Sustainable use of medication

Medication waste and feasibility of redispensing

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Charlotte Bekker

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Duurzaam gebruik van geneesmiddelen

Verspilling van geneesmiddelen en haalbaarheid van heruitgifte (met een samenvatting in het Nederlands)

Proefschrift

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Charlotte Linde Bekker

geboren op 9 maart 1990 te Zevenaar

Promotoren:
Prof. dr. A.C.G. Egberts
Prof. dr. M.L. Bouvy

Copromotoren:
Dr. B.J.F. van den Bemt
Dr. H. Gardarsdottir

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Chapter 1

General introduction

Medication waste

Medication is important in healthcare and society at large for the prevention and treatment of symptoms and diseases. The point prevalence of the use of one or more prescription medications is at least 50% across all ages and both sexes in most countries[1,2]. The spending on medication accounts for more than one-sixth of the global healthcare costs[3]. In the Netherlands, pharmaceutical spending accounts for a relatively low proportion of all healthcare spending (8%)[4]. Over the past years, pharmaceutical spending has increased considerably. This is primarily attributable to the introduction of new, expensive, targeted therapies. For example, total global spending on oncology medication rose by 14.9% in 2016 due to the increased availability and use of more expensive therapies[5]. Similarly, spending on medication for the treatment of hepatitis C virus has substantially increased, from $78 million in 2009 to $18 billion in 2015 in the United States[6]. These expensive medications, including biological therapies and tyrosine kinase inhibitors, account for one-third of total pharmaceutical spending in the Netherlands, although these are used by a relatively small number of patients[7]. Other factors that contribute to this rise in pharmaceutical spending include the aging population, and as follows a higher prevalence of people with chronic diseases the increasing number of chronically ill people, and the use of combination therapies.

Studies have shown that many patients do not use all medication that they get dispensed[8–10]. Medication waste refers to any medication that remains unused throughout the entire pharmaceutical supply and use chain[11]. This waste can have considerable implications both economically, due to the financial loss, and environmentally, when disposed of directly in the environment. Prevention of medication waste may significantly contribute to cost containment in healthcare and thus to effective utilisation of healthcare resources as well as to limit the environmental pollution from medication waste.

Multiple studies have attempted to estimate the quantity and cost of unused medication after dispensing. It is difficult to obtain precise estimates on the magnitude of medication waste due to the multitude of disposal routes (e.g. disposal at pharmacies[12–17], chemical waste depots[15], or through household garbage[18]), as well as continued home storage of medication that is no longer used[19–22]. Furthermore, healthcare systems and prescription policies vary considerably between countries, which hamper comparison of such results. Despite these difficulties, the available data do indicate that the financial loss attributable to medication waste is substantial. It has been estimated that at least 3-6% of total pharmaceutical spending remains unused[15,18]. The annual value of wasted medication has been estimated at approximately €100 million in the Netherlands, £300 million in the United Kingdom and up to $5.8 billion in the United States[9,15,19].

Apart from the economic impact, medication waste also has an environmental impact. Not all patients dispose of their unused medication properly[23]. Dutch estimates indicate that only 54% of all patients return their unused medication to the pharmacy[8]. Negative environmental consequences arise when patients improperly discard their unused medication through, for instance, the household garbage, toilet, or sink. Active pharmaceutical ingredients have been detected in surface, ground, and drinking water[24,25]. There is a growing concern that these residues may have detrimental effects on aquatic species and ecosystems. For instance, steroid hormones found in rivers have been linked with disrupted sexual reproductive

physiology in wild fish species resulting in intersexuality[26]. Another example is metformin, a widely prescribed medication for diabetic patients, which induces comparable endocrine-disrupting effects in fish exposed to the concentrations found in surface water[27]. Although this environmental contamination with pharmaceutical products is partly due to the excretion by the patient after medication intake, the inappropriate disposal of unused medication also contributes and is potentially preventable.

Causes of medication waste in the pharmaceutical supply and use chain

Medication waste can occur throughout the entire pharmaceutical supply and use chain (Figure 1). The primary responsibility of this chain is to ensure a timely availability of the right medication with the right quality for the right patient. The first part of this chain is primarily product oriented (i.e. product quality, distribution) and the second part is primarily patient oriented (i.e. pharmaceutical care, medication use). The studies in this thesis focus on waste that occurs in the second part of the chain, after the product has been dispensed to the patient. However, this waste is partly caused by various stakeholders involved in the complete supply and use chain.

The product oriented part of the pharmaceutical supply and use chain includes the development, manufacturing, distribution and dispensing of medication. To ensure a consistently high quality of the medication, the European Union provides guidance for manufacturers on Good Manufacturing Practice (GMP) (EU Directive 2003/94/EC). After manufacturing, distributors, such as wholesalers, take responsibility for storage and/or further distribution to pharmacies, which require that they comply with international guidelines on Good Distribution Practice (GDP) (EU Directive 2013/C 343/01). This first part of the chain also involves dispensing the correct amount needed for a patient's therapy. Medication waste can relate to various aspects of this part. Manufactured package sizes of medication can contribute to waste at the level of the patient. For example, most cancer medication intended for administration through infusion is only manufactured in a limited variety of dosage strengths. As these are prescribed in a patient tailored dose based on body size (i.e. mg/kg or mg/m2) that usually does not match the quantity available in a vial, the unused content of the vial often has to be discarded. It has been estimated that in oncology care in the US, around $1.8 billion is wasted annually on discarded infused cancer medication[28]. For medication dispensed in solid dosage forms, such as tablets and capsules, there are often regulatory constraints in place that do not allow for splitting medication packages into smaller quantities. As a consequence, excessive medication quantities that are dispensed to patients eventually go unused and wasted. In Sweden, the Swedish Medicinal Agencies only allows for splitting packages in exceptional circumstances where the treating physician cannot be contacted and the patient is in need of medication 29. In this case, a small quantity can be dispensed to cover the time period until the patient can consult the physician. Moreover, the requirement for not allowing splitting packages is also a protective measure such as in the case of the highly toxic oral anti-cancer medication. The original packaging of oral anti-cancer medication may sometimes only be adapted in special "down flow workstations" to protect personnel. However, these workstations are expensive and require GMP compliance. Most pharmacists therefore dispense complete packages to patients.

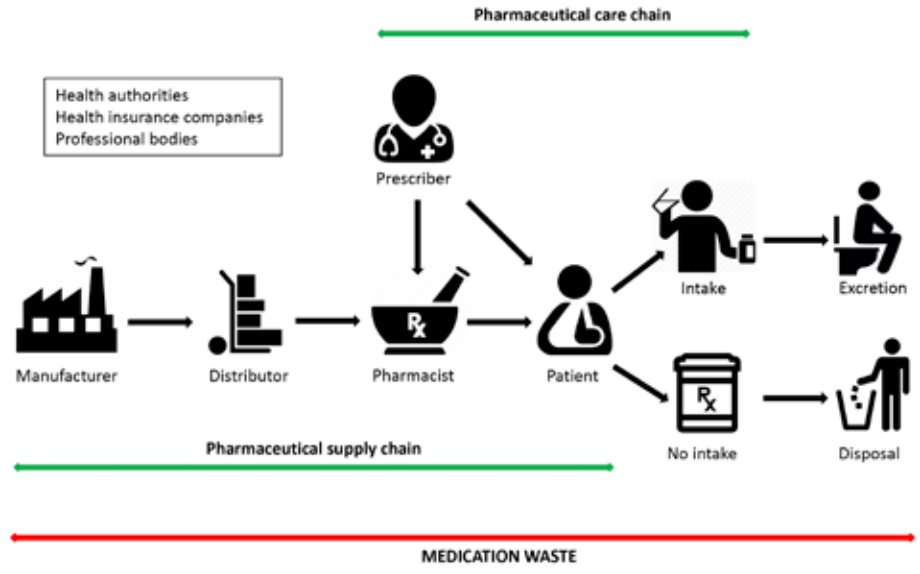

Figure 1: Schematic presentation of the pharmaceutical supply and use chain for prescription medications.

The patient oriented part of the pharmaceutical supply and use chain includes pharmacotherapy initiation, dispensing and use of medication. Multiple events at the prescriber, pharmacist and patient level may cause medication waste. Medication quantities that are prescribed and dispensed are often regulated through national regulations set by either health authorities or third party payers. For instance, most European countries installed prescription durations between one and three months[30]. The reason for these varying prescription durations can be related to economical as well as clinical considerations. However, prescription durations that are longer than 60 days have been associated with more medication waste per prescription[31,32]. Furthermore, patients often receive an excessive supply of medication for redundant treatment durations that not all are needed which results in waste[13,33]. In this part of the chain, this could be due to an excessive quantity prescribed or dispensed. Finally, medication waste may (un)intentionally occur at the patient level. Therapy changes have found to be a frequently reported cause of medication waste by patients[12–14,34]. For instance, early therapy discontinuation due to unsatisfactory effects or the occurrence of side effects is frequently unpredictable and may result in waste if patients have not used all of their dispensed medication. In addition, non-adherence to treatment regimens could result in medication remaining unused. Furthermore, in some countries larger package sizes are cheaper in comparison to smaller sizes, as smaller sizes are not as frequently dispensed. For example, in Sweden, the medication Atorvastatin 20 milligram, 30 tablets costs 65.24 SEK, whereas 100 tablets costs 57.49 SEK[35].

Minimisation of medication waste is thus highly desired from an economic as well as from an environmental perspective. The International Pharmaceutical Federation (FIP) has also discussed the environmental burden of medication waste and advocated for the "green

pharmacy". The FIP emphasises that stakeholders, including pharmacists, should show joint leadership to minimise waste[36]. In the Netherlands, the societal problem of medication waste has gained increased awareness in the past years. The Dutch Ministry of Health conducted a survey among the public to identify sources as well as solutions to waste in healthcare[37]. Also, in 2011 the award for the best healthcare idea in the Netherlands went to 'the redispensing of unused medication' waste-minimising intervention[38]. However, although different initiatives have been noted for waste minimisation, the implementation thereof seems to be hampered by different factors or stakeholders within the pharmaceutical supply and use chain[39]. While the public advocates for redispensing unused medication, professionals voice concerns regarding the quality of medication that is returned to pharmacies. As a result, redispensing unused medication has not been implemented in clinical practice[40]. Similar waste-minimising approaches, such as dispensing limited quantities to patients, have been suggested[41] but are unlikely to be cost-effective for all types of medication. Multiple studies focussed on reasons why patients end up with unused medication, but few studies have reported on interventions aiming to reduce waste[10]. Therefore, the effectiveness of waste minimising actions remains unclear. Moreover, the feasibility of implementation of waste-minimising measures in practice as well as requirements to enable implementation has not been investigated. For instance, information about daily practices of pharmacists to minimise medication waste is limited. Prevention is the preferable solution for waste minimisation; however, few studies have investigated whether medication waste can be prevented. The British National Health System (NHS) reported that less than 50% of medication waste is preventable but acknowledged that this was a rough estimate[9]. In addition, it is currently unknown if waste-preventive measures are effective for specific patient and medication groups. Previously it was discussed that expensive medication therapies contribute significantly to healthcare spending. Most studies that estimated the extent of medication waste focussed on waste within the community pharmacy setting. However, in many countries expensive medication is dispensed by the outpatient or hospital pharmacy and not much is known about the magnitude here.

Redispensing unused medication

Medication waste is only partially preventable, and should therefore be accompanied by other waste-minimising approaches. Throughout society, recycling programmes for the sustainable use of different resources have been put into place, such as recycling of disposed paper, glass, clothes, and electronic materials. A similar approach could be implemented for medication waste, which includes the redispensing of medication that is returned unused to pharmacies. Redispensing has the potential to contribute to waste minimisation and sustainable use of medication. A survey carried out by the Dutch Ministry of Health in 2013 received numerous proposals from the public and healthcare professionals on ideas for waste reduction in the healthcare system[37]. Most of the respondents specifically mentioned medication waste and advocated for the redispensing of unused medication. The potential of redispensing has been discussed by healthcare professionals as well[42–45]. In addition, studies have shown that a substantial proportion of medication left unused by patients remain in their unopened and intact outer packaging. According to Mackridge et al., one-third of medication that was returned unused to primary healthcare facilities in the UK was potentially suitable for redispensing[12]. In Singapore, it was estimated that as much as 90% of returned medication from healthcare facilities and patients was suitable for redispensing, if opened medication packages were also considered[46]. Estimates from the US indicate that around 10 million unused medication prescriptions discarded by long term care facilities (e.g. nursing homes) could be recycled[47].

Despite the potential benefits, redispensing is not a common pharmacy practice. Many national legislation policies or guidelines state that medication that is returned by patients should not re-enter the pharmaceutical supply and use chain and must be destroyed. This is primarily due to concerns regarding the product quality of medication that has left the supervised storage within the pharmacy setting. Medication stored at patients' homes is prone to tampering and poor storage conditions that could lead to product degradation and instability, thus decreasing efficacy and/or increasing toxicity when redispensed. One should therefore establish the product quality of returned medication to provide assurance that the medication is still of high quality and safe to use. Redispensing only takes place in very specific situations, such as the redistribution of medication to patients in need that has been donated by healthcare facilities and, thus, has been continuously supervised[48]. Several states in the US allow pharmacies to collect unused prescription medication returned by healthcare facilities if the medication is still packed in its original, sealed packaging[49]. The medication is checked by a pharmacist who ensures the product integrity before redispensing these to people who cannot afford normal healthcare. In Oklahoma, the collection of medication from nursing homes resulted in savings of over $22 million from 2004 to March 2018[50].

To determine if a redispensing process can be implemented in standard pharmacy practice a comprehensive assessment regarding the feasibility of redispensing should be conducted. The possibility of redispensing unused medication in the community and outpatient pharmacy setting is currently unexplored. Favourable outcomes of a redispensing process also depend on people's acceptance of this concept. Implementation is likely to be more successful when supported by stakeholders and patients. However, few studies have identified their views on the redispensing of unused medication. Furthermore, advocates of embedding redispensing in clinical practice believe that cost savings can be achieved; however, the actual amount of these cost savings is currently unknown. Redispensing unused medication in clinical practice will require additional activities and, thus, costs for pharmacies, making implementation only feasible when the benefits outweigh the costs. Therefore, it is prudent to explore the potential costs of implementing a redispensing process and the cost savings that could be achieved.

Objective of this thesis

The overall objectives of this thesis are to investigate medication waste among patients in terms of quantity, cost, preventability, and currently implemented waste-reducing measures. In addition, the feasibility of redispensing medication that remains unused by patients will be investigated.

Outline of this thesis

Chapter 2 focuses on medication waste whereas chapters 3 and 4 focus on the feasibility and economic aspects of redispensing. **Chapter 2.1** quantifies the extent and preventability of unused medication that is returned to community pharmacies and the possibility of redispensing this returned medication. The extent of unused medication for two expensive medication therapies, namely oral anti-cancer and biological disease-modifying anti-rheumatic drugs, among outpatient pharmacy patients who discontinued therapy, is assessed in terms of quantity and cost in **Chapter 2.2**. Activities that community and hospital pharmacists presently undertake to reduce medication waste are identified, and the importance of these activities for waste reduction and the feasibility of implementing these in clinical practice are presented in **Chapter 2.3**.

Chapter 3 addresses the feasibility of redispensing unused medication returned to pharmacies by patients in terms of stakeholders' views. In **Chapter 3.1**, the views of stakeholders on redispensing and the requirements that should be met for safe redispensing are presented, while **Chapter 3.2** specifically describes the willingness of patients to use medication that is returned unused by another patient.

In **Chapter 4**, the economic considerations of redispensing are discussed. **Chapter 4.1** presents the costs that are associated with the redispensing process in the pharmacy along with an illustration of the cost-benefit threshold. Next, cost savings generated by an outpatient pharmacy through redispensing post-exposure prophylaxis medication used for human immunodeficiency virus (HIV) contaminations are presented in **Chapter 4.2**.

Finally, in **Chapter 5**, the overall findings of this thesis are discussed from a broader perspective and recommendations for waste minimisation are provided.

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Chapter 2

Medication waste

Chapter 2.1

Patient and medication factors associated with preventable medication waste and possibilities for redispensing

Charlotte L Bekker
Bart JF van den Bemt
Antoine CG Egberts
Marcel L Bouvy
Helga Gardarsdottir

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Abstract

Background
Knowledge on factors related to preventable medication waste and waste-reducing interventions, including redispensing unused medications, is needed to maximise effectiveness.

