioning of information must then be developed. This is also related to earlier potential levers, e.g. under 3.2.1.

The pharmacy can also exchange information with physicians who prescribe medicinal products. Furthermore, general pharmacists have a structured cooperation with the GPs in their area through Pharmaco-Therapeutic Consultation Groups (FTC groups). In approximately 800 FTC groups, pharmacists and GPs discuss pharmaceutical treatment and products, and aim to reach consensus concerning their prescribing and information policy. As FTC groups are autonomous, their quality varies. Good FTC groups are associated with more effective and more efficient prescribing by their members (Schafer et al., 2010).

In order to reduce the wastage of medicinal products and stimulate the dispensing of medicinal products in appropriate amounts, health care insurers may determine a maximum reimbursement period for medicinal products in cases of first time use; they usually limit the dispensation of new medicinal products to around 15 days. However, 28% of newly prescribed medicinal products are still dispensed for a period longer than 15 days, which amongst other things is due to efficiency considerations in the pharmaceutical practice (SFK, 2014).

The quantity of medicinal products issued to the patient could be more targeted.

This may lead to different package volumes and potentially less waste of unused medicinal products. In the case of diclofenac we see an annual reduction of its use after advice to prescribe naproxen instead of diclofenac because of cardiovascular side effects after high doses (SFK, 2015b). Because of these risks, it is reasonable to expect that physicians currently target the use to a maximum necessary to reduce the pain. Further reduction of prescription of the medicinal product based on environmental reasons seems unlikely.

In hospital pharmacies, the process between receiving a prescription and delivering it to the patient is more complex due to the larger number of logistical steps within the hospital. Furthermore, hospital pharmacies often do not dispense medicinal products directly to patients; this mostly happens through nurses and doctors. Hospital pharmacies do not have direct interaction with health care insurers either, as they are financed through the hospital's budget. In the Netherlands, hospitals have their own formulary of medicinal products, which includes a list of preferred medicinal products for each illness. Medical specialists can only prescribe those medicinal products that are included in the formulary. This list is determined by hospital pharmacists and based on considerations of efficacy, safety, convenience for users and efficiency.

Hospital pharmacists could base their choices for which medication to include in their Formulary also on environmental aspects.

Pharmacists do not have access to a systematic and publicly available database with environmental information. For this lever to become practice, a database of environmental effects of medicinal products (i.e. diclofenac) and their medical alternatives needs to be developed.

In order to increase the chance of use of this information, a system would be needed that gives pharmacists easy access to all information that they need when issuing the medicinal product.

Adherence to prescribed medicinal products

After receiving medicinal products, medicine adherence is largely the responsibility of the patient. Research shows that some patient groups find it more difficult to adhere to therapy than others. For instance, medicine adherence is often worse among older people compared with younger people. The type of symptoms and type of medicinal products also influence adherence, as well as how many times a day medicinal product should be taken (Paes and Smit, 2005).

Interventions to improve adherence to medicine therapy could be supported since it will also lead to a decrease of the amount of unused and/or out-of-date medicinal products.

Such interventions may increase awareness of users, leading to other choices for pharmaceutical care, and more specific attention for disposal of pharmaceutical waste. Increased adherence would improve the results of pharmaceutical care, but it might reduce medicinal product use and subsequent negative business consequences.

6.1.2

Actors

Patient

Often, the patient initiates the prescription process; the experience of symptoms may lead the patient to take action (i.e. see a doctor and possibly receive a medicinal product prescription). The decision to consult a doctor is based on a complex process in which physical, psychological and social factors play a role (Campbell and Roland, 1996).

People with similar symptoms are known to decide differently when to see a doctor (Paes and Smit, 2005). Consulting behaviour is influenced by beliefs about the illness, such as perception of susceptibility and severity, and the advantages and disadvantages of seeking care; when people perceive their complaint to be serious and when they expect the care provided by the physician to be effective, they are more likely to consult a physician. Consultation is more likely when people feel they need more information about what affects them. Contextual factors such as social support and advice from (lay) others may also influence consulting behaviour (Paes and Smit, 2005, Campbell and Roland, 1996, Rosenstock, 1966, van de Kar et al., 1992).

Prescriber of medicinal products

The Dutch Medicines Act dictates that the prescription of medicinal products is a reserved procedure, which means that health professionals are not allowed to prescribe medicinal products unless this is registered in the Dutch Individual Healthcare Professions Act (BIG Act). In the Netherlands, doctors, dentists and midwives are qualified to prescribe medicinal products. Since 2012, nurse specialists and physician assistants have been allowed to prescribe medicinal products as well, though constrained to the less complex types of medication. Nurses working in specific areas such as diabetes care may prescribe medicinal products, but also under certain conditions.

- **General Practitioner**

The GP is an important actor in the Dutch health care system. The GP has a gate-keeping function, which means that access to hospital care and specialist care requires a referral by the GP.

GPs prescribe 75% of all medicinal products and 65% of all consultations in the Netherlands end with a prescription (de Jong, 2008).

- **The medical specialist**

Medical specialists in secondary care receive patients after referral from a GP. They provide both inpatient and outpatient hospital care. A considerable part of the contact between the hospital specialist and the patients takes place via hospital nurses. In the Netherlands, hospitals have their own formulary of medicinal products, which includes a list of preferred medicinal products for each illness. Medical specialists can only prescribe those medicinal products that are included in the formulary. This list is determined by hospital pharmacists and based on considerations of efficacy, safety, convenience for users and efficiency (NZa, 2015).

- **Other health care professionals authorized to prescribe medicinal products**

Other health professionals who are allowed to prescribe medicinal products are dentists, midwives, specialist nurses and physician assistants. Midwives and dentists are allowed to prescribe medicinal products within their competence and area of expertise. Specialist nurses and physician assistants are allowed to prescribe medicinal products within their area of expertise, as long as it concerns less complex, routine prescriptions with low risk and they follow national guidelines and protocols. Furthermore, since 2014, two other groups of nurses can apply to have a prescription competence mark in their BIG registry. This concerns nurses who completed training in diabetic care or asthma/COPD care (KNMG artseninfolijn, 2014).

Prescribers of medicinal products are influenced by other actors as well, such as the industry (see chapter 5.3.1.), health insurers (see below), pharmacies (see below), colleagues and patients themselves (Denig and Haaijer-Ruskamp, 2005).

Health care insurer

Insurers are influenced by other actors. First, they interact with other insurers in a (regulated) competitive way. Furthermore, they are influenced by law and regulations and financial considerations. Several institutions supervise insurers: The Dutch Bank (DNB) is prudential supervisor, The NZa monitors the general interests of consumers (e.g. supervising the availability of (correct) choice information, commercials) and the Authority for Consumers and Markets (ACM) supervises competition between health care insurers.

Pharmacy

- **Community pharmacy**

Pharmacies interact with several actors in the medicinal chain, but they primarily interact with patients, to whom they dispense medicinal products and to whom they provide pharmaceutical care. The interaction with the prescribers of medicinal products mainly concerns checking prescriptions and structural contact and information exchange during FTC groups. Furthermore, pharmacies have to deal with health insurers, as they reimburse pharmacies for their activities. Pharmacies are represented by

professional organisations such as The Royal Dutch Association for Pharmacy (KNMP) and the Association for Chain Pharmacies (ASKA). The quality of pharmacies is influenced by the KNMP quality policy and the Harmonisation of Quality Assessments in Health Care (HKZ) certification.

- **Hospital pharmacy**

Since hospital pharmacies are employed by the hospital, they do not have a commercial aspect. Hospital pharmacies primarily have to deal with medical specialists and nurses (Buurma et al., 2005). In the Netherlands, hospitals have their own formulary of medicinal products. Furthermore, hospitals have an outpatient pharmacy, which dispenses medicinal products to patients who have been discharged or who have received a prescription from a medical specialist in the outpatient clinic. Hospital pharmacies are represented by professional organisations such as the Dutch Association of Hospital Pharmacists (NVZA) and the Dutch Association for Outpatient Pharmacy (NVPF).

Ministry of Health, Welfare and Sports

The Ministry of Health, Welfare and Sports ultimately decides on the contents of the statutory insured package. Furthermore, it is involved in the setting of maximum prices and reimbursement limits for medicinal products, as well as setting (maximum) tariffs for performance directions and DBGs. The Dutch Health Care Authority is the independent implementing body concerned with these tasks.

6.2 Self-medication

6.2.1 Processes

Self-medication products consist of over-the-counter medicinal products and consumer products that are used in case of health problems (e.g. food supplements, vitamins). Patients self-medicate when they purchase medicinal products without prescription. However, physicians may also advise patients to purchase OTC medicinal products when appropriate, instead of prescribing a prescription-only medicinal product. In 2014, 75% of the total share of OTC medicinal product sales comprised OTC medication sold by drugstores. For the other 25%, 11% was sold by supermarkets and 14% was sold by pharmacies. In the Netherlands, the revenue share of over-the-counter medication sales amounted to 13% of total revenue in the pharmaceutical market in 2012 (Neprofarm, 2015).

When purchasing self-medication products, the patient buys a medicinal product based on their own experiences or the experience of others. Furthermore, the decision may be based on advice from a physician. The purchase of a product may also be influenced by advertising.