Objective
To assess patient and medication factors associated with preventable medication waste and possibilities for redispensing unused medications.

Setting
Dutch community pharmacies.

Methods
In this cross-sectional study, pharmacy-staff registered patient and medication characteristics of prescription medications returned to 41 Dutch community pharmacies during one week in 2014. Medications were classified as preventable waste if the remaining amount could have been prevented and as theoretically eligible for redispensing if the package was unopened, undamaged and ≥6 months until the expiry date. Associations were analysed using multivariate logistic regression.

Main outcome measures
Proportion of medications classified as preventable waste and as eligible for redispensing, including factors associated with these medications

Results
Overall, 279 persons returned 759 (low-cost) medications, and 39.3% was classified as preventable waste. These medications were more frequently used by men than women (OR; 1.7 [1.2-2.3]) and by older (>65 years) than younger patients (OR; 1.4 [1.0-2.0]). Medications dispensed for longer periods were more often unnecessary wasted (1-3 months OR; 1.8 [1.1-3.0], >3 months 3.2 [1.5-6.9]). Of all returned medications, 19.1% was eligible for redispensing. These medications were more frequently used by men than women (OR; 1.9 [1.3-2.9]). Medications chronically used were more frequently eligible for redispensing than acute use (OR; 2.1 [1.0-4.3]), and used for longer periods (1-3 months OR; 4.6 [2.3-8.9], >3 months 7.8 [3.3-18.5]).

Conclusions
Over one-third of waste due to medications returned to community pharmacies can be prevented. One-fifth of returned medications can be redispensed, but this seems less interesting from an economic viewpoint.

2.1

Introduction

Medications account for almost one-fifth of health care spending in developed countries[1]. However, patients do not use a substantial proportion of medications dispensed to them[2–9], contributing to suboptimal treatment outcomes, financial waste and harm to the environment.

Various stakeholders in the medication supply chain, from manufacturer to patient, contribute to medication waste. Manufacturers may produce unnecessarily large packages with quantities that exceed the amount required for treatment. Pharmacists are not always allowed to split packages into smaller quantities and thus dispense excessive amounts to the patient. In addition, prescribers may prescribe medications for a longer period than the patient actually needs. Even if there is no waste of medication in the situations above, side effects, unsatisfactory treatment responses or early discontinuation during medication use may lead to therapy changes that may result in an excess of dispensed medication[3,6–10]. Patients keep the remaining amounts for later use, discard them with the household garbage or return them to pharmacies and waste depots[11–15].

Although many studies have described which medications are returned to pharmacies and for which reasons, knowledge of the factors relating to medication waste is lacking[16]. If information were to be available on which medications are frequently unnecessary wasted, by which patients and in which situations, then waste-reducing interventions can specifically target these. Moreover, part of the medication waste often concerns unopened packages, including medications of good quality. A possible intervention to decrease the waste of these good quality medications might be the redispensing of these medications. In most countries, redispensing unused medications is not done in clinical practice due to lack of insight in the quality or legal restraints. However, the debate about redispensing as waste-reducing intervention is ongoing[17–21]. Therefore, more information is needed to assess which medications that remain unused by the patient could be eligible for redispensing.

Aim of the study
The aim of this study is to assess which patient-related and medication-related factors are associated with preventable medication waste and to explore possibilities for redispensing unused medications.

Ethics approval
The study was approved by the UPPER institutional review board of the Utrecht University, the Netherlands (UP1408).

Method

Design
This cross-sectional study was conducted in May 2014 in 41 Dutch community pharmacies that are part of the Utrecht Pharmacy Practice network for Education and Research (UPPER) of the department of Pharmaceutical Sciences of the Utrecht University[22]. The pharmacies were located in both urban and rural areas and covered 2.1% of the total number of community pharmacies (n=1981).

Data collection

Prescription medications that were returned as a routine practice to the participating community pharmacies during five consecutive working days in the study period were included in this study. Medications dispensed outside the Netherlands, extemporaneously compounded medications and medical devices such as wound dressings and testing materials were excluded. Pharmacy students holding a bachelor's degree in pharmacy analysed the waste and collected the data during their final internship prior to receiving their pharmacy master's degree. Students received both oral and written instructions before the start of the study. For each returned medication, a written record form was completed with information directly obtained from the person who returned the medication, after verbal consent and information derived from the medication label.

- The following patient characteristics were recorded anonymously: patient's gender and age, type of prescriber (general practitioner, medical specialist, dentist or other), reason for use and reason(s) for returning the medication (patient deceased, condition resolved, passed expiration date, no/insufficient effect, treatment changed, adverse events, inconvenience of use, other [further specified] or unknown). Furthermore, details about the person who returned the medication (e.g. user, family, relative, health professional or other) were also registered.
- The following medication characteristics were recorded: medication name, strength, returned amount (number of tablets or capsules, liquids were estimated in milliliter, dermatologicals were estimated in grams), amount initially dispensed, prescribed dosage regimen, expiration date, whether the package was returned unopened (i.e. unused, yes/no) and whether the package was undamaged (yes/no). The returned medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system of the WHO[23].

Data were entered on site into the online survey tool Lime survey. The first author randomly checked 10% of the entered patients' data sheets in terms of data entry and data validity. Data was considered as precise as less than 1% of all entered variables were found to be incorrect. Subsequently, the economic value of each individual returned medication was calculated by using the Dutch medication prices of May 2014[24]. The lowest registered price of each medication unit was used to determine the minimal economic value of each returned medication unit. The total economic value was calculated by multiplying the returned number of units of a medication (e.g. number of tablets) by the unit price.

Each pharmacy received a unique study code. The study code list could only be accessed by an independent researcher who was not a member of the study group.

Primary outcomes

All returned medications were classified according to their preventability of medication waste and eligibility for redispensing.

Firstly, predefined criteria were used to assess the preventability of the medication waste. This assessment was done by the pharmacy student who collected the data. This assessment was based on the patient- and medication information and subsequently judged on preventability when one of the following criteria was full filled: (I) when larger amounts of medication were prescribed than needed for the expected duration of use, (II) when excessive medication amounts were prescribed for a terminal patient, (III) when a pharmacist dispensed more than the prescribed amount, (IV) in case of a prescription error (e.g. wrong strength prescribed), (V) when a refill that was no longer needed was dispensed or (VI) when patients had side effects or insufficient effect of treatment at the moment of a refill, but still collected the medication. Medications that could be classified neither as preventable waste nor as inevitable waste, due to insufficient data that was not registered, were excluded from further analysis.

Secondly, the returned medications were classified theoretically as eligible for redispensing when these met all of the following criteria: (I) the package was unopened, (II) the package was undamaged, and (III) there was at least 6 months between the date of returning (end of study date) and the expiry date.

Analysis

Regarding proportions, descriptive analyses were made and expressed as percentages, whereas medians with interquartile ranges (IQR) were analysed for averages. A univariate analysis was initially conducted in order to assess potential associations between explanatory variables and the primary outcomes waste (yes/no) and eligibility for redispensing (yes/no). This was followed by a full model multivariate logistic regression analysis. Explanatory variables included in both analyses were patient's gender and age, reason for returning the medication, duration of use (determined by a clinical pharmacologist), unit price and amount dispensed (converted into days by dividing by the daily dose). In addition, regarding medication waste, the prescriber of the returned medication was also included but not considered as a potential association for medications' eligibility for redispensing.

The definition of waste could have been biased by the subjective judgement of the student who collected the medications at the pharmacy. Therefore, to enhance validity a sensitivity analysis was conducted to which a returned medication classified as waste at a certain pharmacy was matched to a returned medication classified as no waste at the same pharmacy. Conditional logistic regression, with controlling for the pharmacy level, was subsequently applied. All statistical analyses were performed in STATA13.

Results

Characteristics of the returned medications and users

In total, 279 persons returned 759 prescription medications. Medications were most often returned by the consumer (59.9%), followed by a family member (31.5%). The returned medications were most frequently used for gastro-intestinal disorders (18.5%), nervous system disorders (17.8%) and cardiovascular disorders (18.1%).

The estimated total economic value of all returned medications was €7,916 with a median value of €1.75 per medication (IQR €0.58-6.28). Of the ten most expensive returned medications, half were considered eligible for redispensing (Appendix A).

Medications were returned primarily because 'patient was deceased' (22.4%), 'condition had resolved' (19.9%) and 'passed expiry date' (14.6%) Some patients reported 'other' reasons such as discontinuation of treatment during pregnancy, switching to a multi-dose dispensing

system or 'spring-cleaning' of the house. The main reasons for returning medications that were eligible for redispensing were 'patient was deceased' (30.3%) and 'treatment changed' (19.3%) (Table 1).

Table 1: Patients' reasons for returning the medication.

Reasons for returning	All medication n=759* (%)	Medication eligible for redispensing n=145* (%)
Patient was deceased	170 (22.4)	44 (30.3)
Condition had resolved	151 (19.9)	17 (11.7)
Passed expiry date	111 (14.6)	-
Other	81 (10.7)	23 (15.9)
No/insufficient effect	73 (9.6)	18 (12.4)
Treatment changed	68 (9.0)	28 (19.3)
Unknown	54 (7.1)	5 (3.5)
Adverse events	55 (7.3)	12 (8.3)
Inconvenience of use	10 (1.3)	1 (0.7)

*More than one answer possible

Factors associated with preventable medication waste

Of the 759 returned medications, 298 medications (39.3%) were classified as preventable medication waste and 378 medications (49.8%) were classified as inevitable waste. Due to a lack of information, 83 medications could not be classified and were therefore excluded from the analysis. Medications classified as preventable waste were distributed among all therapeutic classes, and had an average economic value of €2.36 (IQR €0.72-9.00). Around 80% of the preventable medication waste was below €15.00. Factors that were associated with potential preventable medication waste are presented in Table 2.

Preventable waste was significantly higher among male patients compared to female patients (OR 1.7 [1.2-2.3]). Medications used by older patients (>65 years) were classified as preventable waste significantly more often than medications that were originally in use by younger patients (<65 years) (OR 1.4 [1.0-2.0]). The type of prescriber, type of medication use, reason for returning the medication and the economic value of a medication unit were not significantly associated with medications defined as preventable waste. However, a significantly increased risk of preventable medication waste was found for medications that were initially dispensed for a longer period (1-3 months OR 1.8 [1.1-3.0] and >3 months OR 3.2 [1.5-6.9]). Sub analyses showed that approximately one-third of the medications used on a chronic basis and two-thirds of the episodic medications were dispensed for less than one month.

The conditional logistic regression showed similar associations, except for two variables that turned out to be significant: reason for returning 'other' (OR 1.9 [1.1-3.4]) and medication units valued €1-5 (OR 0.3 [0.1-0.7]) (Appendix B).

Table 2: Factors associated with preventable medication waste.

Medication waste	Preventable n=298 (%)	Inevitable n=378 (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Patient related				
Gender				
Female	155 (52.0)	243 (64.3)	Ref	Ref
Male	139 (46.6)	129 (34.1)	**1.7 (1.2-2.3)**	**1.7 (1.2-2.3)**
Unknown	4 (1.3)	6 (1.6)	-	-
Age				
0-65	135 (45.3)	212 (56.1)	Ref	Ref
>65	159 (53.4)	160 (42.3)	**1.7 (1.2-2.4)**	**1.4 (1.0-2.0)**
Unknown	4 (1.3)	6 (1.6)	-	-
Medication related				
Prescriber				
General practitioner	163 (54.7)	191 (50.5)	Ref	Ref
Medical specialist	107 (35.9)	127 (33.6)	1.2 (0.8-1.8)	0.9 (0.6-1.3)
Unknown	28 (9.4)	60 (15.9)	-	-
Reasons for returning				
Condition resolved	56 (18.8)	89 (23.5)	Ref	Ref
Adverse events	26 (8.7)	27 (7.1)	1.5 (0.8-2.9)	1.3 (0.7-2.5)
No/insufficient effect	32 (10.7)	35 (9.3)	1.5 (0.8-2.6)	1.3 (0.7-2.3)
Patient was deceased	48 (16.1)	97 (25.7)	0.8 (0.5-1.3)	0.6 (0.4-1.1)
Other	118 (39.6)	126 (33.3)	1.5 (1.0-2.3)	1.5 (1.0-2.4)
Unknown	18 (6.0)	4 (1.1)	-	-
Duration of use				
Acute	47 (15.8)	77 (20.4)	Ref	Ref
Chronic	157 (52.7)	171 (45.2)	1.5 (1.0-2.3)	1.1 (0.7-1.8)
Episodic	94 (31.5)	130 (34.4)	1.2 (0.8-1.9)	1.1 (0.7-1.9)
Price unit				
€0-1	257 (86.2)	306 (81.0)	Ref	Ref
€1-5	22 (7.4)	32 (8.5)	0.8 (0.5-1.4)	0.7 (0.4-1.3)
>€5	15 (5.0)	36 (9.5)	**0.5 (0.3-0.9)**	0.6 (0.3-1.1)
Unknown	4 (1.3)	4 (1.2)	-	-
Amount dispensed				
0-14 days	64 (21.5)	102 (27.0)	Ref	Ref
15-30 days	70 (23.5)	113 (29.9)	1.0 (0.6-1.5)	1.0 (0.6-1.6)
1-3 months	95 (31.9)	87 (23.0)	**1.7 (1.1-2.7)**	**1.8 (1.1-3.0)**
>3 months	25 (8.4)	15 (4.0)	**2.7 (1.3-5.4)**	**3.2 (1.5-6.9)**
Unknown	44 (14.8)	61 (16.1)	-	-

Significant associations are shown in bold

Table 3: Factors associated with medication eligible for redispensing

Redispensing	Eligible n=145 (%)	Not eligible n=614 (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Patient related				
Gender				
Female	67 (46.2)	388 (63.2)	Ref	Ref
Male	78 (53.8)	214 (34.9)	**2.1 (1.5-3.0)**	**1.9 (1.3-2.9)**
Unknown	0 (-)	12 (2)	-	-
Age				
0-65	56 (38.6)	328 (53.4)	Ref	Ref
>65	89 (61.4)	274 (44.6)	**2.3 (1.4-3.7)**	1.3 (0.9-2.0)
Unknown	0 (-)	12 (2.0)	-	-
Medication related				
Reasons for returning				
Condition resolved	17 (11.7)	132 (21.5)	Ref	Ref
Adverse events	12 (8.3)	42 (6.8)	**2.2** (1.0-5.0)	1.7 (0.7-4.1)
No/insufficient effect	15 (10.3)	53 (8.6)	**2.2 (1.0-4.7)**	1.5 (0.7-3.5)
Patient was deceased	44 (30.3)	125 (20.4)	**2.7 (1.5-5.0)**	1.6 (0.8-3.2)
Other	54 (37.2)	242 (39.4)	1.7 (1.0-3.1)	1.3 (0.7-2.4)
Unknown	3 (2.1)	20 (3.3)	-	-
Duration of use				
Acute	12 (8.3)	128 (20.9)	Ref	Ref
Chronic	102 (70.3)	273 (44.5)	**4.0 (2.1-7.5)**	**2.1 (1.0-4.3)**
Episodic	31 (21.4)	213 (34.7)	1.6 (0.8-3.1)	1.6 (0.8-3.4)
Price unit				
€0-1	121 (83.5)	514 (83.7)	Ref	Ref
€1-5	13 (9.0)	45 (7.3)	1.2 (0.6-2.3)	1.6 (0.8-3.4)
>€5	11 (7.6)	47 (7.7)	1.0 (0.5-2.0)	1.5 (0.7-3.3)
Unknown	0 (-)	8 (1.3)	-	-
Amount dispensed				
0-14 days	14 (9.7)	163 (26.6)	Ref	Ref
15-30 days	22 (15.2)	172 (28.0)	1.5 (0.7-3.0)	1.3 (0.6-2.6)
1-3 months	78 (53.8)	130 (21.2)	**7.0 (3.8-12.9)**	**4.6 (2.3-8.9)**
>3 months	20 (13.8)	23 (3.8)	**10.1 (4.5-22.8)**	**7.8 (3.3-18.5)**
Unknown	11 (7.6)	126 (20.5)	-	-

Significant associations are shown in bold

Factors associated with medications eligible for redispensing

Of all of the returned medications, 145 medications (19.1%) were classified theoretically as eligible for redispensing, with a median economic value of €4.60 (IQR €1.45-17.36). Around 80% of the returned medications were below €25.00. Factors that were associated with medications potentially eligible for redispensing are presented in Table 3.