When buying self-medication products, the patient makes a trade-off between the need for the medicinal product, the quality and the price. Some parties, such as the Ministry for Health, Welfare and Sports, the pharmaceutical industry and patient organizations are in favour of self-medication, as they argue that self-medication increases the individuals' responsibility for their own health. Furthermore, it is cheaper (for the patient, in cases in which his mandatory deductible has not yet been used, and for society) and it does not consume the doctor's time.

However, others (such as care providers with practical experience) argue that, due to self-medication, some patients with more serious symptoms fail to go to the doctor or they go too late (Paes and Smit, 2005). Furthermore, it makes medication monitoring more difficult. Another point of consideration is the balance between unlimited access to self-medication products and patients' susceptibility to advertising, and the risk of overmedication or under medication.

Over-the-counter medicinal products could get a rating on environmental friendliness (e.g. with a pictogram), similar to energy labels.

This may raise awareness and influence the choice of users and the way they handle their pharmaceutical waste. In the case of diclofenac, research first needs to evaluate publicly the health consequences and the environmental consequences of diclofenac and its alternatives.

Environmentally unfriendly medicinal products could be charged with a removal fee.

This may lead to a change of the price of products and influence the choice of the medicinal products. In the case of diclofenac, this may increase the price. Insurers may consequently interact with prescribers to evaluate alternatives for diclofenac. Also for the medical alternatives, the information environmental effects should become publicly available and included in the evaluation.

6.2.2

Actors

Patient

Patients can buy OTC medicinal products for a specific symptom from a pharmacy, drugstore or retailer.

Drugstore, pharmacy or retailer

Over-the-counter medicinal products are available at several places, depending on the legal status governing the supply of the medicinal product. They can be sold by pharmacies only, by pharmacies and drugstores only or they can be available for general sale.

A drugstore selling PDO medicinal products is required to have a qualified chemist present at all times when selling OTC medicinal products. They have a responsibility to sell OTC medicinal products only to private users and they need to ask every patient if they need information or advice regarding the OTC medicinal product (the so-called checkout-check).

International comparison

Differences exist in the prescription of medicinal products between the Netherlands, Scotland and Germany (countries also involved in noPILLS in waters!). In all three countries, prescription is influenced by guidelines. However, in Germany there is also a strong influence from the payment system for physicians. The physicians receive a specific budget for a specific period of time for prescribing medicinal products; any overrun of the budget will be borne by the physician. Furthermore, whereas in the Netherlands and Scotland it is conventional that patients have a regular general practitioner, who knows the patient and his or her medical status (or has access to this information via practice records), in Germany this is not the case and patients are able to 'shop around' for a GP. GPs in Germany do not necessarily have an overview of the total medical status of the patient.

In Scotland, physicians will generally only prescribe those medicinal products that are on the formulary of the NHS, which means they will always be reimbursed.

The level of cooperation with pharmacies also differs between the three countries. In the Netherlands, the pharmacist and the physician cooperate relatively closely; pharmacists may consult the doctors when they think that the prescription is not optimal for the patient. In Germany the pharmacist has an advisory role vis-à-vis the physician. In Scotland, there is little cooperation between the community pharmacist and the physician; pharmacists only need to dispense medicinal product and not offer opinions or advice. Readily accessible advice on self-care and appropriate treatment of common conditions, however, is an important part of the role of the pharmacist in the community. For hospital pharmacies, this is different; here, pharmacists are responsible for medication review.

7 Phase 5: Disposal of medicinal products

Medicinal product residues may be excreted by the patient after medicinal product use. Besides this, non-consumption of medicinal products may result in disposal of medicinal products by patients, pharmacies or hospitals or other care institutions. The disposal of medicinal products may involve disposal of unused or expired medicinal products or the disposal of pharmaceutical waste resulting from the processing of medicinal products in hospitals and general pharmacies. Disposal of medicinal products from producing sites is not taken into account.

7.1 Disposal by patients and pharmacies

7.1.1 Processes

About one-third of the patients who use medicinal products in the Netherlands have unused medicinal products in their household occasionally, which they do not intend to use later on. Reasons for having these unused medicinal products include the death of the patient, a change in prescription, overly large package sizes, repeat filling of prescriptions without assessing the amount at hand, not seeing the need for continuing medication following a therapy, change of the doctor's or the patient's subjective perception of an improvement in their condition (Vogler. et al., 2014, Reitsma. et al., 2013).

Although preferably excess or out-of-date medicinal products should be returned to the pharmacy in the Netherlands, patients may dispose of them in several other ways. Surveys undertaken by the European Environment Agency suggest that a considerable amount of excess medicinal products is not returned to pharmacies for proper disposal (European Environmental Agency, 2010). According to a 2013 survey conducted in the Netherlands, about half of all patients return excess medicinal products to the pharmacy or the municipality's hazardous waste department; however, 6% of the patients reported that when they took excess medicinal products to the pharmacy, the pharmacy would not take them back. Approximately one-quarter of patients keep excess medicinal products at home, in case they will need them again sometime. One in 10 people throw excess medicinal products in the bin and 2% have reported that they have disposed of medicinal products in the sewer (toilet/sink) (Reitsma. et al., 2013).

Different factors have been suggested to influence disposal practices. Firstly, the type of medication may influence the way of disposal. During a survey in the Netherlands, when patients were asked how they disposed of particular classes of medicinal products, such as cough syrups, painkillers, and skin ointment or antibiotics, 52% and 42% of the participants said antibiotics and painkillers should be returned to the pharmacy, respectively. However, 27% would dispose of cough medications in the garbage or toilet and 26% in the sewage system. Only 27% of participants would return cough medications to the pharmacy (Blom et al., 1996).

Secondly, the environmental awareness of patients may also influence their disposal practices. In an international review, several studies found that patients who returned excess medicinal products to the pharmacy

did so out of a concern for the environment. On the other hand, patients who disposed of excess medicinal products primarily through the garbage or the sewage system did so for the sake of convenience (Tong et al., 2011). Furthermore, a survey in the Netherlands found that 60% of respondents knew that medicinal residues are found in the environment and that this may cause harm to themselves and the environment. However, this knowledge only moderately correlated with the intention to return excess medicinal products to the pharmacy (Berezowska A, 2009).

Thirdly, patient information and education on proper disposal practices seem important; often, as shown in a New Zealand study, people do not know what to do with excess medicinal products and in the USA it was shown that patients who were informed on how to return excess medicinal products to pharmacies properly were more likely to do so (Tong et al., 2011).

Lastly, the availability of official state guidelines for the disposal of excess medicinal products is a major influence on people's disposal practices. In the UK, more people returned excess medicinal products to pharmacies in 1996 compared to 1986; this may be due to campaigns focused on the proper disposal of medication promoted by the Royal Pharmaceutical Society of Great Britain in the 1990s. Conversely, no official guidelines for pharmaceutical disposal were set in the United States in the 1990s and this situation may have led to people in the US disposing of medicinal products conveniently in the toilet, sink or garbage at that time (Tong et al., 2011).

Patients could take unused and/or expired medicinal products to a collection point for minor chemical waste or bring it back to the pharmacy.

In the Netherlands, collection schemes with pharmacists are common practice. However, sometimes the municipalities charge the pharmacists for disposal of the "minor chemical waste", which discourages their cooperation.

More public awareness could be created of the fact that medicinal products are minor chemical waste, which needs specific handling. If returning medicinal products to the pharmacy is not possible, patients may choose to dispose of them in the garbage bin, but not in the sink or toilet.

Public awareness may lead to changes of disposal behaviour.

A deposit system for excess medicinal products could be applied: reward citizens financially for returning medicinal product to the pharmacy.

This measure may lead to changes of disposal behaviour. Prior to introduction of such a system, the risk of gaming (demanding too much medication to return it later) needs to be established and possible counter measures need to be included in the system.

All pharmacies need to dispose of their own medicinal waste and many pharmacies take in excess medicinal products brought back by patients. The KNMP argues that it is the pharmacists' social responsibility to take in, process and dispose of medicinal waste (KNMP, 2015), since pharmacists are experts in processing medicinal products, liquids and hazardous substances. However, many pharmacies have found that municipalities state that their medicinal waste falls under industrial waste and, as a result, they raise taxes on medicinal waste disposal.

Wanting to avoid extra expenses, pharmacies increasingly choose to refrain from the intake of excess medicinal products. This trend is not welcomed by the KNMP and other parties, such as the Ministry of Health, Welfare and Sports and the Ministry of Infrastructure and the Environment (KNMP, 2014).

The KNMP argues that there should be a clear regulation regarding this subject for all pharmacies in the Netherlands. In their opinion, the pharmacy should be responsible for the intake and processing of excess medicinal products, and the municipal waste service should collect this medicinal waste free of charge. They argue that because excess medicinal products are a form of minor chemical waste, it is primarily the municipalities' responsibility to dispose of this waste; the pharmacies are performing their societal duty by providing an easy (for patients) and responsible (for both patients and environment) manner of disposal, but they feel this should not result in an additional cost burden (KNMP, 2015, KNMP, 2014).

Recently, several parties took an interest in this discussion and the Ministry of Infrastructure and the Environment proposed agreements between municipality, pharmacy and municipal waste services that involve fewer or no barriers with regard to the intake and disposal of excess medicinal products (KNMP, 2014, Ministerie van VWS, 2015b).

Communal taxes that pharmacies have to pay for their company waste should be waived when this waste consists of unused medicinal products.

This measure could encourage pharmacies to organize a collection scheme.

Within the program 'Preventing Wastage in Care', The Dutch Ministry of Health, Welfare and Sports has proposed several additional ways in which the amount of unused medicinal products we dispose of may be reduced. The goal of this program is cost-effective and efficient health care, but some of the measures taken within the program are also beneficial for the environment. For example, the possibility of reissuing returned and unused medicinal products is being investigated. At this moment, this is not possible in the Netherlands because the pharmacy cannot guarantee that the quality of returned unused medicinal products is the same as that of a medicinal product that is dispensed for the first time. However, the KNMP and NVZA are currently investigating the conditions under which it might be a possibility (Ministerie van VWS, 2015a). Another option is to adapt package sizes to treatment durations; however, this is the responsibility of the pharmaceutical company and package sizes are often determined during the registration of medicinal products. Changing this at the national level is often not possible and repackaging leads to shelf-life and responsibility issues (Ministerie van VWS, 2014) (See also potential levers under 5.2.1. and 6.1.1.).

Allow (hospital) pharmacies to reissue unused, returned medicinal products

If the quality of returned unused medicinal products can be guaranteed, this may lead to a decreased need of product and a reduction of the total amount of waste to dispose.

Give users a discount when using reissued unused medicinal products.

This may influence the discharge behaviour of users, and reduce the amount of pharmaceutical waste.

Excretion of medicinal residues after use by patients

After use, medicinal residues are excreted through urine and faeces. Urine is a highly concentrated waste stream, containing relatively high concentrations of nitrate and phosphate, and the main part of the excreted medicinal and hormonal residues. A 2007 study analysed the human excretion pathways of 212 active pharmaceutical ingredients, equalling 1,409 products. On average, 64% of each API was excreted via human urine, and 35% via human faeces (Lienert et al., 2007). The excretion factors differ strongly among APIs. Paracetamol, for example, is only excreted in the original form for 5%, while naproxen for 95% (Vergouwen et al., 2011a).

Following oral or intravenous administration of diclofenac in healthy adults, about 50-70% of a dose is excreted in urine and about 30-35% is excreted in faeces within 96 hours. About 20-30% of a dose is excreted in urine as conjugates (Toxnet, 2015).

For certain specifically toxic medicinal products, the patient could be encouraged to use urine bags.

In principle it is possible, however, the wide use of diclofenac products might lead to enormous increase of the amount of waste in the form of used urine bags. The estimated use in NL is 2.4 mln prescriptions per year. However, pilot studies have shown that people who take contrast liquids for a CT scan are willing to use urine bags 24 hours after taking the liquids (e.g. Diels et al., 2015). This may be an indication that in cases where medicinal product use is limited and its subsequent excretion time as well, urine bags may reduce the excretion of medicinal product residues in the sewage system.

Technologies could be applied to prevent excreted medicinal residues being released into the sewer system, e.g. adapted toilets or mobile toilets (via hospital)

This is possible in hospitals or care centers. At the moment the first hospitals started with actions to provide mobile toilets for patients to use at home during the medication (e.g. Reinier de Graaf Hospital in Delft).

7.1.2

Actors

Patients

As described in Chapter 6.1.1. (adherence), many factors may lead to adherence problems and patients may not always use all of the prescribed or purchased medicinal products. When medicinal products are no longer used or their expiry date has passed, the patient needs to dispose of them. In the disposal behaviour, the patient is influenced by the convenience of different disposal options, his knowledge of the subject, and the information received from the pharmacy and/or health care provider. Furthermore, disposal behaviour may be influenced by regulation and by social surroundings (e.g. media, peers).

Sometimes, when returning unused medicinal products to the pharmacy is not found to be feasible or practical, patients may choose to dispose of them with their household waste. When the medicinal products are disposed of in the household bin, in the Netherlands this waste is

incinerated. However, waste that is flushed down the sink or toilet may enter the environment.

Consumption of medicinal products may also lead to the excretion of medicinal product residues by the patients, which usually end up in the sewer system.

Pharmacy

The pharmacy has been described in previous chapters in the light of its function of buying, preparing and dispensing medicinal products. Yet they also have a function with regard to the disposal of medicinal product waste. This concerns both the pharmacy's own medicinal product waste, as well as the unused medicinal products brought back to pharmacies by patients. In this function, pharmacies are influenced by legislation, both at the national level and from the municipality, and by the standards set by the KNMP. In the Netherlands, pharmacies are not legally required to take back unused medicinal products; most of them, however, provide this service to their patients (KNMP, 2015).

Municipality

The municipality is responsible for the collection and processing of (minor chemical) household waste. This includes the unused or expired medicinal products disposed of by patients. However, there are no strict rules on how this minor chemical waste disposal is organized (Rijksoverheid, 2015). Some municipalities choose to use disposal points; others use a minor chemical waste collection cart, which collects minor chemical waste at people's homes.

Municipalities are not responsible for the collection and processing of medicinal product waste from pharmacies that result from their own activities; this is considered industrial waste and companies themselves are responsible for contracting a waste company for collection and processing.

Excess medicinal products returned to the pharmacy by patients technically fall under minor chemical household waste, although it may be treated by municipalities as industrial waste. This causes issues due to which pharmacies may choose to refrain from taking back excess medicinal products.

The municipality is also responsible for the quality of the sewer system and consequently for the transfer of the medicinal residues in wastewater from households and hospitals to wastewater treatment plants.

7.2 Disposal by hospitals

7.2.1 Processes

Many aspects of hospital waste fall under a specific part of the National Waste Management Plan 2009-2021 (LAP2) called 'Specific Hospital Waste'. This concerns waste such as human or animal anatomical residues and infectious waste. Waste that falls in this sector is required to be disposed of in a specific, regulated manner (Ministerie van I&M, 2014). Medicinal waste is often prevented in hospitals, since units only receive a week's worth of medicinal products from the hospital pharmacy; if these are not all used, they may be able to be reused by the hospital pharmacy due to the controlled storage situation in the hospital. However, sometimes medicinal products expire or need to be

disposed of for some other reason. In this case, they are disposed of in the Specific Hospital Waste bin, which is used not only for medicinal products but also for infection-sensitive materials such as used gloves, needles and human anatomical residues resulting from surgery. By law, hospitals are responsible for the correct disposal of this waste, which is usually collected by a commercial waste-processing company specialized in the collection and decontamination of hospital waste.

Besides disposing of medicinal waste, hospitals are also important point sources where many medicinal residues are excreted into the sewer system. Because hospitals deliver high concentrations of medicinal product residues in relatively small volumes of wastewater, it may be possible to address the issue at the source. In the Netherlands, some pilot studies have examined this possibility (Vergouwen et al., 2011b). For example, Water Authority Groot Salland (WGS) has experimented with the development of a purification concept for the entire wastewater stream from a local hospital, which resulted in the successful removal of certain medicinal residues from the wastewater stream (PILLS, 2012). Furthermore, WGS launched a pilot to examine the acceptance of patients who had to take radiographic iodinated contrast media to undergo a CT scan to use urine bags to prevent the excretion of medicinal residues into the sewer system (WGS, 2014).

A new promising development regarding the treatment and disposal of hospital waste is on-site treatment of hospital waste using the Pharmafilter concept. This technique is used in the Reinier de Graaff Hospital in Delft, the Netherlands, and currently implemented in a number of other hospitals. It concerns an integral concept for the processing of waste streams in hospitals and care homes. Shredders are used instead of the traditional bedpan cleaners and through the sewage system, all waste from the shredders is collected and treated on-site. Almost all types of waste can be shredded and flushed through the existing sewer system. An on-site installation digests and decontaminates the solid waste, and purifies wastewater (see 2.7.2). The concept has been tested in practice and has been found to be successful (Batelaan et al., 2013).

Hospitals could purify their wastewater on-site, e.g., using the Pharmafilter system.

This leads to a decrease of discharge to surface waters.

7.2.2

Actors

Hospital

By law, hospitals are responsible for the correct disposal of this waste, which is usually collected by a commercial waste-processing company specialized in the collection and decontamination of hospital waste.

Waste-processing company

Waste-processing companies specialised in the collection and decontamination of hospital waste are contracted by hospitals. The collect and decontaminate hospital waste, before further processing.

International comparison

The conventional routes for disposal of unused medicinal products differ between Scotland, Germany (North-Rhine Westphalia) and the Netherlands. In contrast to the Netherlands, pharmacies in Scotland are legally required to take back unused medicinal products. Yet not all pharmacies do so and not all pharmacies know the correct protocols for disposing of medicinal waste. Furthermore, taking unused medicinal products back to the pharmacy is not a well-known disposal route for patients. The disposal of medicinal waste by pharmacies and hospitals is paid for by NHS. Nursing homes need to pay for their own disposal. In the Netherlands, municipalities are responsible for the recollection of waste, also for medicinal waste. Medicinal waste may be collected by pharmacies (which is not legally required) or collected as minor chemical waste. In both instances, it is treated further as minor chemical waste.