Medications classified as eligible for redispensing were used by male patients significantly more frequently compared to female patients (OR 1.9 [1.3-2.9]). Medications used on a chronic basis were more frequently eligible for redispensing compared to acute use (OR 2.1 [1.0-4.3]). Of the returned medications that were initially dispensed for a longer period, significantly more medications were eligible for redispensing (1-3 months OR 4.6 [2.3-8.9] and >3 months OR 7.8 [3.3-18.5]). The other variables showed no association with medications eligible for redispensing.

Discussion

This study showed that of the returned medications, more than one-third was perceived as preventable waste. This emphasizes the need to implement waste reducing measures where possible. Moreover, approximately one-fifth of the returned medications were potentially eligible for redispensing. This study also identified several patient- and medication-related factors that were associated with preventable waste and possibilities for redispensing.

Male gender was associated with preventable medication waste. Previous research showed that men more frequently use medications intended for chronic use (like cardiovascular diseases), whereas women more often use medications that are used for acute or episodic treatment (like antibiotics, painkillers and sleeping pills)[25,26]. When assessing the association between the dispensed amount and preventable waste, medications dispensed for a duration exceeding one month were associated with preventable waste. This has also been confirmed by others[27] and indicates that preventable waste depends strongly on the amount of medications dispensed. Furthermore, returned medications classified as waste were more often used by the elderly. An explanation could be that the elderly often use multiple medications, which increases the risk of non-adherence, side-effects and eventually waste[28].

The proportion of medications that was theoretically eligible for redispensing is similar to that reported by others[9,29]. One study found that more than 90% of returned medications were eligible for redispensing, but this study did not apply the criterion that the original outer package must be unopened and intact[30]. However, none of those studies examined determinants of returned medications that are eligible for redispensing. This study shows that eligibility of returned medications for redispensing was specifically associated with male users, chronic therapy duration and a dispensing period of at least one month. To obtain the most benefit from redispensing if implemented in clinical practice, interventions can be specifically designed for medications that are dispensed to male users, and medications that are used on a chronic basis or dispensed for at least one month. Medications dispensed for longer periods more often consist of multiple packages. Therefore it is more likely that at least one package is left unopened and thus eligible for redispensing. This also indicates that interventions for redispensing unused medications should include patients to whom multiple

packages of a medication are dispensed. To make redispensing feasible to implement in practice, multiple stakeholders have reported that patients should be willing to participate in such a system[17]. Redispensing unused medications may succeed if patients are willing to return all their unused medications to the pharmacy, and even more important, are willing to use medications that have been previously dispensed to another patient. In an internet hotline launched by the Dutch Ministry of Health where patients and health care professionals were asked to report on how to combat waste in healthcare, the majority of suggestions made by patients were to redispense unused medications[31]. Hence, this suggests that patients are willing to participate in a redispensing system.

Knowing this, waste reducing interventions should specifically target the amount that is dispensed to patients, such as dispensing medications for shorter periods, which has proven to be effective in reducing waste[32]. However, implementing this approach for all medications might not compensate for the reimbursement of additional dispensing fees by pharmacists. In specific cases of more expensive medications, it may be cost-effective to shorten the dispensing period. Our results showed that the most expensive returned medications consisted of large amounts (Appendix A). Similarly, it is questionable if the redispensing of unused medications is cost saving for all medications. Nevertheless, there are also benefits to be gained by reducing environmental harm. Reducing medication waste at community pharmacies, where the majority of patients use relatively cheap generic medications, requires a multifactorial and medication-specific approach[33]. For example, thoroughly reviewing the medication for older patients, and discussing which medications are needed, could decrease the risk of medications being wasted.

To assess the effectiveness of waste-reducing interventions, studies are needed that assess if changing dispensing from a 3-month to a 1-month supply reduces waste and saves costs, taking into account the low costs of the returned medications. In addition, patients' views on a supply of one month should be determined, as this requires more pharmacy visits and may be a burden to patients. Little research is conducted on redispensing unused medications. Insight into the costs of a redispensing system is needed to determine if implementation is cost-beneficial in the community and/or outpatient pharmacy. Furthermore, patients' views on the redispensing of unused medications should be explored in terms of their willingness to use medications that have been dispensed to another patient.

Limitations

In this study, students subjectively determined if medications were defined as preventable waste, which may limit validity. To enhance validity of this data, student received both oral and written instructions about this classification, with a clear set of criteria. Regarding all data that the students collected, and the personal communication that they had with the persons returning the medications, they were, in our view, best able to make this judgement. This judgement was not reviewed by a second person. In our view, a review of the classifications later on and using the data sheets only would have been less precise compared to the assessment made on site. Furthermore, a sensitivity analysis was conducted that corrected for each pharmacy, i.e. the student that made the judgement in the pharmacy in the analysis. For instance, it may have been that a student more frequently classified returned medications as preventable waste. This analysis presented similar findings on factors that were associated with preventable medication waste, indicating that there was no 'inter-pharmacy' variety in classifications.

Three criteria were used to determine if the medications were potentially eligible for redispensing (package unopened, intact and at least six months until the expiry date). However, no information about the home storage conditions, like temperature exposure, was taken into account. Literature has shown that patients do not always store their medications at the recommended temperature[34]. This might affect the quality of medications and thereby patient safety. Therefore, the proportion of medications that was considered of good quality and eligible for redispensing in this study is likely an overestimation. Further, we found that redispensing unused medications that are returned to community pharmacies is less feasible when considering the small proportion deemed eligible and the low costs of these medications.

No collection campaign was set up prior to the start of this study. Knowing that not all patients return their medications to the pharmacy, but that they also deposit these at chemical waste depots, keep them in the house or dispose of them with the garbage, the absolute extent of waste generated through community pharmacies could not be assessed.

Furthermore, using the lowest medication price unit for the calculations might have resulted in an underestimation of the economic value. For many returned medications, information was lacking on the number of packages that were returned. Medications classified as eligible for redispensing could consist of unopened and opened packages, which might have caused an overestimation of the economic value of these medications. Finally, in the Netherlands, the majority of expensive medications, such as most biologicals, are dispensed by hospital based outpatient pharmacies. These medications are infrequently returned to community pharmacies.

Conclusions

This study shows that over one-third of the waste due to medications returned to the community pharmacies can be prevented. Waste-preventive interventions could specifically target factors that are associated with preventable medication waste, such as the dispensing of medications for longer than one month. Approximately one-fifth of returned medications can be redispensed. However, most medications were of low-cost, which makes redispensing unused medications in the community pharmacy less interesting from an economic point of view.

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Conflicts of Interests

All authors declare they have no conflicts of interest.

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Appendix A: The ten most costly returned medications, the reasons for returning and if they were classified as medication waste and/or eligible for redispensing

Medication (number of returned units)	Economic value (€)	Reason for returning	Preventable waste	Eligible for redispensing*
Fentanyl 50 mcg spray 40 doses (3)	726.00	Patient was deceased		
Ondansetron 16 mg suppository (34)	476.00	Patient was deceased		
Follitropin alpha 900IE/1.5 ml injection (1)	354.00	Unknown		
Ketanserin 20 mg tablet (168)	196.56	Condition resolved	√	√
Methylphenidate 54 mg tablet with controlled release (90)	180.00	Switch from brand to generic, but switched back to brand variant by prescriber	√	
Insulin detemir 100 IE/ml injection (15)	165.00	Therapy changed	√	√
Pregabalin75 mg capsule (128)	128.34	Patient was deceased		√
Eplerenone 25 mg tablet (61)	124.44	No/ insufficient effect		√
Oxycodone 40 mg tablet with controlled release (60)	117.60	Patient was deceased		
Tiotropium bromide 18 mcg inhalation capsules (68)	98.60	Therapy changed	√	√

*Medications were partly eligible for redispensing, as not all returned packages were unopened

Appendix B: Conditional logistic regression, with controlling for the pharmacy level, on factors associated with preventable medication waste.

Medication waste	Preventable n=245 (%)	Inevitable n=245 (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Patient related				
Gender				
Female	120 (49.0)	151 (61.6)	Ref	Ref
Male	121 (49.4)	88 (35.9)	**1.9 (1.3-2.9)**	**1.8 (1.2-2.9)**
Unknown	4 (1.6)	6 (2.5)	-	-
Age				
0-65	103 (42.0)	132 (53.9)	Ref	Ref
>65	138 (56.3)	107 (43.7)	**1.8 (1.2-2.7)**	**1.6 (1.1-2.5)**
Unknown	4 (1.6)	6 (2.5)	-	-
Medication related				
Prescriber				
General practitioner	122 (49.8)	129 (52.7)	Ref	Ref
Medical specialist	98 (40.0)	85 (34.7)	1.3 (0.8-1.9)	1.4 (0.8-2.2)
Unknown	25 (10.2)	31 (12.7)	-	-
Reasons for returning				
Condition resolved	45 (18.4)	57 (23.3)	Ref	Ref
Adverse events	18 (7.4)	19 (7.8)	1.3 (0.6-2.8)	1.0 (0.4-2.2)
No/insufficient effect	28 (11.4)	26 (10.6)	1.5 (0.7-2.9)	1.2 (0.5-2.5)
Patient was deceased	41 (16.7)	62 (25.3)	0.8 (0.4-1.4)	0.6 (0.3-1.1)
Other	103 (42.0)	78 (31.8)	**1.8 (1.1-3.1)**	**1.9 (1.1-3.4)**
Unknown	10 (4.1)	3 (1.2)	-	-
Duration of use				
Acute	39 (15.9)	48 (19.6)	Ref	Ref
Chronic	135 (55.1)	100 (40.8)	**1.7 (1.1-2.9)**	1.0 (0.6-1.8)
Episodic	71 (29.0)	97 (39.6)	0.9 (0.5-1.5)	0.8 (0.5-1.4)
Price unit				
€0-1	217 (88.6)	193 (78.8)	Ref	Ref
€1-5	13 (5.3)	25 (10.2)	**0.5 (0.2-0.9)**	**0.3 (0.1-0.7)**
>€5	13 (5.3)	25 (10.2)	**0.5 (0.2-0.9)**	0.5 (0.2-1.0)
Unknown	2 (0.8)	2 (0.8)	-	-
Amount dispensed				
0-14 days	52 (21.2)	64 (26.1)	Ref	Ref
15-30 days	56 (22.9)	79 (32.2)	0.9 (0.5-1.5)	1.0 (0.6-1.8)
1-3 months	80 (32.7)	45 (18.4)	**2.2 (1.3-3.8)**	**2.4 (1.3-4.3)**
>3 months	21 (8.6)	9 (3.7)	**2.7 (1.2-6.5)**	**3.0 (1.2-7.6)**
Unknown	36 (14.7)	48 (19.6)	-	-

Significant associations are shown in bold

Chapter 2.2

Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy

Charlotte L Bekker
Eward J Melis
Antoine CG Egberts
Marcel L Bouvy
Helga Gardarsdottir
Bart JF van den Bemt

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Abstract

Background
Patients sometimes discontinue the use of expensive oral anti-cancer drug (OACD) or biological disease-modifying anti-rheumatic drug (bDMARD) therapies early, leading to medication waste if the patient has not used all dispensed medication.

Objective
To determine the proportion of patients who have unused OACDs or bDMARDs after therapy discontinuation, and the quantity and economic value of these unused medications. Furthermore, patients' reasons for therapy discontinuation and their disposal method for unused medications were determined.

Methods
In a retrospective follow-up study using a Dutch outpatient pharmacy database, patients (≥ 18 years) who did not refill an OACD or bDMARD prescription, dispensed between November 2015 and February 2016, within two weeks of the prescription end date were contacted by phone and asked about their unused medication and reasons thereof. The economic value was calculated using Dutch medication prices. Data were descriptively analyzed in STATA13.

Results
The database included 1173 patients, of whom 159 likely had discontinued therapy and were contacted. Of these, 88 patients were excluded (39 refilled, 47 missing, and 2 other). Of the 71 patients who had discontinued therapy, 39 (54.9%) had unused medications, comprising 22 OACD users (mean age 63.0 (SD ± 15.9) years, 50.0% female) and 17 bDMARD users (mean age 50.7 (SD ± 13.5) years, 47.1% female). A total of 59 packages were unused, with a total value of €60,341. Unused OACD packages and bDMARD packages had median values of €179 (IQR €24–2487) and €992 (IQR €681–1093), respectively. Patients primarily discontinued therapy due to adverse or insufficient effects.

Conclusions
This study illustrates that more than half of patients discontinuing OACD or bDMARD therapies have unused medication. This emphasizes the need for waste-reducing interventions.

Introduction

Oral anti-cancer drugs (OACDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs) comprise a significant amount of healthcare spending for expensive medications[1], which is expected to increase more than 20% annually[2]. Both OACDs and bDMARDs have had a substantial impact on the treatment of cancer and inflammatory diseases, significantly improving the quality of life of affected patients[3–6]. However, studies have also shown that at least one-third of patients using OACDs or bDMARDs discontinue therapy early due to a lack of efficacy, adverse events, high out-of-pocket costs and negative beliefs about treatment[7–12]. Discontinuation of therapy may lead to medication waste if the patient has not used all of the dispensed medication.

Previous studies have assessed the type and quantity of unused medications that are returned to community pharmacies, revealing that they are generally low-cost medications[13–17]. Some countries have adjusted their dispensing policies in an attempt to manage costs by dispensing more expensive therapies, including OACDs and bDMARDs, only from hospital-based outpatient pharmacies, which might partially explain why low-cost medications are typically those returned to community pharmacies. Patients using expensive therapies may be more likely to return those to the outpatient pharmacy during their regular visits. Furthermore, the number of patients using expensive medications within the general population is relatively low[18] and only half of patients are found to return their unused medications to pharmacies[19]. A more efficient strategy to assess the quantity and value of unused expensive medications would therefore be to personally approach patients who have discontinued their expensive therapy. However, currently little is known about the extent of those expensive medications that remain unused. Such findings are only described in terms of wasted costs without prescribing the exact medication quantity that remain unused[7] or are published in a non-peer-reviewed journal[20]. If such information is available, this may provide guidance for the development of waste-minimizing strategies for expensive medications.

This study aimed to determine the proportion of patients who have unused OACDs or bDMARDs after discontinuation of therapy, and the quantity and economic value of these unused medications. Furthermore, patients' reasons for therapy discontinuation and their disposal method for unused medications were determined.

Methods

Design and setting
This retrospective follow-up study was conducted in the outpatient pharmacy of the University Medical Centre (UMC) Utrecht in the Netherlands from November 2015 until July 2016. The university hospital dispenses medications to approximately 11,000 patients per year, with 900 patients receiving OACDs and 1300 patients receiving bDMARDs. Due to national regulations, OACDs and bDMARDs are predominantly dispensed by hospital-based outpatient pharmacies in the Netherlands.

Ethics and confidentially

Patient data was handled confidentially and according to the Dutch law 'Protection of Personal Data' for medical research. The oral consent of patients was obtained prior to the start of the telephonic survey. The study was approved by the Medical Research and Ethics Committee of the UMC Utrecht (protocol reference number 16-114/C).

Study population

Patients aged ≥18 years who had received an OACD (a cytostatic, hormone antagonist, immunosuppressant or protein kinase inhibitor) or a bDMARD (an interleukin inhibitor, selective immunosuppressant or tumor necrosis factor alpha inhibitor) from the outpatient pharmacy for at least one week between November 2015 until February 2016, either as a first or repeated supply, were considered eligible for study inclusion. OACDs and bDMARDs that can also be dispensed by the community pharmacy were excluded. A detailed overview of the OACDs and bDMARDs included in the study is presented in Appendix A. Information about eligible patients was extracted from the outpatient pharmacy's database, including patient characteristics (gender, age) and information about their dispensed medications, including the dispensing date, medication name, anatomical therapeutic chemical (ATC) classification[21], medication strength, administration form, dispensed quantity and prescribed daily dose. Hospital records were consulted to exclude patients that were terminally ill or deceased. Patients were considered to have discontinued therapy if they did not receive a refill of their medication within two weeks from the theoretical end date of their prescription, or if they switched to a different strength of the same medication or to another type of OACD or bDMARD. Patients identified as discontinuers were contacted by phone by the first author. Those who could not be reached in a first attempt were contacted again on a different day in the same or the following week. Patients who could not be reached by phone received a letter explaining the aim of the study and were requested to contact the researcher.