In NRW, patients are advised to throw unused medicinal products in the bin, since all household waste is incinerated there.

Furthermore, the results from the noPILLS in waters!-project in Scotland and Germany show that people say they are willing to dispose of medicinal products in a more environmentally sensitive manner once they are aware of

International comparison

With regard to treatment of wastewater and household waste, differences exist between the Netherlands, Germany (North Rhine – Westphalia; NRW) and Scotland. Whereas in the Netherlands and Germany, there is a sewer system (almost) everywhere), in rural areas in Scotland, also septic tanks and sump pits are used. The Netherlands and Germany (NRWF), more than 95 % of the wastewater is treated in municipal wastewater treatment plants. In the Netherlands all sewage sludge is incinerated, in NRW most of the sludge is incinerated, but some is used on agricultural land (sometimes after anaerobic digestion to gain energy, sometimes after composting). In Scotland's rural regions, there is strong reliance on private micro-treatment plants and soil infiltration, and about 50% of the wastewater sludge is recovered for recycling to agricultural land. In many of the other German Bundesländer, sewage sludge is also widely applied on agricultural lands.

Similarly, most solid waste is incinerated in North Rhine-Westphalia and the Netherlands; however, in Scotland most of the solid waste is landfilled, with the risk of pollutants leaching into groundwater and surface water. This difference in organization of waste treatment also suggests a different approach to informing the public on how to dispose of excess and out-of-date medicinal products. In Germany most solid waste is incinerated (North Rhine Westphalia) and therefore medicinal product recollection schemes were discontinued, and people are advised to dispose of such waste as solid municipal waste.

8 Phase 6: Treatment of waste containing medicinal residues

8.1 Wastewater treatment

8.1.1 Processes

8.1.1.1 Wastewater collection and transport

After use, residues of medicinal products are excreted by the patient and flushed into the sewer system. Medicinal products may also end up in the sewer system if the patient disposes of them via the toilet or sink. Sewers transport wastewater to the wastewater treatment plant (WWTP). 80% - 90% of the medicinal products in wastewater originate from households. The remaining 10 – 20% originate from hospitals, nursing homes and care homes (van der Hoek et al., 2013). In more rural areas, septic tanks are sometimes used to collect and treat wastewater.

Collection and transport via sewage system

In the Netherlands, almost all wastewater is transported through sewer systems to a treatment plant. The discharge of untreated wastewater into surface water on a regular basis in the Netherlands is negligible (Helpdesk Water, 2015), but occasionally during heavy rainfall, the sewage system may overflow into surface water (Vergouwen et al., 2011a). Insufficient maintenance of sewers (many sewer systems are older than 5 decades) may have led to leakages, resulting in direct pollution of soil and groundwater. Two distinct types of sewer systems exist: mixed sewer systems and separated sewer systems. In mixed sewer systems, both wastewater and rainwater are transported to the treatment plant. The amounts of rainwater can temporarily increase to such an extent that the sewage water is discharged untreated via an overflow into the surface water, thus contaminating the receiving water. In separated sewer systems, the wastewater is transported separately from rainwater to the treatment plant for purification. In this way, discharge via overflow of wastewater is almost absent, because no big variations in the transported water volumes occur. Because of their specific physicochemical properties, partial degradation of some groups of medicinal products may occur during transport in the sewer (van der Hoek et al., 2013, Struijs, 2015).

The design/selection of sewer systems could be improved, including its maintenance to prevent leakages (Municipalities).

This could prevent direct infiltration of diclofenac from sewers into soil and groundwater. Also for other reasons mixed sewer systems are less desired and applied, resulting in reduction of the number of overflow events.

Collection and transport via septic tanks

In rural areas, wastewater may be collected and treated in septic tanks, when construction of a sewer system is not efficient or possible. In a septic tank collection and purification of wastewater occurs, before it is discharged into nearby surface water. This purification is done with help of bacteria that degrade organic contaminants. Medicinal products and medicinal product residues (especially antibiotics) can have negative

effects on these bacteria in the septic tank and, in a worst-case scenario, terminate the purifying functionality of the septic tank.

Use of urine bags during medication with antibiotics (patients)

Diclofenac is not an antibiotic. The wide application of antibiotics makes the application of urine bags less obvious. The use of septic tanks is decreasing in the Netherlands, thus the problem will fade out.

If this happens, untreated wastewater including medicinal products and residues are discharged into nearby surface water. A second risk of the presence of antibiotics in wastewater is the development of antibiotic resistant bacterial communities. Homeowners are advised by manufacturers of septic tanks not to flush away medicinal products via the toilet or sink. Residues excreted by humans, however, cannot be avoided.

Optimization of the septic tank (municipalities)

For diclofenac: Septic tanks are locally applied low cost, low technology devices. Better purification efficiency could be reached by avoiding septic tanks and connect the households with the sewer system.

8.1.1.2 Wastewater treatment

Historically, municipal wastewater as well as industrial process water have been treated before being discharged into surface water for hygienic reasons. Depending on the type of plant, treatment processes can be adapted to the specific compounds present in wastewater. So far, the choice for the type of treatment plant is dependent on the local situation and the (expected) composition of the wastewater. After treatment, in the Netherlands the sludge of the treatment plant is burnt in an incineration plant.

Municipal wastewater treatment

Wastewater treatment plants were originally designed for hygienic reasons, the removal of organic material, including pathogens, nitrogen and phosphate, not specifically for the removal of medicinal residues. Still, a large reduction (on average 65%, van der Hoek et al., 2013) in medicinal residues can be achieved during the normal process of purification. However, depending on their polarity, water solubility and persistence, purification of medicinal residues ranges from 0% to 100% and the remaining may enter the surface waters or sludges (Monteiro and Boxall, 2010, Struijs, 2014, Vergouwen et al., 2011a, Derksen and ter Laak, 2013b). For the removal of the remaining residues, extra purification steps may be required. A distinction can be made between adsorption techniques (such as activated carbon), oxidative techniques (such as ozonation) and membrane filtration. Usually a combination of treatments is required to remove all residues. However, the influent may contain a relatively high amount of poorly biodegradable organic matter, which can limit the effectiveness of the aforementioned techniques. A drawback of destructive techniques such as ozone could be that potentially toxic metabolites of treated medicinal compounds (and other compounds in the wastewater) end up in the water that is discharged. Also membranes are likely to pollute quickly (PILLS, 2012, Bäuerlein et al., 2013).

Because of the high concentrations of organic matter in the wastewater and the consequential high costs related to the application of these techniques for wastewater treatment, most of these treatments are mainly used for the production of drinking water from surface water and, to a lesser extent, the treatment of wastewater (van der Hoek et al., 2013).

Exchange of information on the chemical and ecotoxicological characteristics of medicinal products between the pharmaceutical industry and the manager/developer of the wastewater treatment facilities and techniques

Development of a publicly available database of the chemical characteristics and ecological and ecotoxicological effects of medicinal products would improve the data availability for regulators and water managers. It would provide direction to the development of monitoring programs and treatment facilities. Such information is at present not publicly available, as it is considered trade secret.

Adaptation of legislation ((European) Government)

Based on monitoring and (eco) toxicological information ecological quality standards may be derived. Such standards are absent at present, which hinders risk management.

Optimization of the management of the treatment plant by determining and assessing standards. (Municipality)

Based on ecotoxicological data the municipality might give effluent concentration criteria for diclofenac in the environmental permit.

Application of extra purification steps (Water Authority)

Fent et al. (2006) describe that removal of polar compounds such as diclofenac may be effective by advanced oxidation techniques (e.g. ozonation or UV radiation), sorption to activated carbon, or membrane filtration. Sand filtration and iron flocculation were not shown to be effective. However, the effectiveness of techniques is very much dependent on the total composition of the wastewater, and is not the same for each compound. Therefore, the economic consequences have to be evaluated carefully before investing into these advanced treatment technologies on a larger scale. Diclofenac consists in the order of 0.005% of the total waste concentration of the effluent of wastewater treatment plants.

Make environmental information on medicinal products publicly available to aid the manager/developer of the wastewater treatment facilities and techniques (Industry)

At present, water managers do not have knowledge about the physical, chemical and toxicological characteristics of the compounds they have to purify the water from, e.g. diclofenac. Information provided by producers may help to optimize the purification techniques. On the other hand, wastewater treatment technologists may inform drug developers on the type of chemicals that might cause problems in purification systems. Drug developers may take this information into account as one of the development criteria, when designing new drugs.

Benchmark effectivity of waste treatment (water authorities, governments)

This gives insight in the relative effectiveness of treatment plants, giving possibilities to learn from best practices.

Legislation influences the treatment of wastewater by setting standards for the effluent concentrations and the disposal of the sludge. National legislation is often a translation of EU legislation on, for example, effluent concentrations and surface water quality criteria. Both national and international legislation can determine the choices a municipality makes. By assessing the financial consequences of different treatment processes, the municipality can request changes in the treatment. These considerations are often closely related to the legislation.

As a result of the treatment process (both in the wastewater treatment and septic tank), sludge is produced. This sludge consists largely of organic matter, including medical residues and other contaminants. In the Netherlands sludge is incinerated at special plants, but also in cement kilns and at power plants (de Zeeuw and Baas, 2010). The disposal of sludge from wastewater treatment plants in landfills or the reuse of sludge on agricultural land (as fertilizer) is no longer practised in the Netherlands due to national legislation.

Industrial wastewater treatment

Wastewater from pharmaceutical industries is either treated in the municipal wastewater treatment plant (if the manufacturer is licensed for that) or it is treated at industrial wastewater treatment installations at the production and development site of medicinal products. We have no data on such plants in the Netherlands.

According to Monteiro and Boxall (2010) medicinal products are produced by using organic solvents that are reused in the synthesis process and are then treated or disposed of by incineration. According to Williams (2005), most waste generated during the production process is solid in nature and this material is commonly incinerated, meaning the discharges of medicinal products in wastewater from manufacturing processes are probably small. In Europe, the releases from pharmaceutical manufacturing are generally well-regulated, however in countries with a less stringent environmental policy the concentrations in surface water may be very high (Larsson, 2014).

Optimization production process (Industry)

Optimization of the production process might reduce emissions of diclofenac.

Optimization wastewater treatment (Industry)

Optimization of the wastewater treatment might reduce emissions of diclofenac.

8.1.2

Actors

Government

Currently there is no European regulatory framework in which the environmental consequences of human medicinal product discharge play a role in the admission of medicinal products.

Implementation of legislation on the discharge of medicinal products and environmental quality criteria concerning their concentrations ((European) government)

At the moment there is no legislation at all on maximal risk levels of specific medicinal products. Based on knowledge that can be obtained from public sources, such quality criteria might possibly

be derived for diclofenac. This could then be confronted with the results of the monitoring activities performed within the framework of the European Water Framework Directive.

In the Water Act and the Environmental Management Act, the national government sets regulations governing the transport, collection and discharge of wastewater. These acts state the competent authority for managing wastewater and the regulations for specific discharges. Nationally, the government is developing an approach covering the entire medicinal product chain, from production to the disposal phase, for the reduction of the pollution in surface waters, among other places (I&M, 2014, I&M, 2015).

Competent Authority for the collection of wastewater

In general, in the Netherlands the municipality is the competent authority for the collection of wastewater. Yet sometimes the province or the national government can play this role. In addition, the Water Authorities (responsible for the purification in the treatment plant) can set certain conditions (e.g. regarding quantity of wastewater) that must be taken into consideration.

In the Dutch Environmental Protection Act, it is stipulated that the municipality must collect all wastewater released from parcels within its territory. Furthermore, it is responsible for transport of wastewater through a public sewer system to a sewage treatment plant and to maintain the condition of the sewer. It may also choose to use alternative ways to collect wastewater, such as septic tanks for houses in rural areas. In its decision on the type of sewer system to be used, the municipality is influenced by local factors (such as the amount of rainwater, number of residents and the territory of municipality), financial considerations (such as construction costs or maintenance costs of the sewer) and (inter)national legislation. The municipality is obliged to report a municipal sewage plan, containing issues concerning the management of the sewage.

Water Authorities

A Water Authority (Water Board) is responsible for the management of water in a particular area. In the Netherlands, there are 23 Water Authorities. The members of a Water Authority are elected by public voting. The duties of a Water Authority include:

- water management (quantity and quality of water);
- water safety (e.g. dike maintenance);
- sewage treatment (wastewater treatment).

Water Authorities align with the competent authorities concerning the amount and the way of sewage water transport to the sewage treatment plant. The Water Authority decides which (combination of) wastewater treatment techniques are selected and how to handle the resulting sludge. Sludge from the wastewater treatment can be incinerated, but several initiatives have come forth to recycle (components of) the sludge, in compliance with legislation. Dried sludge can be used as fuel for producing electricity, thus providing economic value, a technology, which is progressively applied.

Pharmaceutical companies

The role of the pharmaceutical industry in wastewater treatment is determined by the treatment of the wastewater that originates during the production process of medicinal products. In this process, the industry is in direct contact with the municipality and the Water Authority via its licensing, depending on regulations on concentrations of compounds in wastewater. In addition, the Water Authority and industry may have direct contact, for example, on how to treat medicinal residues.

Industry lobbies for favourable legislation with regard to production and authorization of medicinal products (Permanand and Mossialos, 2005). However, it is conceivable that, in the near future, this focus will also include the topic of water treatment, due to societal concern as a result of increasing concentrations in surface water and due to the fact that a couple of pharmaceuticals have been added onto the 'watchlist' within the Water Framework Directive (see paragraph 1.2).

The required production process of a medicinal product limits the decisions that the producer can make. Its first priority is to deliver a qualitatively good medicinal product and all other choices will depend on this process.

The producer is restricted by legislation governing the quality of its wastewater. Depending on the required quality, a producer can improve its production process or treatment plant.

8.2 Solid waste treatment

8.2.1

Processes

Minor chemical and hospital waste management

The national legislation governing waste disposal (LAP2) provides guidance for the reuse and disposal of waste in general (including medical waste) (Ministerie van I&M, 2014) 2014) In the Netherlands, unused medicinal products disposed of by patients are classified as minor chemical waste, which should be collected separately from general (household) waste.

Waste disposal is regulated via (inter)national regulations. Minor chemical waste in the Netherlands is always incinerated. Minor chemical waste is incinerated at a high temperature to avoid formation of harmful compounds during incineration.

Unused medicinal products originating from hospitals also have to be processed. These medicinal products are collected in special hospital waste bins, together with infection-sensitive materials such as used gloves, needles and human remains. After decontamination, either by extreme heating under moist conditions (sterilization) (not incineration or dry heating), ozone or radiation, hospital waste is further processed. It can be incinerated as commercial waste or be used as a secondary fuel source in a licensed installation.

Municipal waste incineration

When household waste containing medicinal products is incinerated at municipal waste incineration plants, medicinal residues may be found in the remaining ashes, or be emitted into the air.

Incineration companies have to dispose of the ashes/slag. Ashes can either be landfilled or, under certain regulations in the Netherlands, it is possible to reuse ashes and slag as a building or construction material.

Although leaching from the ashes/slag is controlled and strictly regulated. The reuse of ashes and slag can have financial benefits for the incineration company because the product is no longer classified as waste. If the ashes are landfilled, contact with soil is prevented as much as possible, but emissions as a result of the degradation of the sealing and leakage can still cause contamination of soils. According to Monteiro and Boxall (2010), pollution may also result from disposal of incinerated pharmaceutical waste in landfills that are not well isolated. Either way, the ashes and slag have to comply with the terms and conditions mentioned in the relevant legislation.

**Adaptation of the legislation on reuse of slag and ashes.
(Governments)**

There is no reason to expect diclofenac residues in slag and ashes. If waste is properly incinerated, no medicinal product residues are to be expected in the solid (mineral) rest material.

Incineration of waste also causes emissions into the air via vapours and fly ash. By law, (e.g. Directive 2000/76/EC), measures must be taken to limit emissions into the air. This is usually done with a flue gas cleaning system and air emission registration. Fly ashes, which are caught by the cleaning system, can either be landfilled or reused as building materials with the same (dis)advantages and legislative rules as ashes and slag.

Control effectiveness of cleaning techniques for exhaust gases from waste incineration plants (waste industry, government)

There is no reason to expect diclofenac in exhaust gases. Mineral components in medicinal products (e.g. chloride and metals) may give rise to formation of toxic contaminants in fly ash and exhaust gases.

In the process of waste management, the municipality has to act within the framework of national and international legislation, which is drawn up by the EU and the Dutch government. Both legislation and financial considerations are reasons to determine whether ashes are reused or landfilled. If the ashes have to be landfilled, this will cost money, while reuse can generate money.

Landfilling of waste

In the Netherlands, municipal waste is not landfilled.

Landfilling of sewage sludge or application in agriculture

In the Netherlands sewage sludge is incinerated and neither landfilled, nor applied as fertilizer in agriculture.

8.2.2

Actors

Municipality

After collecting minor chemical waste, the municipality is responsible for further disposal. In the process of solid waste management and disposal, municipalities have to comply with standards set by (inter)national government.

Municipal waste incineration companies

The incineration companies incinerate solid wastes, under environmental legislation from either international law (e.g. Directive 2000/76/EC) or

national legislation (e.g. Environmental Management Act VROM 2004b). For medicinal wastes, two types of incineration companies are relevant: the regular high temperature incineration plants, which specifically meant for incineration of (minor) chemical waste (in the Netherlands also medicinal products) and the special incineration plant ZAVIN. Until 2010, ZAVIN was the only licensed incinerator in the Netherlands to incinerate hospital waste, but with the third amendment to the first National Waste Management Plan (VROM, 2004b), the disposers got the option of pre-treating their waste so that it can be disposed of as commercial waste, thus enabling regular waste companies to incinerate hospital waste as well.

Landfill sites

The EU states that member states should encourage the reuse of waste by removing any harmful substances as much as possible (Directive 2008/98/EC, 2008). Therewith landfilling of medicinal waste is discouraged but not necessarily prohibited.