The selection of discontinuers was performed monthly and the supply of OACDs and bDMARDs was assessed over a retrospective period of four months. Patient data was anonymized using an identification code list that was kept in the pharmacy. Only patients identified as discontinuers were decoded and contacted for this study.

Measurements

Consenting patients were interviewed using a structured closed-ended questionnaire. The questionnaire was developed through discussion by the research group and outcomes of previous conducted studies and pilot-tested in terms of interpretation by interviewing 10 patients using bDMARDs. The questionnaire included questions about whether patients had indeed discontinued therapy, and whether they had unused medications as a result. Patients who indicated they had unused medications were asked about the duration of their therapy, the reason for therapy discontinuation, the number of unused packages (if possible with the number of capsules, tablets or syringes), the number of unused packages that were unopened (i.e. not used at all), the reason for having unused medications and how they had disposed of the unused medications. Only medications dispensed by the hospital-based outpatient pharmacy of the UMC Utrecht were included.

The outcomes of this study included the determination of the proportion of patients who had unused OACDs or bDMARDs after therapy discontinuation. Furthermore, the quantity unused

packages among patients who had discontinued therapy, including the economic value and the quantity of unopened packages, was assessed. The economic value was calculated using the Dutch medication prices in 2016[22], excluding value-added tax, which was corrected for the unused quantity (number of capsules, tablets and syringes). Therefore, unit costs (cost of one tablet/syringe) were multiplied with the reported quantity. If patients were unable to report the unused quantity, these medications were excluded from the cost calculations.

Analysis

Descriptive analyses were performed. Proportions were expressed as percentages, while averages were expressed as means with standard deviations (SD) or as medians with interquartile ranges (IQR) if non-normally distributed. Outcomes were differentiated between OACDs and bDMARDs. The following co-variates were assessed for patients that had unused medications: patient demographics (gender, age), type of OACD or bDMARD, duration of medication use (<6 months, 6–12 months and ≥12 months), reasons for discontinuation (adverse effects, condition resolved, no/insufficient effect, therapy changed, other [further specified]) and disposal practices of the unused medications (kept at home [for later use, no time for disposal, other], returned to the pharmacy [community/outpatient], other [further specified]). All analyses were performed in STATA13.

Results

Over a period of four months, 605 patients received OACDs and 568 patients received bDMARDs from the outpatient pharmacy. After excluding patients who received a refill, were terminally ill or deceased, 90 patients using OACDs and 69 patients using bDMARDs were identified as likely discontinuers of these therapies and were contacted by phone. Of these, 23 (25.6%) and 24 (34.8%) patients, respectively could not be contacted, and some patients reported that they were still using the medication and had received a refill during the identification procedure, while others could not be contacted. A total of 71 patients confirmed that they had discontinued therapy and were included in this study, of whom 48 patients discontinued an OACD therapy (mean age 62.6 (SD ± 13.0) years, 52.1% female) and 23 patients discontinued a bDMARD therapy (mean age 50.3 (SD ± 12.0) years, 43.5% female). Information about patient inclusion is depicted in Figure 1.

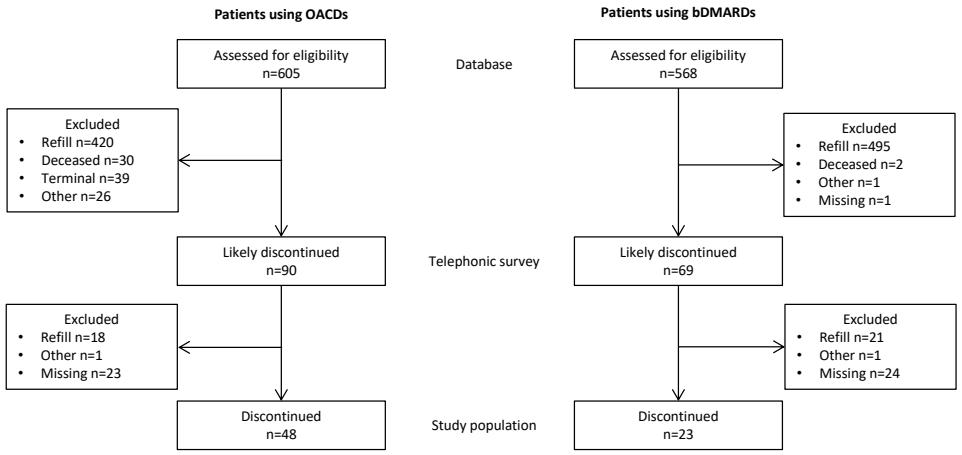

Figure 1: Procedure for the identification of patients who discontinued therapy. Patients categorized as "other" were excluded due to other reasons (e.g. went to another hospital) and those categorized as "missing" could not be contacted.

Proportion of patients with unused medication

Of the 71 patients who had discontinued therapy, 39 (54.9%) reported that they had unused medication. Five patients (7.0%) were unable to remember the precise quantity of unused medication. Specifically, 48 patients discontinued OACD therapy, of whom 22 patients (45.8%) had unused medication (mean age 63.0 (SD ± 15.9) years, 50.0% female). Twenty-three patients discontinued bDMARD therapy, of whom 17 patients (72.0%) had unused medication (mean age 50.7 (SD ± 13.5) years, 47.1% female).

A total of 39.1% of patients who discontinued OACD therapy with unused medication had been undergoing treatment for <6 months, while 17.4% and 30.4% of patients underwent treatment 6–12 months and ≥12 months, respectively (13.1% unknown). A total of 47.1% of patients who discontinued bDMARD therapy with unused medication had been undergoing treatment for 6–12 months, while 23.5% and 23.5% of these patients underwent treatment for <6 months and ≥12 months, respectively (5.9% unknown).

The primary reason given for OACD therapy discontinuation was adverse effects (50.0%), while insufficient effect was the main reason for patients discontinuing a bDMARD therapy (64.7%, Table 1). For both medication groups, most patients who had discontinued therapy due to adverse effects had been using the medication for less than half a year, whereas all patients who had discontinued due to insufficient effects had been using the medication for more than half a year.

Patients reported that they had unused medication because they discontinued therapy earlier than planned, e.g. their doctor told them to stop taking the medication. Other patients stated that the pharmacist had supplied too much or that they had not started using the medication at all. The majority of patients kept their unused medication at home (63.6% of the OACD users and 52.9% of the bDMARD users) or returned them to the pharmacy (27.3% and 47.1%, respectively), of which half of the patients returned them to the outpatient pharmacy.

Table 1: Patients' reasons for therapy discontinuation, for having unused medication and their method for its disposal.

	Patients with unused OACDs n=23[a,b] N (%)	Patients with unused bDMARDs n=17[b] N (%)
Reason for discontinuation		
Adverse effects	10 (43.5)	3 (17.6)
Condition resolved	3 (13.0)	-
Therapy changed	4 (17.4)	3 (17.6)
Insufficient effect	4 (17.4)	11 (64.7)
Other	4 (17.4)	1 (5.9)
Reason for unused medication		
Early discontinuation	19 (82.6)	13 (76.5)
Pharmacy supplied too much	1 (4.3)	2 (11.8)
Other	4 (17.4)	3 (17.6)
Disposal practice		
Kept at home	14 (60.9)	9 (52.9)
For later use	*6 (42.9)*	*3 (33.3)*
No possibility/time for disposal	*5 (35.7)*	*2 (22.2)*
Other	*2 (14.3)*	*4 (44.4)*
Unknown	*2 (14.3)*	-
Returned to pharmacy	6 (26.1)	8 (47.1)
Outpatient pharmacy	*3 (50.0)*	*4 (50.0)*
Community pharmacy	*2 (33.3)*	*3 (37.5)*
Unknown	*1 (16.7)*	*1 (12.5)*
Other	3 (13.0)	-

[a]There were 22 patients, one of whom had two types of unused medications.
[b]More than one answer possible and therefore the sum exceed 100%.

Quantity and economic value of unused medication

A total of 59 packages were unused, with a total value of €60,341 (Table 2). The majority of the unused packages were unopened (n=42, 71.2%) and had a total economic value of €48,349. The 22 patients with unused OACDs had, on average, one unused package, which had a median value of €179 (IQR €24–2487). Overall, 17 different types of OACDs were unused, of which 20.0% contained ruxolitinib. The 17 patients with unused bDMARDs had an average of two unused packages, each with a median value of €992 (IQR €681–1093). The majority of unused bDMARDs contained adalimumab (47.1%).

Table 2: The quantity and economic value of unused OACDs and bDMARDs packages among patients who discontinued therapy, including the number of unopened packages.

	Quantity N	Total economic value (€)	Median value per package (€) (IQR)	Median value per patient (€) (IQR)
OACDs and bDMARDs				
Unused packages	59	60,341	826 (179-1093)	1101 (367-2597)
Unopened packages	*42 (71.2%)*	*48,349 (80.1%)*	*1083 (551-1451)*	*2165 (1083-2717)*
OACDs				
Unused packages	31	34,536a	179 (24-2487)	367 (48-4235)
Unopened packages	*20 (64.5%)*	*26,044 (75.4%)*	*1800 (24-3580)*	*2602 (112-5401)*
bDMARDs				
Unused packages	28	25,806	992 (681-1093)	1362 (960-2176)
Unopened packages	*22 (78.6%)*	*22,304 (84.4%)*	*1083 (1083-1093)*	*1101 (1093-2165)*

[a]The economic value could only be estimated for 28 packages.

Discussion

In this study, unused OACDs and bDMARDs among patients discontinuing therapy were assessed. Both therapies significantly contribute to the cost spent on medications. It was found that 55% of these patients had unused medication. These medications were of high economic value, approximately €1100 per patient, and more than two-third of the unused medications included packages that were still unopened. Patients with unused medication had discontinued these therapies primarily due to adverse or insufficient effects. These outcomes emphasize the financial loss that occurs when these medications remain unused and show the need and possibilities for waste-prevention.

Overall, it was estimated that around €7.7 million was spent on OACDs and bDMARDs that were dispensed to the 1173 patients during the inclusion period, of which approximately 0.8% (€60.341 of €7.7 million) was wasted as patients had unused medication due to therapy discontinuation. These findings correspond with those of a previous study estimating the economic value of unused medications among patients discontinuing OACD, bDMARD or growth hormone therapies early, which found that less than 1% of the money spent on these medications was wasted[20]. Both the previous and current studies indicate that only small quantities of OACD and bDMARDs medications dispensed to patients are unused. However, these medications are so expensive that, for the outpatient pharmacy in this study, at least €180,000 is wasted annually when the study results are extrapolated. There are approximately 80 hospital-based outpatient pharmacies in the Netherlands. The outpatient pharmacy that was included in this study covers 5.9% on the national expenditures of OACDs therapies and 1.7% of the expenditures on bDMARDs therapies. When these results are extrapolated to the national level, the yearly value of unused expensive medications will be at least €6 million. Furthermore, it was unable to include all patients who were considered to have discontinued therapy due to a low response rate for this telephonic survey. These findings are therefore likely to be an underestimation of the absolute quantity of unused OACDs and bDMARDs.

These outcomes demonstrate that a significant amount of money is wasted when patients discontinue expensive therapies, and that the minimization of unused medication is therefore necessary.

Of the general Dutch population that use prescription medications on a regular basis, one-third has medications that remain unused[23]. In this study, the prevalence of unused medications is lower when compared to the general Dutch population. This is primarily due to the study design, as only patients who had discontinued therapy were specifically asked if a quantity of the OACDs or bDMARDs that was dispensed during the study period remained unused. The number of patients using expensive medications compared to the general population is relatively low. Nevertheless, this suggests that the quantities of medications that remain unused among the general population are also of great concern.

Various interventions can be implemented to reduce the amount of unused medication when patients discontinue therapies, such as dispensing smaller medication amounts or redispensing unopened medication packages. In this study, many patients had unopened packages at home, the number of which would likely be reduced or prevented if patients had received a smaller amount of medication, such as a one-month or a one-package supply. Dispensing smaller amounts will increase the dispensing fee, which is not cost-effective when medications are relatively cheap[24,25]. However, in the case of expensive medications, the dispensing fee is a fraction of their value and dispensing smaller amounts would likely lead to savings. This idea should be evaluated taking into account the patient perspective and their willingness to receive smaller amounts, as shorter refill intervals may be a burden to some patients because of the increased number of pharmacy visits. From a societal perspective and the high costs associated with these therapies, however, asking for such co-operation could be justified. Moreover, not all medications are available in small package amounts. Manufacturers sometimes produce large package sizes that pharmacists are not permitted to split into smaller amounts, and are thereby obliged to supply as large quantities. For the successful implementation of dispensing smaller amounts, a joint initiative may be necessary, involving the prescriber, the pharmacist, the patient, and stakeholders of government and industry.

In some cases, waste cannot be prevented, such as when patients develop side effects or with intentional non-adherence. In general, if patients have unused medication packages that are completely unopened, these may still be of good quality and could be redispensed to another patient to reduce medication waste. This could be hypothetically feasible if several requirements are fulfilled[26,27]. Primarily and most importantly, the quality of the medications must be guaranteed by monitoring the patients' storage conditions at home. Previous research has demonstrated that the majority of patients store their OACDs, which require room temperature storage, within the recommended temperature range[28], indicating that these medications might be suitable for redispensing. With regards to bDMARDs, which require refrigeration, studies report that most patients do not store these correctly at home, making these less suitable for redispensing[29,30]. Furthermore, redispensing should be in compliance with national regulations. In the Netherlands, redispensing is not prohibited by law and may thus be feasible, although this would require adjustments in clinical guidelines of pharmacist organizations as they are currently not allowed to take back medication that has left the pharmacy. However, feasibility of redispensing strongly depends on a country's policy.

When developing waste-reducing interventions, not only patient utilization healthcare patterns such as the amount of medication that is supplied and the number of medications regularly used should be taken into account, but also patient awareness regarding medication waste should be increased, and education about safe disposal of unused medications[31,32].

The quantity of unused medications among patients discontinuing OACD or bDMARD therapies was explicitly assessed. In clinical practice, it would be useful to be able to predict which patients are likely to discontinue therapy. Here, it is shown that patients who recently started therapy (<6 months) discontinued therapies primarily due to adverse effects, while those who were using these medications for a longer period commonly discontinued therapies due to inefficacy. These differences may reflect opportunities to target specific patients for waste-reducing interventions. A management program for patients using OACDs, which consisted of intensive care offered by healthcare providers focusing on the early identification of adverse effects, showed that the amount of medication waste due to therapy discontinuation could be reduced by 30%[7]. Implementing such a program might be valuable for patients beginning therapy. For patients who are in a later stage of therapy, the physician evaluates whether the therapy is effective, and decides if the therapy should be (dis)continued. These decisions are often based on national disease-specific treatment guidelines. To tackle medication waste in the later stages of therapy, patients should only receive the amount of medication needed until the next consultation with their physician. Some countries have implemented guidelines restricting the period for which medications can be prescribed, such as prior authorization in the US and a one-month prescription period for expensive medications in the Netherlands.

Limitations

The number of patients using OACDs and bDMARDs assessed for discontinuation of therapies was large enough to enable us to satisfactorily determine the outcome measures.
However, some limitations should be noted. It was not possible to include all patients who were considered to have discontinued therapy. In addition, terminally ill and deceased patients were not included and non-adherence among patients was not taken into account. Patients may also have given socially desired answers as they could be embarrassed about having unused expensive medication at home. Therefore, this study might underestimate the absolute quantity and value of unused expensive medications. Furthermore, patients may have incorrectly reported the amount of unused medication due to a recall-bias. However, to minimize this risk the recall period was limited to four months. Lastly, this single-center study may hamper the generalizability of the outcomes to other centers.

Conclusions

Both OACD and bDMARD therapies comprise a major part of the costs spent on expensive therapies, and this study shows that more than half of patients who discontinue OACD or bDMARD therapies have unused medications, worth around €1100 per patient. These findings emphasize the need for waste-reducing interventions to save costs.

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Conflicts of interest

None.

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Appendix A: Oral anti-cancer drugs (OACDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs) included in this study.