In the Netherlands it is not allowed to landfill minor chemical waste unless it cannot be recycled or incinerated. In such cases, it needs to be stored at a landfill under safe conditions. For most medicinal products this is not the case (with a possible exclusion of radioactive materials). In practice, medicinal product waste is not landfilled in the Netherlands.

Hospitals

By law the hospitals are responsible for the correct disposal of their waste, which is usually done by a commercial company, specialized in the collection and decontamination of hospital waste. This waste is incinerated.

A new development related to the treatment and waste disposal of medicinal products in hospitals, is the onsite treatment of virtually all hospital waste and not only medicinal product residues in wastewater. This Pharmafilter technique is developed and used in the hospital Reinier de Graaf Gasthuis in Delft, the Netherlands. The aim is to use (biodegradable) bioplastics in disposables (e.g. bedpans, intravenous bags and urinals made from bioplastic), that can be digested together with kitchen waste and primary sludge. The shredded material, together with leftover food and other specific hospital waste is flushed, together with the wastewater from showers, washbasins and toilets, through the existing internal sewer system of the hospital. Thus the waste will contain medicinal residues, cytostatics, contrast liquids and endocrine substances. An on-site purification plant cleans, digests and decontaminates the solid waste, thereby producing biogas. The solid residue (remaining plastic and other materials) that has not been digested is recycled. All wastewater is purified. First results proved to be positive: approximately 100 medicinal residues were tested and no observable traces (all below detection limit) were found. This also applies to fire retardants, hormone-disturbing substances and X-ray contrast fluids (Batelaan et al., 2013). The purified wastewater is reused in the hospital as grey water for the flushing of toilets and filling of boilers. Unused medicinal products are not discarded via the Pharmafilter but collected and returned to the hospital pharmacy for further processing. Because of the success of the Pharmafilter, other hospitals are implementing it as well. In the Netherlands there are now three Pharmafilters in use.

Implementing hospital on-site treatment systems like Pharmafilter (Hospitals)

Application of on-site wastewater treatment prevents discharge of diclofenac residues from hospitals into wastewater.

Replacing reusable bedpans and urinals with single use products that are shredded has been found to be efficient for care workers and decreases infection rates.

Non-profit organizations / general public

Both non-profit organizations and the public can influence the decision-making by the municipality. By questioning, lobbying, protesting or through public debate, they can raise awareness for improvements or more environmentally friendly or socially acceptable choices.

Non-profit organizations and the public can also influence (inter)national policymaking. For the EU legislative process, the public and (non-profit) organizations can usually participate via consultation procedures.

European government

National legislation is often an interpretation of the international legislation of the EU. Based on 'Impact assessments', the EU investigates the potential of new policies by determining the economic, social and environmental consequences that they may have. If the European Commission, the European Parliament and the Council agree on the proposed legislation, it is adopted.

For waste management and disposal, several Directives are relevant, such as:

- Directive 2008/98/EC on waste (and repealing certain Directives);
 - Directive 2000/76/EC on the incineration of waste;
 - Directive 1999/31/EC on landfill of waste.
- After adoption by the European Parliament such directives have to be implemented in the national legislation of the member states.

Dutch government

Member states incorporate European Directives in their national legislation. According to the Dutch Environmental Management Act and various international guidelines, (which the Netherlands periodically publishes one or more waste management plans. In 2003, the first National Waste Management Plan (LAP) (VROM, 2004a, VROM, 2004b) was enforced and was in effect from 2003 to 2009. The current second LAP is valid from 2009 to 2015 and looks ahead to 2021. In the LAP, the general waste management policy is described, including an annex that elaborates on policy with respect to specific (categories of) waste. The 'traditional' activities, such as waste separation, collection, recovery, incineration and landfilling are discussed, as are monitoring and enforcement.

9 Phase 7: Fate of medicinal residues

9.1 Fate in the environment

9.1.1 Processes

Fate in surface water

Purified wastewater that is discharged into surface water still contains medicinal product residues. Another possible exposure pathway to surface water is the disposal of sewage sludge on agricultural soils and possible runoff after rainfall. In the Netherlands, however, the reuse of sewage sludge for agriculture is not allowed, but in other countries this can be a relevant exposure route. In the Netherlands the application of manure on agricultural land is a route for spreading of medicinal residues from veterinary use into the environment.

Currently, the measured levels of individual pharmaceutical residues in surface water are below therapeutic concentrations, (van der Aa et al., 2011a, Moermond, 2014), but the concentrations are increasing, as is the number of different medicinal product residues detected (Monteiro and Boxall, 2010). It is known that some medicinal product residues have a direct effect on aquatic organisms (e.g. hormone disruption and behavioural changes). Many publications on effects of pharmaceutical residues in surface water are being published (e.g. Arnold et al., 2014, Brodin et al., 2014, Gaw et al., 2014, Küster and Adler, 2014, Säfholm et al., 2014, Derksen and ter Laak, 2013b, Derksen, 2015, Vergouwen et al., 2011a). The fate of medicinal product residues in the aquatic environment is determined by sorption to sediments and/or degradation by abiotic and/or biotic processes. Hydrophobic compounds may sorb to sediments whilst hydrophilic compounds may be degraded. Abiotic degradation may occur via hydrolysis or photodegradation. Microbial degradation in surface water usually proceeds much slower than during sewage treatment, because surface waters have much less diversity and density of bacteria (Monteiro and Boxall, 2010). Furthermore, organisms in water are exposed to the dissolved medicinal compounds via dermal contact or consumption of water and dissolved organic compounds with medicinal residues to them.

Fate in groundwater and soil

Via natural processes, the medicinal product residues in surface water can also migrate to groundwater. The amount in which this happens depends on the physicochemical properties of medicinal residues, the (biological) degradation of the medicinal residues (original active pharmaceutical ingredients, as well as their metabolites), and the sorption thereof, to dissolved organic matter in surface water or to soil and sediment particles.

Surface water and groundwater are in open contact with each other. The rate of exchange of surface water and groundwater depends on the local situation. When the groundwater level is high, e.g. in the Netherlands, where the groundwater level is often less than 50 cm below the surface level, there is open and direct contact between groundwater and surface water, resulting in a very quick exchange.

Also in sandy regions, the infiltration of surface water to the groundwater may be very fast. In clay soils the infiltration will be

slower. However, due to inhomogeneities in soil, it is hard to predict how fast chemical compounds present in surface waters will partition in the groundwater.

In the Netherlands, medicinal products in groundwater reservoirs have been observed and are measured in concentrations up to more than 100 ng/L (Versteegh et al., 2007, Houtman et al., 2014).

Possible contamination pathways for soil and subsequently groundwater are: the disposal of sewage sludge on agricultural soils and subsequent leaching to ground waters after rainfall, leaching from (old) landfills that contain medicinal product residues or via direct contact with surface water. The first two routes are less likely in the Netherlands, because by law landfilling medicinal product waste or reuse of contaminated sludge on soil is not allowed. Old landfills might still release some medical residues, but not to a large extent. In the case of broken sewers, groundwater can be contaminated directly with medicinal product residues.

Like for surface water, also in soil and groundwater, the medicinal residues can have direct effects on the ecosystem. Sorption of medicinal product residues in soils is an important process because their association with soil particles affects potential mobility (Karthikeyan and Bleam, 2003) and availability for degradation. Due to a wide range of chemical properties and soil types, sorption of the same compound in different soil types can vary significantly. According to (Díaz-Cruz et al., 2003), the more important mechanisms for sorption are associated with organic matter, ion exchange, surface adsorption to mineral constituents, hydrogen bonding and formation of complexes with ions such as Ca^{2+} , Mg^{2+} , Fe^{3+} or Al^{3+} . These processes are applied in purification of waters for the production of drinking water by infiltration of surface water in the dunes and by induced bank filtration, where surface waters are infiltrated in soils by pumping from a nearby waterbody, so-called riverbank filtration (Ray, 2002).

Environmental characteristics such as climate and soil type also affect the fate and behaviour of medicinal residues. Potential bioaccumulation and the persistence of released medicinal products and the combined effects of several medicinal products are of concern (Monteiro and Boxall, 2010).

Diclofenac is highly soluble and will therefore be mobile and available for exposure to organisms in surface waters and transport to groundwater. Diclofenac degradation in surface water occurs mainly under influence of sunlight (photolysis). Some of the phototransformation products of diclofenac carry a higher toxicity than the parent compound, as has been reported by several studies on the toxicology of diclofenac in algae (Schulze et al., 2010). In soil and groundwater, the degradation is very slow.

A special point of concern is application of diclofenac as a veterinary drug. The experience with predators (vultures) preying on diclofenac treated cattle carcasses, points to the proper discharge of such carcasses (Oaks et al., 2004, Arnold et al., 2014). An additional point of attention is that the waste from farms where cattle is treated with diclofenac is not treated in a sewage treatment plant (STP) and this might lead to increased diclofenac concentrations in the environment, when it is spread with the manure.

Diclofenac can be found in the environment in surface waters, and in groundwater bodies. Based on a review of (Toxnet, 2015) concentrations in surface waters are in general the order of 100-200 ng/L. In Spain, concentrations up to more than 3000 ng/L were measured. Acuña et al. (2015) report a median concentration of 21 +/- 722 ng/L as a result of a literature review covering 38 countries. Versteegh et al. (2007) report diclofenac in a concentration up to 84 ng/L in surface water that is used for drinking water, 12 ng/L in groundwater and 18 ng/L in drinking water.