OACDs	bDMARDs
L01AA Nitrogen mustard analogues	L04AA Selective immunosuppressants
L01AD Alkyl sulfonates	L04AB Tumor necrosis factor alpha inhibitors
L01AX Other alkylating agents	L04AC Interleukin inhibitors
L01BB Purine analogues	
L01BC Pyrimidine analogues	
L01CB Podophyllotoxin derivatives	
L01XB Methylhydrazines	
L01XE Protein kinase inhibitors	
L01XX Other antineoplastic agents	
L02BA Anti-estrogens	
L02BB Anti-androgens	
L02BG Aromatase inhibitors	
L04AX Other immunosuppressants	

Chapter 2.3

Pharmacists' activities to reduce medication waste: an international survey

Charlotte L Bekker
Helga Gardarsdottir
Antoine CG Egberts
Marcel L Bouvy
Bart JF van den Bemt

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Abstract

Objectives
To identify activities that pharmacists undertake to reduce medication waste, and to assess the extent to which these activities are implemented, their importance for waste-reduction and feasibility for broad implementation.

Methods
A two-phase survey was conducted among community and hospital pharmacists working in different developed countries. Phase one used an open-ended questionnaire to identify activities undertaken by pharmacists. Answers were thematically analysed to construct a list of medication waste-reducing activities. In phase two, a questionnaire was disseminated among pharmacists from different countries, to assess if these activities are implemented (yes/no), their importance and feasibility (1 to 5 ranking scale).

Results
In phase one, 53 pharmacists participated and 14 activities were identified. These were categorized into the pharmaceutical supply chain: prescribing, dispensing (pharmacy/patient-related) and leftover stage. In phase two, 89 pharmacists participated. Most activities were implemented by a minority of pharmacists. Reducing medication amounts in stock was most frequently implemented (dispensing stage pharmacy-related; 86%), followed by collecting unused medications (leftover stage; 77%) and performing a medication review (dispensing stage; 68%). Waste-reducing activities in the dispensing stage activities were both considered most important and feasible (ranked 4). Overall, most activities scored higher on importance than on feasibility.

Conclusions
Pharmacists have various opportunities to reduce medication waste throughout the pharmaceutical supply chain, however, not all are broadly implemented. Pharmacists consider waste-reducing activities important, but they are less certain about the feasibility for implementation in practice.

Introduction

Medication waste can occur in all stages of the pharmaceutical supply chain. For instance, physicians may prescribe unnecessarily large quantities (prescribing stage). During the dispensing stage, pharmacists dispense larger quantities as manufacturers' package sizes may exceed the amount required for treatment. Once medication has been supplied to the patient, early treatment changes, for example, due to some side effects or unsatisfactorily efficacy, can lead to an excessive amount of unused medication at home. Moreover, low adherence of patients to treatment regimens can contribute to medication waste as well. Finally, medications that are left unused and of good quality, are generally destroyed if returned to the pharmacy[1–5].

There is increased awareness of the financial impact of medication waste[6–9]. Health care budgets are limited and unused medications can be considered a waste of resources. It is important that patients dispose of these properly, for instance, by returning these to pharmacies or chemical waste depots. However, patients sometimes incorrectly dispose of unused medications through household garbage, the toilet, or sink, with the risk of polluting the environment[10]. Active pharmaceutical ingredients have been detected in surface, ground, and drinking water[11,12] that may have detrimental effects on aquatic species and ecosystems[13,14]. Efforts to reduce medication waste and the undesirable economic and environmental burden are, therefore, warranted.

Pharmacists are key players in the pharmaceutical supply chain and are in a position to contribute to the reduction of medication waste[15]. One can presume that individual pharmacists have already initiated various strategies to reduce this waste. However, information about activities that are implemented in practice to reduce waste is limited. The availability of such information could facilitate an exchange of knowledge between pharmacists on how to reduce medication waste and could promote the implementation of such activities in daily practice. Therefore, the aim of this study was to identify activities that individual pharmacists have currently undertaken in community and hospital pharmacies in developed countries to reduce medication waste. Moreover, this study aimed to assess the extent to which these activities are implemented, the importance of the activities for reducing waste, and the feasibility for broadly implementing these activities in daily practice.

Methods

Study design
This survey consisted of two phases: an exploratory phase of which the results were used for the subsequent assessment phase. The study was conducted between July 2014 and October 2016. The first phase aimed to identify activities currently undertaken by individual pharmacists and the second phase aimed to assess the extent to which these activities are implemented and their importance and feasibility (see Figure 1 for overview).

EXPLORATORY PHASE

Questionnaire
Open-ended online questionnaire

Participants
Community and hospital pharmacists working in Western countries

Outcome
Inventory of waste reducing activities currently undertaken by individual pharmacists

ASSESSMENT PHASE

Questionnaire
Closed-ended paper questionnaire including the activities identified in the exploratory phase

Participants
New set of community and hospital pharmacists working in Western countries

Outcomes
Assessment of the frequency that the activities are implemented
Assessment of the importance of the activities to reduce medication waste according to pharmacists
Assessment of the feasibility of the activities to implement in daily practice according to pharmacists

Figure 1: Overview of the main methods used for the two phases.

Ethics

All data were analysed anonymously. Under Dutch law, no approval from an Ethical Review Board was required as only health care professionals were involved.

Phase one: exploration

Participants' inclusion and data collection

working in a community, hospital or academic setting located in a country with a ranking of 'very high' on the human development index[16] were eligible for participation. Pharmacists were approached through (inter)national organizations of pharmacists or through the personal network of the research group. Pharmacists received an email invitation explaining the purpose of the study that included a link to the questionnaire. Non-responders received two reminders, the first reminder was sent two weeks after the initial invitation and the second two weeks thereafter. Countries were only included in the analysis if two pharmacists from that country completely filled in the questionnaire.

Questionnaire

Activities that individual pharmacists have implemented to reduce medication waste were explored by an open-ended questionnaire that was created in an online survey tool. The questionnaire was developed by the research group and pre-tested in terms of interpretation by a pharmacist who was not involved in the study. The questionnaire consisted of three sections (see Appendix A): the prescribing, the dispensing and the leftover stage. Each section consisted of several questions that focused on activities implemented to reduce medication waste. As the community and hospital setting may differ, hospital pharmacists were asked two additional questions regarding activities implemented during the (preparation prior to) administration of medications and activities implemented at the hospitals' wards. Pharmacists' country of origin and work setting (community pharmacy/hospital pharmacy/academic) were recorded as well.

Data analysis

Data from the questionnaires were exported to Microsoft Excel version 2010 (Microsoft, Albuquerque, United States) and analysed using thematic content analysis[17]. Pharmacists' answers were coded by the first researcher and reviewed by the second researcher[18]. Any disagreements between the two researchers were discussed until consensus was reached. Hereafter, both researchers independently categorized the activities into the three previous defined stages according to their content which they subsequently discussed until both agreed.

Phase two: assessment of implementation, importance and feasibility

Participants' inclusion and data collection

A questionnaire was constructed based on the results of the first phase. This questionnaire was distributed among pharmacists participating in the 45th European Symposium on Clinical Pharmacy that was held in Oslo, Norway, in October 2016. Only questionnaires completed by pharmacists working in a country, as defined in phase one, were included in the analysis.

Questionnaire

Questions were formulated for all activities that were identified during the first phase of the study and divided into the predefined stages (Appendix B). The questionnaire was also pre-tested by a pharmacist not involved in the research study. For each activity, pharmacists were asked to indicate whether the activity was implemented in their country (yes/no), to rank the importance of the activity to reduce waste and the feasibility to implement in practice. Answers were measured on a scale with a range from one, denoting the activity as not important or feasible, to five, very important or feasible. In addition, pharmacists were able to add other activities if these were not included. Their country of origin and work setting (community pharmacy/hospital pharmacy/academic/other) were recorded as well.

Data analysis

Data from the questionnaires were imported in Microsoft Excel and descriptively analysed (frequencies and percentages). To equally weigh the frequency scores, more than 50% of the pharmacists within a country should have reported implementing the activity, because activities taken by fewer than half of the pharmacists within a country were assumed to be taken at random and therefore not counted. The importance and feasibility ranking scales were assessed as medians with interquartile ranges. First, the median ranking for each activity

within each country was determined. Subsequently, the median ranking for all activities were calculated and averaged per stage. All analyses were performed in STATA version 13 (StataCorp, College Station, United States) and Microsoft Excel.

Results

Fifty-three pharmacists from 19 developed countries were included in the first phase of the study (Appendix C). The activities currently undertaken by individual pharmacists to reduce medication waste were categorized into the prescribing, dispensing and leftover stage. During the analysis, two subthemes within the dispensing stage were added, i.e., activities related to the pharmacy or to the patient's medication therapy and storage practices. In total, 14 main activities were identified (Table 1).

Eighty-nine pharmacists from 22 developed countries were included in the second phase (Appendix D). The pharmacists reported no new activities on top of the activities that were identified in phase one. Results of the two phases are presented together per stage hereafter to facilitate a comprehensive presentation.

Table 1: Estimated frequency of activities implemented to reduce medication waste. A country was considered to have implemented an activity if more than 50% of the pharmacists within that country reported that the activity is implemented.

Activity	Countries (n=22) n (%)
The prescribing stage	
Prescribers tailor prescription amounts	7 (31.8)
Counsel prescribers on efficient prescribing	7 (31.8)
The dispensing stage	
Pharmacy related	
Pharmacists adjust prescribed amounts	10 (45.5)
Dispense opened medication package	11 (50.0)
Use dose-dispensing system	12 (54.5)
Manage medication amounts in stock	19 (86.4)
Limiting storage amounts	18 (94.7)
Exchange medications with other pharmacies	14 (73.7)
Pooling patients	
Patient related	7 (31.8)
Store patient's medications	2 (9.1)
Review patient's medications	15 (68.2)
Discuss needed quantity	5 (22.7)
Use home medications during hospitalization	10 (45.5)
The leftover stage	
Collect unused medications	17 (77.3)
Donate unused medications	4 (18.2)
Redispense unused medications	0 (0)

The prescribing stage

To reduce medication waste in the prescribing stage, two main activities that were undertaken were identified. Namely, prescribers could tailor the prescribed amount and pharmacists could counsel prescribers on the prescribed amount. Most pharmacists mentioned that prescribers tailor the amount based on medication characteristics (e.g., cost), on patient characteristics (e.g., age) and the expected duration of time until symptoms should resolve. Some pharmacists remarked that they counsel prescribers on how to prevent waste. For instance, by recommending the duration of use for each prescription whenever possible.

Activities in the prescribing stage were reported to be implemented by approximately one-third of the countries (Table 1). On average, these activities were considered important for reducing waste (median ranking 4), and were ranked neutral in terms of the feasibility of their implementation in practice (median ranking 3, Figures 2 and 3).

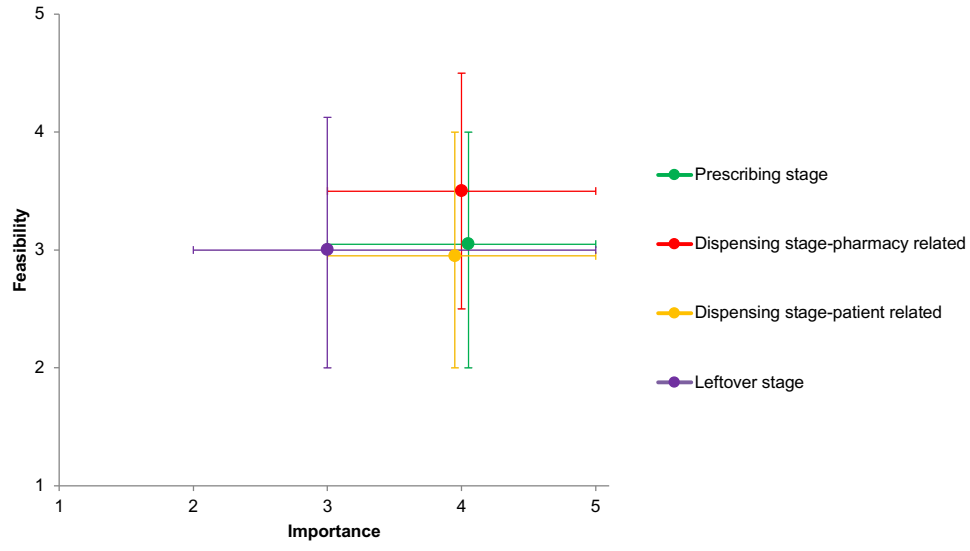

Figure 2: For each stage of the pharmaceutical supply chain, median importance ranking to reduce medication waste and median feasibility ranking to implement in practice (with upper and lower quartile) given by the pharmacists.

The dispensing stage

Pharmacy related activities

Activities undertaken by pharmacists to reduce medication waste in the dispensing phase focused mainly on dispensing smaller amounts to the patient, by adjusting the amount of prescribed medications to the treatment duration, dispensing opened medication packages and using dose-dispensing systems. Most pharmacists indicated that the number of days for which medications can be dispensed is limited by law and generally concerns a three-month supply. Some pharmacists mentioned that they are allowed to adjust the amount of medications prescribed without consulting the prescriber. One example of such an activity

is when a pharmacist notices that a physician has prescribed more than needed, they inform the patient and reduce the dispensed amount. However, this approach is not achievable for all pharmacists as it was frequently reported that pharmacists are only allowed to dispense complete medication packages, even when the prescribed amount is less. Concerning internal waste management at the pharmacy, pharmacists mentioned that they manage the amount of medications kept in stock. For example, some pharmacies exchange medications that are rarely used or that are close to the expiry date to prevent disposal. In some hospital pharmacies, patients who are treated with parenteral medications are scheduled on the same day in order to pool injection vials.

Stock management was most frequently reported activity implemented to reduce medication waste, in 86.4% of the responding countries. Of these countries, 94.7% indicated that they limit the amount of medications that are kept in stock and 73.7% collaborated with other pharmacies to exchange medications. The other pharmacy-related activities of the dispensing stage were reported to be implemented by approximately half of the countries. The activities were ranked the highest in terms of importance and feasibility. Of all activities, using dose-dispensing systems and stock management ranked highest concerning their importance for reducing waste (median ranking >4), but lower on feasibility for implementation (median ranking 3 and 4 respectively).

Patient related activities

Patient-related activities for reducing waste reported in the dispensing stage aimed at optimizing medication therapy and storage management by the patient. These include storing the majority of patient's medications at the pharmacy, reviewing the patient's medications, and starting a dialogue with the patient about the quantity needed. Furthermore, through discussion with the patient, pharmacists try to adjust the dispensed amount to the patient's actual needs, and to increase their awareness about waste. Some hospital pharmacists reported that patients are allowed to use their own home medications during hospital admission, thereby reducing medication waste.

Sixty-eight percent of the responding countries reported to perform medication reviews. Only 9.1% of the countries stored patients' medications at the pharmacy and this was considered less feasible (median ranking 2). Overall, patient-related activities in the dispensing stage were considered important for reducing waste (median ranking 4), but scored lower on feasibility for implementation (median ranking 3).