Acuña et al. (2015) report in their review a great number of LOEC (Lowest Observed Effect Concentration) values for surface water organisms. They range from 10 ng/L to 40 mg/L. The relationship between the LOEC values and the environmental concentrations in that review is given in figure 3 (paragraph 2.2): LOEC values are partly overlapping with the observed concentrations in freshwater ecosystems. Reviews of ecotoxicity of diclofenac for different organisms can also be found in Fent et al. (2006) and Toxnet (2015). A mixture of NSAID (diclofenac, ibuprofen, naproxen, acetylsalicylic acid) has been evaluated using acute Daphnia and algal tests. Toxicity of the mixture was found at concentrations at which the single compound showed no or only little effects. The mixture toxicity followed the concept of concentration addition, which means that the concentrations of each compound behaved in an additive fashion (Fent et al., 2006). These data indicate that for the acute toxicity of this group of pharmaceuticals, concentration addition can be assumed, which means that the concentration of each individual pharmaceutical has to be added for the combination effects. This implies that compounds occurring at concentrations below their individual NOEC can nevertheless contribute to the total effect of the mixture. Studies on the Eurasian otter (Lutra lutra), indicates that oral and/or dermal exposure to diclofenac and ibuprofen is taking place in the UK. Renal lesions observed during carcass necropsies have prompted recommendations that future studies examine exposure of otters to nephrotoxic agents such as NSAIDs. In general, top predators are likely to be most susceptible to pharmaceuticals that bioaccumulate and bioconcentrate in prey (Arnold et al., 2014, Shore et al., 2014). The bioconcentration factors of diclofenac in aquatic species factors were 10-2700 in the liver of fish and 5-1000 in the kidney, depending on exposure concentrations (Fent et al., 2006). Diclofenac is on the Watch list of substances for Union-wide monitoring as set out in Article 8b of Directive 2008/105/EC (2008). Article 8b of Directive 2008/105/EC provides for the establishment of a watch list of, in the first instance, up to 10 substances or groups of substances for which Union-wide monitoring data are to be gathered for the purpose of supporting future prioritisation exercises in accordance with Article 16 of Directive 2000/60/EC of the European Parliament and of the Council.

9.1.2 *Actors*

There are no actors involved directly in this process. Reduction of the existing pharmaceutical load in groundwater is only influenced by local autonomous environmental processes. To prevent a new pharmaceutical load in surface water and groundwater, action can be taken by actors higher up in the chain.

Indirect actors that play a role are the general public (they enjoy recreation in the environment), environmental and nature organizations (they aim to protect the intrinsic value of ecosystems) and the general public, including governments, who profit from ecosystem services (e.g. TEEB, 2010).

9.2 **Residues in natural resources for human consumption**

9.2.1 *Drinking water*

9.2.1.1 Processes

In the Netherlands, almost 40% of the drinking water originates from surface water and 60% originates from groundwater (van der Hoek et al., 2013).

For the purification of both groundwater and surface water for use as drinking water, the purification of medicinal product residues results in additional costs because an additional purification step has to be added. A distinction can be made between adsorptive techniques (activated carbon), oxidative techniques (ozone, or irradiation with UV light combined with a dose of hydrogen peroxide) and membrane filtration (nanofiltration and reversed osmosis). Activated carbon removes mainly non-polar substances. More polar compounds, including most medicinal products, are only partially removed (Fent et al., 2006).

Using additional treatment steps to improve the drinking water quality (producers and consumers).

Diclofenac can be degraded by oxidative techniques. However, also other compounds are degraded under such conditions, resulting in uncontrolled formation of toxic compounds.

When oxidative techniques are used, medicinal residues undergo a chemical reaction. In general, the degradation of medicinal products using these processes is high, but not all medicinal products can be degraded. Moreover, these reactions also result in reaction products of the other chemical compounds in the wastewater, which remain present in the water. Membranes create a waste stream (concentrate) in which the removed medicinal products are present in a concentrated form (Bäuerlein et al., 2013). For all these techniques, the removal costs are relatively high, and increasing the treatment level may not always be a sustainable option for economic reasons as well as for the use of basic materials and the creation of waste.

The summed concentration of medicinal products in drinking water in the Netherlands is on average 100 ng/L in drinking waters produced from Rhine and Meuse water, and up to 150 ng/L in drinking water produced from groundwater (Houtman et al., 2014). This is in the same range as reported earlier by Versteegh et al. (2007). The quality of surface water as a source for drinking water is under pressure due to climate change (Wuijts et al., 2012).

9.2.1.2 Actors

Drinking water companies and food industry

The drinking water company is responsible for the delivery of high quality drinking water. This drinking water originates from either surface water or groundwater. To remove medicinal products from surface or groundwater the drinking water companies have to use additional treatment steps. This entails additional costs for the companies. Factors that influence the decision on the type of treatment are: volume and of quality source water, financial aspects, type of compounds present and technical possibilities.

Next to drinking water companies, also the food industry uses great amounts of water, e.g. the canning industry, breweries and producers of mineral water.

Consumer

The consumer of drinking water expects water of good quality. This is interpreted in several ways by different groups of consumers. Some groups define good quality as being in compliance with the maximum allowable concentrations of contaminants; other groups do not want any traces of contaminants in their drinking water.

Versteegh et al. (2007) and Houtman et al. (2014) report the presence of diclofenac in drinking water. So far, it is assumed that the concentrations are low enough to not expect human health effects. However, the use of medicinal products will increase due to economic and demographic developments and this means that action must be taken to prevent increased concentrations in drinking water and in the environment.

Public awareness-raising on the possibility that the concentration of pharmaceutical residues in drinking water might increase to unacceptable concentrations

For diclofenac, Houtman et al. (2014) conclude that effects are not to be expected.

Installation of an extra purification device at the tap in the houses

For diclofenac this is an option. In other countries, the application of filters on drinking water taps is applied and also in the Netherlands such filters are for sale.

It must be clear that the use of bottles drinking water in The Netherlands is not an option, as the quality of the Dutch drinking water is better than the quality of water from plastic bottles.

9.2.2 Crops

9.2.2.1 Processes

Surface water is also used for the irrigation of agricultural land by farmers. The extent to which the uptake of medicinal residues by crops and farm animals might be possible is unclear. Another potential source of pharmaceutical ingredients is through the application of animal manure in agriculture.

Both surface water and groundwater can be used by farmers for the irrigation of crops in agricultural lands. Some medicinal products can bind very strongly to soil. Uptake by plants is only relevant for medicinal products with a high mobility. There are no data known of medicinal contamination of plants for human consumption.

9.2.2.2 Actors

Agricultural sector

The agricultural sector in the Netherlands does not use sludge from sewage water treatment plants, but irrigation water can also contain traces of medicinal residues. The agricultural sector depends on a good supply of irrigation water to guarantee a good yield from their crops. The agricultural sector also uses veterinary medicinal products, which are not taken into account in this report. The use of medicinal products may lead to soil and water contamination via the application of manure. This is potentially an important route for the spreading of medicinal residues, but also for the spreading of antibiotics and antibiotic resistant pathogens.

10 General discussion, conclusions and suggestions for further advancement

10.1 Conclusion

Balancing the benefits of pharmaceutical care and minimizing the potential environmental harm of it, requires careful consideration of all stakes and benefits of those involved. This report may be one of the first tentative steps in that process. We present differences in the processes involved in the medicinal product chain and deduce their drivers.

In the entire medicinal product chain - from development to the waste processing stages - these differences in processes and/or their drivers indicate where measures could be taken, which may reduce environmental harm while maintaining the benefits of human pharmaceutical care. Further analysis of such differences might lead to identification of best practices. An example of an observed different process is that in some countries, oral diclofenac is issued exclusively on prescription, while in other countries it is also available over the counter (OTC).

Throughout the paragraphs, tentative suggestions for more levers have been made. An integral assessment of the practical feasibility of intervening through these levers, or combination of levers, is necessary by weighing the positive and negative effects these interventions may have. A case wise integrated societal cost benefit analysis of all aspects, processes and important actors in the medicinal product chain is necessary to identify the most feasible combination of measures. Cases can be selected based on current knowledge of potential environmental harm.

10.2 Discussion

This report takes a macro perspective on the medicinal product chain and suggests a capita selecta of potential levers to reduce the emission of medicinal product residues into the environment. As far as we know, this is the first time that the pathway from development of an active pharmaceutical ingredient (API) to emission into the environment has been described as one single chain of processes. Even though none of the knowledge presented in this study is unique or new, the novelty lies in the combination of specific fields: for environmental scientists the information in the parts of human pharmaceutical care may be new, and for scientists with expertise in medicine or pharmaceutical care, the environmental processes will contain new information.