2.3

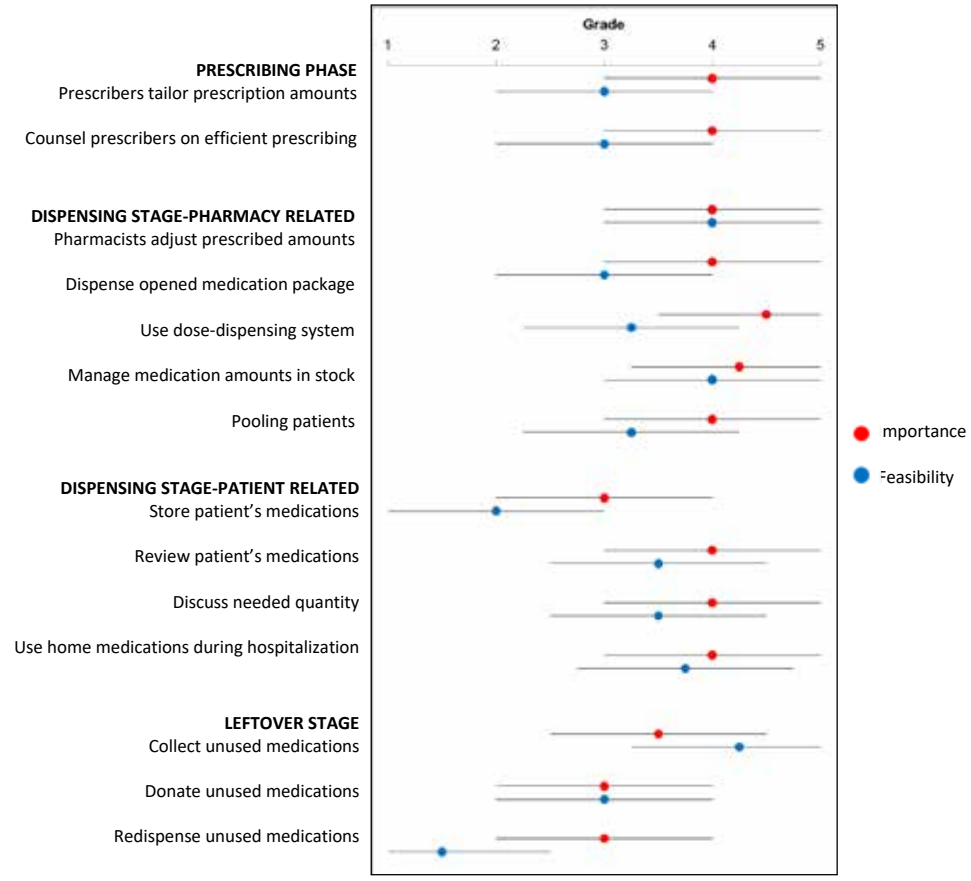

Figure 3: For each activity, median importance ranking to reduce medication waste and median feasibility ranking to implement in practice (with upper and lower quartile) given by the pharmacists.

The leftover stage

Three waste-reducing activities were identified in the leftover stage. Community and hospital pharmacists mentioned that the amount of unused medications is collected in the pharmacy for safe disposal. A few pharmacists indicated that these medications are donated to charities for people in need. As a last activity, hospital pharmacists mentioned that unused medications were redispensed, under the condition that the medications were stored at the hospital ward and had not been dispensed to patients.

Of the responding countries, 77.3% reported collecting unused medications and 18.2% donating unused medications. None of the countries reported redispensing unused medications returned by patients. Activities aimed at tackling medication waste during the leftover stage scored lowest in terms of both importance and feasibility (median rankings 3).

Discussion

This study shows that pharmacists undertake several activities to limit medication waste in all stages of the pharmaceutical supply chain. More than half of the participating countries reported using dose-dispensing systems, managing the amount of medication in stock, performing medication reviews, and collecting unused medications. Pharmacists considered activities of the prescribing and dispensing stage most important for reducing medication waste and pharmacy-related activities of the dispensing stage most feasible for implementation in practice. Most activities scored lower in terms of feasibility than importance.

This is the first study that gives an overview of activities taken by community and hospital pharmacists. For this study, several limitations could be identified. Most importantly, only pharmacists were consulted. It is possible that other healthcare professionals would identify other medication waste-reducing activities. Also, not all pharmacists of the countries approached responded to the survey, hence, some activities might have been missed. However, no additional activities were mentioned in the second phase of the study that included other countries as well. Therefore, one can assume that the list of potential activities to reduce waste is comprehensive. Third, the second researcher was not blinded for the coding of the first researcher. However, the pharmacists mentioned concrete activities and thus the risk of misclassification is considered minimal. Fourth, not all questionnaires were fully completed. We found that the reported answers of uncompleted questionnaires did not differ from the fully completed questionnaires. Hence, it is assumed that the missing answers would not have altered the findings. Fifth, the respondents and the activities they reported might not necessarily be representative for their whole country. However, it still enabled us to report on activities that pharmacists have implemented to reduce medication waste and to indicate which activities are implemented most frequently. Sixth, only activities implemented by the majority of pharmacists within a country were considered to be implemented by that country. This could have resulted in an underestimation of the frequency that activities were taken. Finally, this study involved pharmacists working in developed countries, and any generalization of our results with respect to other countries should be viewed with caution.

Many pharmacists considered the waste-reducing activities as important, which emphasizes the necessity for interventions that aim to combat medication waste. The study suggests that activities that are related to the organization of the pharmacy and the dispensing stage were most often implemented and were considered most feasible. Overall, activities that focus on waste prevention were found to be most promising. But as not all activities were considered achievable to implement in practice, this may suggest that barriers hamper feasible implementation and a need for feasible waste-reducing interventions. Looking at the current evidence of potential interventions, an example of a waste-reducing activity in the prescribing stage is to dispense smaller amounts of expensive medications. Limiting the amount of medication supplied for a first time to a two-week period, followed by 30 days for a repeat prescription[19], may decrease the risk of unused medications and unnecessary waste. Patients receiving medications for more than 30 days are more likely to waste a part of those medications[20,21]. Additionally, pharmacists could also supply a trial prescription amount to the patient at the start of treatment and supply the remainder when the medication is well tolerated. Paterson et al. showed that a split-fill supply could reduce the cost of medication waste[22]. Regarding the dispensing stage, studies show that increasing the frequency of medication batch preparations or scheduling patients with the same therapy on the same day in the hospital pharmacy could reduce medication waste and expenditures[23–25]. However, applying such strategies in the community pharmacy is not financially feasible as large quantities of relatively low-cost medications are generally dispensed and additional dispensing fees may outweigh the savings on medication costs[26]. Pharmacists should, therefore, consider the individual medication costs when deciding if smaller amounts should be dispensed to the patient, as this may not always save costs, however, it might still reduce the risk of environmental pollution.

It is important not to focus on waste reduction by prescribers and pharmacists but also to increase patients' awareness of medication waste. Patients often only pay a part of the medication cost out of pocket and are not always aware of the total cost of medication. Governments and health care authorities have started campaigns to raise patients' awareness about medication prices, including displaying the price on the medication package or on the dosage label[27]. Furthermore, discussing the quantity dispensed with the patient could reduce the supply of unwanted medications and, potentially, medication waste[28]. If adherence of patients to their treatment regimen could be increased, medication waste might be reduced as well. Moreover, medication reviews could be periodically conducted to identify medication therapies that are dispensed to patients but no longer needed or non-adherence. Unnecessary medication therapies could thereby be discontinued helping to reduce the waste of unnecessary healthcare costs. Regarding the leftover stage, very few interventions have been investigated and most studies assess the amount and economic value of medications returned to pharmacies[2,4,29–31]. The donation of medications to other countries is disapproved of by the World Health Organization[32]. The question as to whether medications returned to pharmacies could be redispensed remains hypothetical[33,34], as many prerequisites need to be addressed in order to redispense unused medications, such as how to ascertain the quality of the medications, the patients trust in redispensed medications, and the legal- and financial feasibility[35,36].

Multiple interventions seem promising for reducing medication waste. However, it seems that various barriers hamper their implementation. Barriers one could think of are each nation's reimbursement systems which influence how medications are prescribed, dispensed and collected at the pharmacy. Furthermore, legislation could be challenging to the implementation of waste-reducing activities. Some of the respondents reported that different activities, such as splitting packages into smaller quantities, are not legally allowed. Even within a country, pharmacists can counteract waste differently as this will also depend on the availability of resources in the pharmacy, like sufficient knowledge of pharmacy workers of the possibilities to reduce medication waste and the monetary budget. For the successful implementation of waste-reducing interventions, such barriers should be identified and overcome first.

Conclusions

This study demonstrates that pharmacists have developed many activities to reduce medication waste in all stages of the pharmaceutical supply chain. However, not all potential activities to reduce medication waste have been implemented in daily practice. Activities focusing on waste prevention seem most promising. Even though pharmacists consider activities for reducing medication waste important, they are less certain about the feasibility of broadly implementing these activities in daily clinical practice.

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Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

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Appendix A: Questionnaire of phase one

1. Which initiatives are taken nationally and in pharmacies to minimize medication waste?
   - Initiatives taken by prescribers
   - Initiatives taken in the pharmacy during dispensing
   - Initiatives taken for leftover unused medications

Prescribing stage
2. Which phases are taken by prescribers to minimize medication waste?
3. In which cases is the number of drugs prescribed tailored on a patient's health condition?
4. In which cases is the number of drugs prescribed tailored on costs or on other drug characteristics?

Dispensing stage
5. Which initiatives are taken in pharmacies during the dispensing of medications?
6. What is the maximum amount of days for which medications can be dispensed in your country?
7. Which initiatives are taken at the different departments of the hospital?
8. Which initiatives are taken in the hospital pharmacy while preparing/compounding the medication?

Leftover stage
9. What is done with unused medications that are returned to the pharmacy?

Appendix B: Questionnaire of phase two

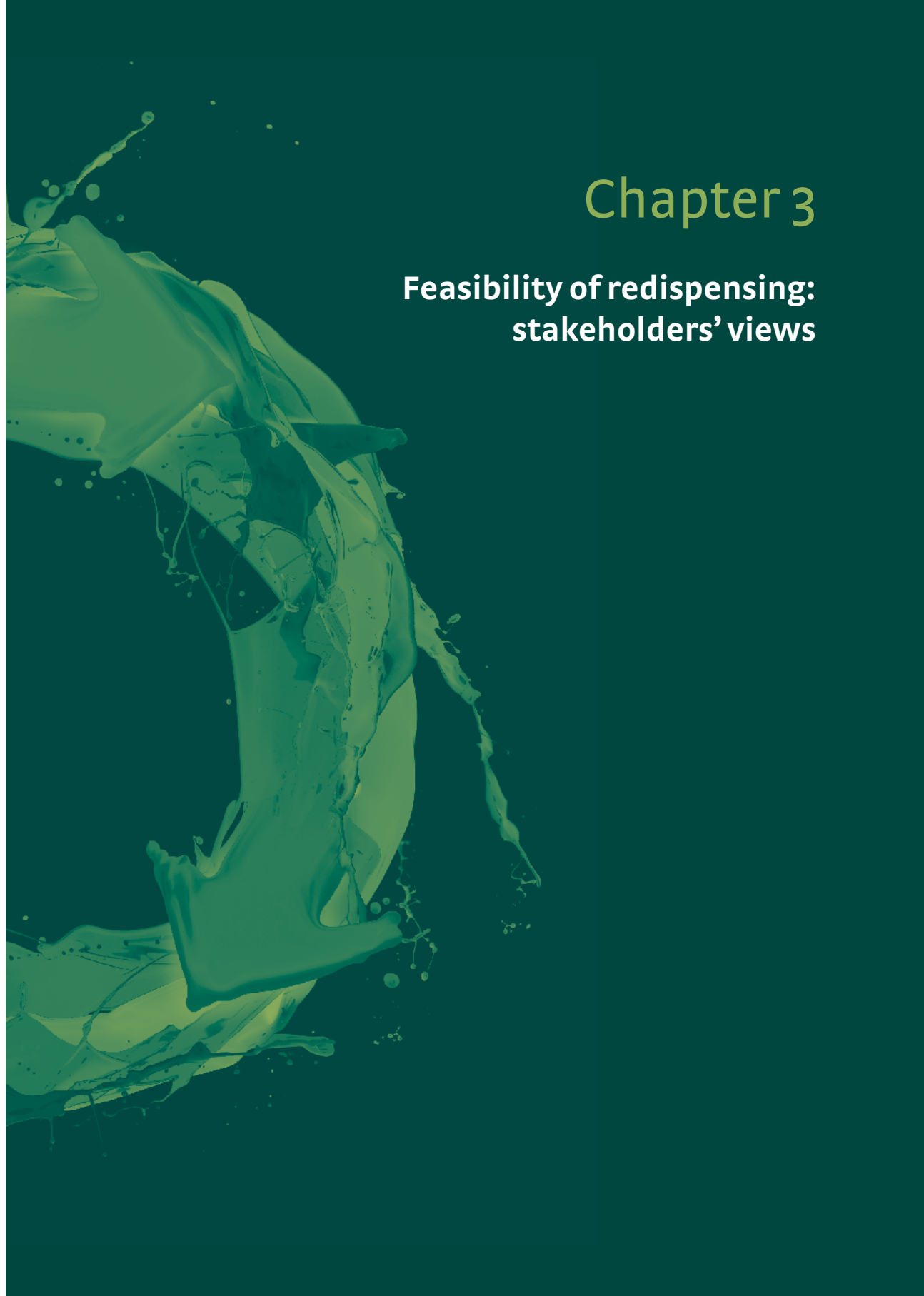
	Activity taken in your country		Important for decreasing medication waste	Feasible to implement in practice
	Yes	No	1(not)-5(very)	1(not)-5(very)
The prescribing stage				
Do prescribers tailor the amount of medications that they prescribe in order to limit medication waste?				
Do pharmacists counsel physicians on how to combat potential medication waste?				
The dispensing stage				
Are pharmacists allowed to adjust the prescribed amount during dispensing in order to limit potential medication waste?				
Are pharmacist allowed to remove medication from the original package in order to limit potential medication waste (e.g. split packages)?				
Are pharmacists using (unit) dose dispensing systems?				
Are pharmacists managing the amount of medications that is kept in stock in the pharmacy in order to limit medication waste? If yes, how? • Limiting the amount that is kept in stock • Collaborating with other pharmacies to exchange almost expired medications • Other:				
Are pharmacists in the hospital pharmacy scheduling patients on the same day so that medication is prepared at once in order to limit medication waste (e.g. pooling of patients with IV drugs)?				
Please explain other actions taken during dispensing that limit medication waste:				
Optimizing stock management by the patient				
Are pharmacists enabling patients to store a part of their prescribed medications in the pharmacy?				
Are pharmacists reviewing patient's medications in order to limit medication waste (e.g. medication review, optimization of pharmacotherapy)?				
Are pharmacists discussing the quantity needed for symptom improvement with the patient in order to limit medication waste (increase awareness about waste)?				
Are patients allowed to bring their home medication to the hospital and use this during hospitalization?				
Please explain other actions discussed during patient's counselling that limit medication waste:				
The leftover stage				
Are pharmacists collecting unused medications so they can dispose of them safely?				
Are pharmacists allowed to donate unused medications that are returned to the pharmacy to other countries or people in need?				
Can unused medications that are returned to pharmacies by patients be re-dispensed to a different patient? • If yes, do the returned medications need to apply with specific criteria? Which criteria?				

Appendix C: Number of pharmacists per country of origin and work setting that participated in phase one

n=19	Total n=53	Community pharmacy n=39	Hospital pharmacy n=14
Australia	2	2	
Belgium	4	3	1
Canada	2	2	
Croatia	2	2	
Denmark	3	2	1
Estonia	5	4	1
Finland	2	1	1
France	2	1	1
Iceland	8	8	
Ireland	2	1	1
Italy	2		2
Malta	2	1	1
Netherlands	4	3	1
New Zealand	2	1	1
Norway	2	1	1
Spain	2	2	
Switzerland	3	2	1
United Kingdom	2	2	
United States	2	1	1

Appendix D: Number of pharmacists per country of origin and work setting that participated in phase two. 12 pharmacists were working in multiple settings and therefore the total sum exceeds 89.

n=22	Total n=89	Community pharmacy n=13	Hospital pharmacy n=66	Academic n=15	Other n=7
Australia	1		1		
Austria	11		11	1	
Belgium	2		2		
Canada	2	2		1	
Croatia	1	1			
Denmark	1	1		1	
Estonia	2		2		
Finland	1				1
France	6		6	2	
Germany	2	2		1	
Ireland	1			1	
Italy	2		2		
Netherlands	5	2	1	1	1
Norway	24		21	2	1
Portugal	4	1	2	1	1
Romania	2		2		
Slovakia	1		1		
Slovenia	4		3	1	
Spain	8	1	7		1
Sweden	1		1		
Switzerland	6	2	4	3	
United Kingdom	2	1			2



Chapter 3

Feasibility of redispensing: stakeholders' views

Chapter 3.1

Redispensing of medicines unused by patients: a qualitative study among stakeholders

Charlotte L Bekker
Helga Gardarsdottir
Antoine CG Egberts
Marcel L Bouvy
Bart JF van den Bemt

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Abstract

Background
Medication waste has undesirable economic and environmental consequences. This waste is partly unavoidable, but might be reduced by redispensing medicines unused by patients. However, there is little knowledge of stakeholders' views on the redispensing.

Objective
To identify the stakeholders' views on the redispensing of medicines unused by patients.

Setting
Dutch healthcare system

Methods
Semi-structured interviews were conducted with 19 Dutch stakeholders from September 2014 until April 2015. The interview guide included two themes: medication waste and redispensing of unused medicines. The latter included qualitative-, legal- and financial aspects and stakeholder involvement, with specific attention to the patient. Interview transcripts were subjected to thematic content analysis.

Main outcome measure
Requirements related to the redispensing of unused medicines.

Results
All stakeholders considered the redispensing of medicines desirable if the implementation is feasible and the requirements for the safe redispensing are met. All of them pointed out that the product quality of redispensed medicines should be guaranteed and that it should be clear who is responsible for the quality of redispensed medicines. The stakeholders stated that transparent communication to patients is essential to guarantee trust in the redispensing system and that patients should be willing to use redispensed medicines. Moreover, the redispensing system's benefits should outweigh the costs and a minimal economic value of medicines suitable for redispensing should be determined.

Conclusions
Redispensing unused medicines could decrease medication waste if several requirements are met. For successful implementation of a redispensing system, all relevant stakeholders should be involved and cooperate as a joint-force.

Introduction

Spending on prescription medicines has increased substantially over the past decades due to increased use and the introduction of new expensive medicines[1]. It is known that not all prescribed medicines are used. Medication waste refers to any medicine that expires or remains unused throughout the medicines supply chain[2]. These unused medicines are commonly disposed with household waste, returned to the pharmacy or collected through chemical waste programs and subsequently destroyed[3]. This waste has undesirable implications both economically, as it costs the health system hundreds of millions every year[4–6], and environmentally, as pharmaceuticals end up in the environment.

Factors that contribute to medication waste are apparent in all phases of the pharmaceutical supply chain, for instance, by producing inadequate package sizes, prescribing or dispensing more medicines than required, low adherence or the occurrence of unpredictable treatment changes due to unsatisfactory treatment response or the occurrence of side effects[7–14]. A variety of stakeholders is involved in this chain, such as the manufacturer, prescriber, pharmacist, user and regulator.

Medication waste can only be partially prevented[4]. It may be reduced by the redispensing of medicines unused by the patient that are returned to a pharmacy. An internet hotline launched by the Dutch Ministry received numerous proposals from patients on how to reduce waste in health care, the majority of which suggested the redispensing of unused medicines[15]. Moreover, it has been proposed several times that the recycling of unused medicines can be very beneficial for the healthcare budget[12,16–20]. However, sparse information is available regarding the stakeholders' views on the feasibility of redispensing unused medicines. Moreover, the requirements, including product quality requirements and the financial aspects of a redispensing system, have not been thoroughly investigated. Consultations with stakeholders are important in facilitating health policy decision-making[21].

Aim of the study
The aim of this study was therefore to identify the stakeholders' views on the redispensing of medicines unused by the patient.

Ethics approval
Under Dutch law, this study did not require the approval of an Ethical Review Board. The study protocol was internally reviewed by the local scientific committee of the Sint Maartenskliniek.

Method

A qualitative study[22] was performed by conducting semi-structured interviews with Dutch stakeholders from September 2014 until April 2015. This method enables an in-depth identification of the stakeholders' views, as topics can be more thoroughly discussed. To include the relevant stakeholders that were considered most informative to the subject of the study, purposive sampling was used. Therefore, a list of stakeholders was compiled by two researchers and then thoroughly discussed with the other members of the research group. A member of each stakeholder (healthcare professionals, health authorities, health insurance

companies, patient- and consumer organisations, pharmaceutical industry representatives and wholesalers) was subsequently approached by email and invited to participate. Members were chosen based on their expertise and asked to represent their organisation. Furthermore, interviewees were asked to check the list of stakeholders for completeness.

Data collection

The stakeholders' views towards the redispensing of unused medicines were examined. An interview guide (overview Table 1 and framing of questions Table 2) was developed to that end and included two themes: 1) the extent of medication waste and opportunities to decrease waste and 2) the redispensing of unused medicines (all administration forms). The study into the second theme was more in-depth, including such issues as product quality, legal- and financial aspects, patient attitude and stakeholder involvement. Beside these themes, any other issue could be addressed at the end of the interview.

The interview guide was pilot-tested on content validity and interpretation by interviewing an independent expert. The semi-structured interviews were conducted face-to-face or by phone. All interviews were conducted by a first researcher (PhD candidate, female) with training in interviewing skills and with no relation to the stakeholders. Besides the interviewee and the main researcher, no one else was present during the interviews. Interviewees gave oral consent for audio recording and anonymity was guaranteed. The interviews were transcribed verbatim and, to ensure the correct interpretation, each interviewee received a summary of the transcripts and could provide feedback on the data.

Table 1: Overview of the interview guide

1. Medication waste
Extent of the problem and perceived need for action
Opportunities to decrease medication waste
2. Redispensing of unused medicines
General view on redispensing
For which medicines applicable
Product quality
Quality criteria
Monitoring of quality criteria
Logistical aspects taken into account
Patient attitude
Factors regarding dispensing that are important to patients
Informing patients on redispensing
Patient's preferences for participating in the redispensing system
Stakeholder involvement
Consequences for stakeholders
Legal aspects
Legal constraints
Responsibility for the redispensing system
Financial aspects
Minimal economic value
Financial handling taken into account (e.g. reimbursements)

Data analysis

The transcripts were analysed thematically[23] using MAXQDA[24]. First, relevant text fragments were selected individually by two researchers and then compared to ensure no data would be missed. Second, the first researcher performed the open coding of the fragments[25]. The second researcher reviewed the open coding of ten randomly chosen codes of five transcripts. The researchers agreed on 96% of the open coding and the remaining discrepancies were resolved by consensus. Lastly, the first researcher applied axial and selective coding[25]. Relationships between the open codes were identified with axial coding and the codes were labelled into themes. Using selective coding, the themes were sorted into the previously defined themes as used in the interview guide. This process was reviewed in its entirety by the second researcher until both researchers fully agreed on the content of the themes. Prior to the last interview, saturation of the themes was achieved as no new themes emerged. As this study aimed to broadly explore all of the stakeholders' views, no similarities or contradictions in the views of different stakeholders were explored. Checklists were used to ensure comprehensive reporting of qualitative research[26,27].

Table 2: Leading questions of the full interview guide

1. Medication waste
What is your opinion on the waste of medicines
Which options could decrease this waste
2. Redispensing of unused medicines
What is your opinion on the redispensing of unused medicines
Which medicines would be suitable for this
Product quality
Which quality criteria are important to redispensing
Why do you think these are important
How can these criteria be fulfilled
What should be arranged logistically (e.g. track and trace)
Patient attitude
What is important to the patient when medicines are redispensed
What do you think about the possibility to choose between a new and redispensed medicine
Should the patient be informed on whether he/she receives redispensed medicine or not
Which (dis)advantages do you foresee
Stakeholder involvement
Which consequences (positive/negative) do you foresee for
I. Pharmacists
II. Manufacturers
Legal aspects
What should be changed legally to make redispensing possible
Who should take responsibility for a redispensing system
Financial aspects
What should be arranged financially to make redispensing possible I. Patient incentive for returning medicine II. Medicines cheaper for next patient III. Pharmacy incentive
What would be the effect on the health care premium
How should reimbursement systems be organised
Are there other themes you want to mention

Results

All of the Dutch stakeholders approached were willing to participate in the study. In total, 19 interviews with stakeholders were held, one of which was conducted with two interviewees at the same time for the sake of convenience (both were representatives from two insurance companies). Stakeholders originated from the following professional fields: 3 community pharmacy employees/organisations, 3 hospital pharmacy employees/organisations, 3 medical specialists/organisations, 3 health authorities, 2 healthcare insurance companies, 2 patient/consumer organisations, 2 pharmaceutical industry representatives and 1 wholesaler. Of all interviews, 15 were held face-to-face and 4 by phone due to practical reasons (Table 3). The median duration of an interview was 32 minutes (range 12 to 56). The themes are discussed below and anonymous stakeholder quotations are presented as illustrations.

Table 3: Demographic characteristics of the interviewees

Interviewee	Gender	Profession	Representative of organisation
1	M	Hospital pharmacist	-
2	F	Pharmacy technician	-
3	M	Chairman	Pharmaceutical industry
4	F	Advising pharmacist	Healthcare insurance company
5	M	Healthcare purchaser	Healthcare insurance company
6	M	Healthcare purchaser	Healthcare insurance company
7	M	Campaign manager	Consumer organisation
8	M	Manager	Pharmacy organisation
9	M	Hospital pharmacist	Hospital pharmacists' organisation
10	F	Director	Outpatient pharmacists' organisation
11	M	Project leader	Health authority
12	M	Senior advisor	Pharmaceutical industry
13	F	Senior assessor	Health authority
14	F	Senior advisor	Medical specialists' organisation
15	M	Senior advisor	Medical specialists' organisation
16	M	Pharmacist	Wholesaler
17	M	Senior advisor	Patients' organisation
18	F	Board member	Community pharmacy employees
19	M	Chairman	Medical specialists' organisation
20	M	Senior assessor	Health authority

Medication waste

All stakeholders considered medication waste to be undesirable and expressed the importance of the prevention of waste. Most of the stakeholders were aware of the large amounts of unused medicines that are returned to pharmacies and acknowledged the economic and environmental consequences of unused medicines. Many causes of waste were put forward, such as non-adherence, overprescribing and –dispensing, and the discontinuity of care related to hospital admissions. It was expressed that, in order to prevent medication waste, "*It is better to tackle the waste at the source*" (interviewee 20, male, health authority).

Redispensing of unused medicines

All stakeholders stated that the redispensing of unused medicines is desirable if the implementation in clinical practice is feasible. Possible benefits associated with the redispensing of unused medicines were stated, including containment of health care costs and reducing environmental contamination: "*It is nonsense when things are thrown away unused*" (interviewee 12, male, pharmaceutical industry). Medicines for redispensing should be selected based on price (from a cost-effective viewpoint, preferably expensive prescription medicines), storage conditions (temperature sensitive medicines are at an increased risk for quality changes) and package types (blister packs preferable to opened medicine jars). All stakeholders named several requirements that should be met for the safe redispensing of unused medicines, which are shown in Figure 1.

Figure 1: Two central requirements related to the redispensing of unused medicines could be identified from the analysis: patient willingness to use and trust redispensed medicines and guaranteed product quality of redispensed medicines (all administration forms). These are surrounded by the requirements of the redispensing system: legal feasibility, financial aspects that should be taken into account and the roles stakeholders can fulfil

Product quality

Stakeholders identified guaranteed product quality as an essential requirement. Redispensed medicines have to meet the same standard quality requirements as 'new' medicines: *"You should do it in such a way that you can guarantee an unaffected efficacy of the medicine"* (interviewee 1, male hospital pharmacist). To ensure the quality of redispensed medicines, stakeholders pointed out the need to monitor the storage conditions of medicines at a patient's home. The factors put forward as being of influence to the quality were: temperature, light, humidity, agitation, and lapsed expiration date. They mentioned that the quality of the medicine packaging and information leaflet could also be used as an indicator for storage conditions, as these should not be damaged. A health authority stakeholder suggested that concentrations of active drug substances and metabolites should be assessed in extreme conditions (e.g. extreme heat) to predict the likelihood of sustained quality.

Stakeholders from pharmaceutical industry- and pharmacy representatives pointed out that special attention should be paid to the possible introduction of counterfeit medicines within the redispensing system. Currently, the complete chain from manufacturers to wholesalers is regulated according to the Good Distribution Practice (GDP) guidelines. GDP should also apply to redispensing. In addition, some stakeholders, such as a wholesaler, specialist- and pharmacist organisation, pointed out that a track and trace system could be used to decrease the chance of errors within the system. It was suggested that manufacturers should play a role in the quality control, for instance, by adding a track and trace system to the packages. A health insurance company remarked that monitoring the quality of medicines should not expand too much, as this would make it almost impossible to design a practical redispensing system.

Patient attitude

Stakeholders commonly mentioned the importance of the patient's trust in the redispensing system. According to them, guaranteeing the patient's privacy (which medicines they use) and the quality and safety of the medicines are important to patients. A redispensing program is only successful if patients are willing to participate, as they have to return unused medicines to the pharmacy and must be willing to accept redispensed medicines. Furthermore, patient's awareness regarding medication waste should be increased. Communication about the redispensing system and product quality to patients was therefore important. Stakeholders agreed that information should be provided in a transparent manner, with all healthcare professionals disseminating the same message.

Several stakeholders suggested the possibility of using incentives to stimulate patients to participate in the program, such as lowering health premiums with discounts or granting refunds directly. One comment reads, *"If the patient is not interested in bringing it back, and the benefit goes to the health insurances or the pharmacy or whoever, there is no reward for the patient for bringing it back"* (interviewee 16, male, wholesaler). A health authority and pharmaceutical industry representative remarked that using incentives also has drawbacks as it may imply a second-best medicine, whereas redispensed medicines should become standard. Another interviewee stated, *"There is no difference in the quality. That is the starting point. There is no difference in the quality, so why should we compensate someone? You are getting a good medicine"* (interviewee 17, male, patients' organisation).

Some of the stakeholders mentioned that patients are worried about the affordability of healthcare, and will agree to use redispensed medicines. On the other hand, some stakeholders expect difficulties as patients might be less willing to use medicines that were already stored at another patient's home.

Stakeholder involvement

Stakeholders mentioned several roles that some stakeholders could fulfil in the redispensing of unused medicines. If pharmacists were to fulfil a major executive role in the redispensing, stakeholders acknowledge that this would include extra tasks for which they should be financially compensated. Nonetheless, a wholesaler, pharmacist- and patient/consumer organisation highlighted that caution is warranted for creating a negative image of pharmacists. Their involvement in the redispensing of unused medicines should be based on an intrinsic motivation to decrease waste and not to benefit from the potential cost savings. Stakeholders considered health insurance companies eligible for stimulating redispensing. For manufacturers, some stakeholders foresaw negative consequences like declines in turnovers, while others saw this as a relative decrease with little impact. Stakeholders mentioned social involvement as the primary reason for manufacturers to contribute to a redispensing system. Some stakeholders had opposing views on each other's opinions on the redispensing of unused medicines. Non-pharmacy related stakeholders supposed that pharmacists are less motivated to redispense medicines, while the latter said that they are motivated. Pharmacy related stakeholders felt that health insurance companies would be less prepared to compensate them for redispensing of medicines. The insurance companies reported to be willing to provide financial compensation for the redispensing of medicines.

Legal aspects

Opinions on the legal feasibility of redispensing unused medicines were divided. A health authority stakeholder said that, according to current legislation, it is legal to redispense medicines. However, some pharmacy organisations and a health insurance company mentioned that all medicines that are returned to pharmacies have to be destroyed, as stated in professional standards. Therefore, even if legislation does not prohibit redispensing, professional standards need to be adjusted as health care professionals follow both.

Virtually all stakeholders stated that it is critical to identify which stakeholders are responsible for the redispensing system, and especially for the quality of redispensed medicines. The majority of stakeholders indicated that pharmacists are capable of fulfilling this role, as they are already responsible for the quality of dispensed medicines. A pharmacy organisation also identified wholesalers as a responsible stakeholder.

Financial aspects

Stakeholders frequently named cost aspects of the redispensing system as an important requirement. Namely, the financial benefits of a redispensing system must outweigh the costs of implementing such a system. Therefore, a minimal economic value of the medicines that could be redispensed should be determined: *"But the most important thing is to make a model with the financial benefits"* (interviewee 1, male, hospital pharmacist). The financial benefits could be shared among patients, pharmacists and health insurance companies or used for research.

Lastly, stakeholders mentioned that financial handling, with declaring and crediting the redispensed medicines, should be properly organised. This implies the adaption of pharmacy information systems and reimbursement software of health insurance companies.

Discussion

To our knowledge, this is the first study that provides insights into stakeholders' views on the redispensing of medicines unused by patients. In general, medication waste was considered to be an expanding problem that occurs in all parts of the pharmaceutical supply chain. Stakeholders therefore addressed that interventions aiming to avoid this waste should be implemented in the complete chain. Recently, key themes aligned with solutions for minimising medication waste were identified, namely practitioner effects (medication review and better communication), patient effects (reassurance of medication availability), political effects (implementing solutions) and societal effects (awareness and education)[28]. Our findings align with what others have concluded, namely that medication waste is a multi-causal problem that requires a multi-factorial approach for minimization. Nevertheless, all stakeholders had a positive attitude towards the redispensing of the non-preventable part of medication waste. The most important requirements of a redispensing system that were identified were related to the quality assurance of redispensed medicines, the responsibility for this quality and it was highlighted that patients' trust and willingness in a redispensing system was crucial. Furthermore, the benefit-cost ratio of redispensing should be evaluated to define a minimal economic value of medicines suitable for redispensing. The proposed requirements are in line with views of others on the redispensing of unused medicines[19]. Pharmacists' criteria on the redistribution of medicines have been assessed and the quality and safety of the medicines was of most importance here as well[29]. This study contributes to the sparse information regarding the redispensing of unused medicines and provides key points for the implementation of such a system.