Some of the seemingly arbitrary differences in processes in use and removal and/or their drivers presented in this report illustrate that neither pharmaceutical care nor removal of medicinal product residues from the sewage water are deterministic, fixed processes, guided by either clinical or technical rationality alone. The combination of reasons and drivers determines the outcome and impact of these processes. Currently, the most prominent drivers for the development and use of medicinal products are a desired clinical outcome and patient characteristics. However, those aspects are not the only drivers of development and use of medicinal products. During development, use

and disposal, individuals such as scientists, regulatory agencies, prescribers, patients and water quality managers make choices in their own national and systemic context. We illustrated that the actors involved in these processes in the medicinal product chain, balance a number of benefits when choosing what to do, for instance health gain, environmental damage, legal issues, budgetary considerations (costs and benefits), peer group behaviour and practical issues such as time pressure, habit or history. For example, national effectuation of EU legislation differs between member states, which affects pharmaceutical care and removal efficiency. Furthermore, reimbursement systems differ between geographic regions, which influences pharmaceutical care. Additionally, geographic properties, political prioritization of costs and available infrastructure affect how extensively wastewater is purified. As such, the processes of pharmaceutical care and removal of medicinal product residues are determined by stakeholders' deliberation and social processes. This implies that actors can choose to change these processes. During the writing of this report, we experienced that due to e.g. habits and history, a segregation between the health care field and environmental field are present. If we are able to bridge the gap between these fields, we may find implementable levers in the system to reduce the environmental burden of pharmaceutical care, while preserving their benefits.

The environmental problems, which were the motivation for this investigation, emerge at the end of the medicinal product chain. After medicinal product use, a 'cocktail' of medicinal product residues enters the sewer. With current practices, this cocktail is only partly removed before entering the environment. The purpose of these compounds is to be active in the human body. Consequently, they possess a number of characteristics that by definition cause them to affect organisms in the environment. They are taken up easily by organisms, they are biologically active in relatively low concentrations and they are not readily degraded in a biological system. All these excreted medicinal product residues enter the environment, either via wastewater or as solid waste.

In the ecosystem, where organisms use the surface water and groundwater as a habitat, pharmaceutical compounds may affect their behaviour, health and survival, thereby influencing the composition and functioning of the living environment.

Since it is very expensive to prevent the discharge into the environment using only end-of-pipe technologies, preventive actions earlier in the medicinal product chain may be more cost effective. It is necessary to reduce the amount of medicinal product residues entering the waste phase, e.g. by developing new pharmaceutical compounds with favourable properties for the purification process, stimulating different use of medicinal products, applying collection schemes or separation solutions for surplus medicinal products, aiming to reduce emission of medicinal product residues into the environment.

Feedback mechanisms

Similar to other problems of collective action, there is no single "problem owner" to the problem of medicinal product residues in the environment. Environmental organisations deal with the waste of medicinal products, and organisations who work in health care focus on

the use of medicinal products. The environmental consequences of medicinal product residues are not experienced during development and use of medicinal products, while the actors involved in the water purification are not aware of processes that determine pharmaceutical care. For the topic of this report, it is crucial to emphasize that a feedback between the environmental part of the chain and the health part is still missing. To put it in lay terms: the producer, doctor and patient are not confronted with the environmental problems caused by pharmaceutical care for the manager of the wastewater plant, and with the subsequent effects on ecosystems and environmental quality. Currently, the water quality manager has to solve these problems in an end-of-pipe approach. Water treatment techniques are not effective in preventing medicinal product residues ending up in the environment. Levers to introduce such feedback mechanisms on system level may address this caveat. Most of the levers presented in this report are based either on the feedback by exchange of information or on financial interventions. These two feedback mechanisms are explained in the following paragraphs.

Feedback via information exchange

Feedback mechanisms based on information exchanges from the 'top' of the chain to the 'bottom' of the chain and reverse may be used to remove medicinal product residue more effectively in the removal phase or to choose environmentally friendly alternatives in the development phase. The flow of information would need to contain the characteristics of the medicinal products developed and produced by the pharmaceutical industry and the pharmaceutical residues that are present in the environment in water bodies. This would require the pharmaceutical industry to provide physicochemical and ecotoxicological data publicly for all substances on the market. For substances introduced after 2006, some of these data are present in the market authorisation dossiers, but not publicly available. For substances that entered the market earlier, these data need to be collected and, if not present, even be determined and made available.

Organizations responsible for water quality might do research on the chemical and physical characteristics of compounds that may cause problems in the environment and / or that are not removed in wastewater treatment systems. The developers and the pharmaceutical industry may take knowledge on environmental fate and impact into account when developing new medicinal products. Furthermore, exchange of knowledge on the analytical techniques to determine the presence of medicinal product residues in environmental compartments would be very helpful. Here, lessons may be learned from the EU legislation on persistent plant protection products and biocides. In some 20 years, it has proven to be possible to develop alternatives for the most recalcitrant and environmentally unfriendly compounds, without harming food production. The same might be possible with respect to medicinal products too.

Feedback via financial considerations

Feedback mechanisms based on financial considerations become rational after realizing that society will pay for the removal of medicinal product residue anyway: either as payer of premiums in the health care system, or as payer of taxes for environmental management. It may be subject

of subsequent study to determine which financial incentives optimally reduce the total sum of health care premiums and environmental taxes for society.

A way to transfer the costs and benefits in the medicinal product chain to actors that are able to take preventive action, is to incorporate the waste handling and the environmental consequences in the price of medicinal products. This may take the form of 'green pricing' of medicinal products in combination with 'the polluter pays principle'. For the citizens (either in their roles as patients, as premium payers or as tax payers), this would imply that the costs that result from removal of medicinal product residues would be transferred from their environmental taxes to their health care premiums¹. This would remove the time lag between gaining the benefits of pharmaceutical care and the incurred costs caused by the medicinal product use. It would also directly tie the size of the removal costs to the consequential environmental damage. Green pricing of medicinal products may subsequently activate the power of the consumer. Instead of being confronted with water purification taxes, they are confronted with increased costs in their role as patient / health care insurance premium payer. This may generate consumer demand for less environmentally damaging medicinal products (as alternatives for existing products), to reduce their health care insurance premium. Legislation could provide possibilities for the pharmaceutical industry to develop new (greener) medicinal products, by innovation-stimulating measures. Therewith, producers answer to consumer demand by considering environmental properties in the development of alternative products. The producer can also be stimulated, either through legislation or market demand, to develop environmentally friendly medicinal products for new therapies. These processes will take probably years to decades to change. However, in other areas, such as pesticide regulation, it proved to be possible to find alternatives for environmentally damaging compounds within 20 years without damaging food production and –safety.

Instruments to organize feedback (via legislation or voluntarily)

Feedback mechanisms, like information exchange or financial incentives, can be stimulated by the government for example through legislation or voluntarily through an appeal on societal responsibility. Adaptation of (EU and/or national) legislation may be necessary to initiate many of the levers that are suggested in this report, either through stimulating or through restrictive legislation. The principal aim of medicinal products is to improve human health. All actions, especially in the first phases of the chain, focus primarily on that goal without taking into consideration possible unintentional effects after use. In the assessment of new products for approving entry to the market, human health and human safety considerations are the main criteria until now. If environmental risks should be taken into account regarding marketing authorization of new medicinal products, it would be preferable to address this at the regulatory level, in order to balance all risks and benefits of a medicinal product.

¹ In some health care systems, the health care is also paid in taxes. For these systems, the transfer would be from the environmental tax to the health care tax.

10.3 Suggestions for further advancement

Integral policymaking with respect to medicinal product residues in the wastewater will demand for scientific instruments to weigh the feasibility and effectiveness of levers. A number of methods could be applied and/or combined for this purpose.

Methods for weighing of societal cost-benefits

In the environmental sciences, the Life Cycle Analysis is a well-established method to quantify the environmental damage (in PAF) and loss of DALY's as a result of human activity. In this methodology, PAF and DALY's are weighed against each other to provide an integrated impact assessment (please refer to <http://www.lcia-recipe.net/file-cabinet> for more information). In health care, many costs-benefits analyses are performed on various (new) developments in the health care systems. A body of these studies involve medicinal products and possible alternatives (please refer to <http://kosteneffectiviteit-preventie.rivm.nl/> for a comprehensive database of CEA's in health care). Since both methods aim to express their results (partly) in DALY's, a comparison should be possible in principle.

Combining these two existing methods could result in a science-based weighing of the health gain by medicinal products versus their environmental effects. Using such an integral method will enable quantification of the environmental problem and relate it to the costs of changes in the pharmaceutical care system necessary to decrease negative environmental effects of medicinal product residues.

Societal acceptance of measures

For policymaking purposes, information has to be gathered on the advantages and disadvantages for all actors of measures to reduce the environmental effects of medicinal product residues. Societal acceptance of any measure to reduce medicinal product residues is likely (but not solely) to be affected by the societal cost-benefit ratio of the measures. However, the costs and the benefits may not be evenly spread between actors, causing a loss for some actors if something changes in the status quo, even though the cost-benefit ratio of society as a whole is positive. Those actors that suffer disadvantages from particular measures are likely to oppose and block a measure that could be beneficial for the majority of people. Identifying the actors that suffer disadvantages, and the size thereof, may provide for new opportunities to compensate them if a measure is implemented.

A number of methods, both qualitative and quantitative, is available to gain knowledge on the positions of different actors and stakeholders when something is changed in the medicinal product chain. Using a number of methods, data can be gathered from experts. There are a number of analytical tools available to code and aggregate the information from the interviews to a higher level.

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