Stakeholders had comparable opinions on the redispensing of medicines and related requirements. Most importantly, they unanimously stated that the product quality of redispensed medicines should be guaranteed. Furthermore, the following factors that can affect the quality should be ensured: temperature, light, humidity, agitation, and lapsed expiration date. According to guidelines on packaging for pharmaceutical products[30], packages must protect the products against light and moisture. Agitation, such as shaking, may affect liquid drug formulations but not the quality of solid dosage forms like tablets. Light, humidity and agitation are therefore unlikely to affect the quality of these medicines when packed properly. As for the quality assurance of solid dosage forms, only temperature monitoring is needed, which can easily be done using a temperature sensitive label, we consider these type of medicines the most appropriate for redispensing (blister packs and unopened medicine jars).

Besides consensus on discussed themes, some controversies were also identified. First, we observed differences in stakeholders' views on legal constraints. In The Netherlands, medical practices are based on the Dutch Medicines Act, which refers to the European GDP with respect to the (re)distribution of medicines[31]. The latter states that medicines that have left the distribution centre can return in stock if several factors concerning good product quality

control can be confirmed. Thus, according to the law, medicines can be redispensed as long as their quality is guaranteed.

Second, different views existed on whether incentives should be used to stimulate patient participation in a redispensing program. On the one hand, triggering patients to return unused medicines and rewarding this willingness might increase the amount of returned medication. However, on the downside, incentives might imply inferior product quality. Before medicines can be redispensed in practice, the use of incentives in a redispensing system requires further investigation.

Lastly, some stakeholders had misperceptions of the views of other stakeholders. Health insurance companies and pharmacists were perceived as negative towards the redispensing of unused medicines. However, on the contrary, these stakeholders had a positive view towards the redispensing of unused medicines. Some stakeholders thought that patient willingness to participate in a redispensing program would be minimal. In contrast, patient related stakeholders emphasised that patients are highly willing to participate. Stakeholders should clarify their willingness for redispensing unused medicines among one and another to facilitate a strong collaboration.

Although we aimed at involving all relevant stakeholders, some stakeholders still may have been missed. Interviewees, however, confirmed the completeness of our stakeholder list and all stakeholders agreed to participate. Moreover, no new themes emerged in the final interviews and therefore we consider the collected data to be comprehensive. As the main researcher subjectively interpreted the data, researcher bias could have occurred. However, as the data were also independently analysed by the second researcher and discussed until both fully agreed about the content, the risk of researcher bias was minimised. To succeed with a redispensing system, patients have to be willing to participate. In this study, only the views of patient/consumer organisations were identified, which might differ from individual patients' views on the redispensing of medicines. Furthermore, the study was performed in The Netherlands, which might hamper generalizability of our results to other countries. Reimbursement systems in particular can differ among countries. However, in our view, medication waste is an international problem and the two major themes, namely product quality and patient's trust, will be of importance in each setting.

Conclusions

Medication waste is a general problem that requires a multi-dimensional approach. Nevertheless, unused medicines can be redispensed to reduce medication waste if several requirements are met. This enhances the idea of diminishing medication waste by redispensing unused medicines, eventually decreasing health care expenditures and environmental harm. The future development of a redispensing system needs criteria to define the product quality and minimal economic value of medicines that are suitable for redispensing. Moreover, possible legal constraints should be solved. Eventually, all requirements for redispensing unused medicines should be integrated into clinical and regulatory guidelines.

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Conflict of Interests
C. Bekker reports grants from Pfizer, during the conduct of the study. Dr. Gardarsdottir reports grants from Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu], outside the submitted work. All other authors declare they have no conflict of interests.

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Chapter 3.2

Willingness of patients to use unused medication returned to the pharmacy by another patient: a cross-sectional survey

Charlotte L Bekker
Bart JF van den Bemt
Antoine CG Egberts
Marcel L Bouvy
Helga Gardarsdottir

Submitted

Abstract

Objectives
Redispensing by pharmacies of medication unused by another patient could contribute to optimal use of healthcare resources. This study aimed to assess patient willingness to use medication returned by another patient and patient characteristics associated with this willingness.

Design
Cross-sectional survey.

Setting
41 community and 5 outpatient pharmacies in the Netherlands.

Participants
Total of 2,215 pharmacy visitors.

Primary and secondary outcome measures
Patients completed a questionnaire regarding their willingness to use medication returned unused to the pharmacy by another patient, assuming quality was guaranteed. Secondary outcome measures included patient sociodemographic characteristics that were associated with patient willingness, analysed using logistic regression analysis and reported as odds ratios (OR) with 95% confidence intervals.

Results
Of the 2,215 patients (mean [SD] age 50.6 [18.0] years; 61.4% female), 61.2% was willing to use medication returned unused to the pharmacy by another patient. Patients who were unwilling mostly found it risky. Men were more willing to use returned medication (OR 1.3 [1.1–1.6]), as did patients with a high educational level (OR 1.8 [1.3–2.5]), those who regularly use 1–3 medications (OR 1.3 [1.1–1.7]), those who returned medication to the pharmacy for disposal (OR 1.5 [1.0–2.3]) and those who ever had unused medication themselves (OR 1.3 [1.1-1.6]). Patients with non-Dutch cultural background were less willing to use returned medication (OR 0.3 [0.3–0.4]).

Conclusions
When quality is guaranteed, a substantial proportion of patients are willing to use medication returned unused to the pharmacy by another patient. This suggests that implementation of redispensing may be supported by patients.

Introduction

Up to one-third of patients do not use all medication dispensed by their pharmacy[1,2], leading to a waste of healthcare resources and environmental pollution[2,3]. Previous studies reported that 20–90% of medications dispensed but unused by patients still are in their unopened and intact packaging[4–8]. Patients either dispose these unused medications at home (e.g. household waste) or return these to pharmacies who discard these as special waste[9]. Redispensing these unused medications could contribute to waste-reduction. Although medications that remain unused by patients in healthcare institutions are occasionally redispensed to patients who cannot afford healthcare[10,11], this is no standard practice (*Bekker, submitted*), primarily due to uncertainties surrounding the quality assurance of returned medications and legal constraints including product liability.

Stakeholders are positive regarding implementation of a redispensing process[12,13]; however, they explicitly stated that successful implementation relies heavily on patient support. A qualitative study with 19 participants from the United Kingdom showed that people would generally agree to use redispensed medications if safety and product quality is guaranteed[14]. Other surveys from the UK and the Netherlands showed that people would accept redispensed medications[15–17], however, these studies involved small study populations and did not determine which patient groups would be more or less willing to use redispensed medications. This study therefore aims to assess patient willingness to use medication returned unused to the pharmacy by another patient and patient characteristics associated with this willingness.

Methods

A survey was conducted in 41 community pharmacies and 5 outpatient pharmacies, involved in the UPPER network of the Utrecht University[18], between April and December 2014 in the Netherlands (approved by the Institutional Review Board [UP1408]).

In each participating pharmacy, approximately 50 adult (≥18 years) visitors completed a questionnaire in writing while waiting or orally in case of returning medication for disposal. Visitors were asked about their willingness to use medication returned unused to the pharmacy by another patient if the quality was guaranteed, with multiple answer options: “yes, it is a shame to destroy good-quality medications”; “yes, if these medications are cheaper or free”; “no, I don’t want second-hand medications”; “no, I find it risky”; or “other”. Besides registering their sociodemographic characteristics age, gender, educational level (“low”/”medium”/”high”) and cultural background (“Dutch”/”other”), visitors were asked whether they had ever had unused medications themselves (“yes”/“no”/“don’t know”), and the number of prescription medications they regularly use (“none”/”1–3”/”≥4”).

Data were presented in proportions or means with standard deviation (SD). Associations between patient characteristics and willingness to use returned medications (answers categorized into yes/no) were analyzed in STATA13, using univariate and multivariate logistic regression analyses (full model with complete cases), reported as odds ratios (OR) with 95% confidence intervals (CI). To assess if hierarchical data structure (patients clustered within pharmacy) influenced our outcomes, multilevel sensitivity analysis was conducted.

Results

A total of 2,215 patients (mean [SD] age 50.6 [18.0] years, 61.4% female) participated, 88.8% of whom were community pharmacy visitors. Of all patients, 142 (6.4%) were returning medication for disposal. Most patients had a Dutch cultural background (77.8%), a medium educational level (48.2%) and regularly used 1-3 prescription medications (45.9%). A total of 1,436 (64.8%) patients had ever had unused medications themselves.

Over half of patients were willing to use medication returned unused to the pharmacy by another patient (61.2%, Table 1). Of these, 88.4% was willing because they found it a shame to destroy good-quality medications and 19.9% if these were cheaper or free. Some patients explicitly reported that they were only willing if these were returned in original, unopened packages. Of patients who were not willing to use returned medications, most found it risky (64.1%) or did not want to use second-hand medications (41.1%). Other reasons included not knowing how medications were handled and stored by other patients and how quality could be monitored.

Table 1: Patient willingness to use returned medication. *Patients could report multiple answers

	Patients n=2,215 (n, %)
Willing*	1355 (61.2)
-Yes, it's a shame to destroy good quality medication	1198 (88.4)
-Yes, if this medication is cheaper or for free	269 (19.9)
-Other	35 (2.6)
Unwilling*	869 (39.2)
- No, I find it risky	557 (64.1)
- No, I don't want to use second-hand medication	357 (41.1)
-Other	8 (0.9)

Men were more willing to use returned medication (OR 1.3 95%CI [1.1–1.6]), as did patients with a high educational level (OR 1.8 95%CI [1.3–2.5], Table 2). Furthermore, patients who regularly use 1–3 prescription medications were more willing to use returned medication (OR 1.3 95%CI [1.1–1.7]), also patients who were questioned as they returned medication (OR 1.5 95%CI [1.0–2.3]) and patients who had ever had unused medications themselves (OR 1.3 95%CI [1.1-1.6]). Patients with non-Dutch cultural background were less willing to use returned medication (OR 0.3 95%CI [0.3–0.4]). Age and type of pharmacy were not associated with patient willingness to use returned medication. Sensitivity analysis demonstrated similar associations.

Table 2: Patient characteristics associated with willingness to use medication returned by another patient (n=2,136*).

Characteristic	**Willing n=1,310 (n [%])**	**Unwilling n=826 (n [%])**	**Crude OR (95% CI)**	**Adjusted OR** (95% CI)**
Gender				
Female	782 (59.7)	538 (65.1)	Ref	Ref
Male	528 (40.3)	288 (34.9)	**1.3 (1.1–1.5)**	**1.3 (1.1–1.6)**
Age				
18–40	402 (30.7)	341 (38.0)	Ref	Ref
41–65	580 (44.3)	307 (37.2)	**1.5 (1.2–1.8)**	1.2 (0.9–1.5)
>65	328 (25.0)	205 (24.8)	1.2 (1.0–1.6)	0.8 (0.6–1.1)
Educational level				
Low	124 (9.4)	126 (15.2)	Ref	Ref
Medium	618 (47.2)	430 (52.1)	**1.5 (1.1–1.9)**	1.3 (0.9–1.7)
High	568 (43.4)	270 (32.7)	**2.1 (1.6–2.8)**	**1.8 (1.3–2.5)**
Cultural background				
Dutch	1,132 (86.4)	532 (64.4)	Ref	Ref
Other	178 (13.6)	294 (35.6)	**0.3 (0.2–0.4)**	**0.3 (0.3–0.4)**
Medications regularly used				
None	320 (24.4)	252 (30.5)	Ref	Ref
1–3	616 (47.0)	355 (43.0)	**1.4 (1.1–1.7)**	**1.3 (1.1–1.7)**
≥4	374 (28.6)	219 (26.5)	**1.3 (1.1–1.7)**	1.3 (1.0–1.7)
Type of pharmacy				
Community	1,146 (87.5)	745 (90.2)	Ref	Ref
Outpatient	164 (12.5)	81 (9.8)	1.3 (1.0–1.7)	1.2 (0.9–1.6)
Returning medication				
No	1,210 (92.4)	790 (95.6)	Ref	Ref
Yes	100 (7.6)	36 (4.4)	**1.8 (1.2–2.7)**	**1.5 (1.0–2.3)**
Ever having any unused medication				
No	393 (30.0)	317 (38.4)	Ref	Ref
Yes	905 (69.1)	483 (58.5)	**1.5 (1.3-1.8)**	**1.3 (1.1-1.6)**
Don't know	12 (0.9)	26 (3.2)	-	-

Significant associations are shown in bold.
*For 79 (3.6%) patients, sociodemographic data was missing. Associations between patient characteristics and willingness to use returned medications were analysed for the remaining 2,136 patients.
**Multivariate logistic regression analysis was conducted

Discussion

This study shows that a substantial proportion of patients are willing to use medication returned to the pharmacy by another patient when the quality is guaranteed. Males, patients with a high education, those regularly using medications, those returning medication to the pharmacy for disposal and those who ever had unused medications themselves were in particular more willing to use returned medications.

Worldwide, increased attention is being paid to sustainable environment, including green pharmacy practices, of which redispensing represents an important component[19]. Patient support for redispensing is crucial[12,13]. Our findings in a large patient sample are consistent with previous, smaller, studies, which found that 50–95% of patients would accept medication returned by other patients[15–17]. We found that patients who were less supportive primarily had concerns about risks, including tampering with the medication, inadequate storage conditions and reliability of the quality assurance. Few studies have identified patient barriers and facilitators to redispensing unused medications by pharmacies. Almahad et al. interviewed 19 patients ≥40 years and concluded that many are in favor of redispensing because it could reduce the negative consequences of waste[14]. Potential disadvantages identified by these patients included improper storage of medication, medication errors introduced by patients, and counterfeit medications entering the system. We found that less willing patients had more often non-Dutch cultural backgrounds. Before considering implementation of redispensing, concerns of less willing patients should be identified in-depth and barriers should be overcome. Interventions aiming at behavioral changes may be required for ultimately increasing patient support, such as raising awareness on waste and using (monetary) incentives.

This study captured the willingness on redispensing in a large patient sample. However, we cannot assure that this is identical if implemented in practice. Furthermore, pharmacy visitors may not be representative of the general population; however, they may well reflect the most likely people to receive returned medications. Lastly, patients who returned medications to community pharmacies for disposal were interviewed, and may have given what they considered to be socially desirable answers.

Conclusions

A substantial proportion of patients are willing to use medication returned unused to the pharmacy by another patient when the quality is guaranteed, suggesting that implementation of redispensing may be supported by patients.

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Conflicts of interest
The authors declare that they have no conflicts of interest to disclose.

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Chapter 4

Feasibility of redispensing: economic considerations

Chapter 4.1

What does it cost to redispense unused medications in the pharmacy? A micro-costing study

Charlotte L Bekker
Helga Gardarsdottir
Antoine CG Egberts
Erik A Molenaar
Marcel L Bouvy
Bart JF van den Bemt
Anke M Hövels

Submitted

Abstract

Background
Redispensing unused medications that have been returned to pharmacies may reduce waste and healthcare costs. However, little is known regarding the extra costs associated with this process, nor the price level of medications for which this is economically beneficial.

Objective
To assess costs associated with redispensing unused medications in the pharmacy and the price level at which redispensing becomes cost-beneficial.

Methods
A micro-costing study was conducted in four Dutch outpatient pharmacies for medications requiring room-temperature storage and requiring refrigeration. First, the pharmacy's necessary additional process steps and resources for redispensing were identified. Second, time required for each process step was simulated. Third, required resources were quantified by calculating labour, purchasing and overhead costs. Lastly, a model with different scenarios was constructed to calculate the price level of a single medication package at which redispensing becomes cost-beneficial.

Results
Three main additional process steps for redispensing were identified: (1)pack medications with product quality indicators before dispensing, (2)assess quality of medications returned to the pharmacy (temperature storage, package integrity, expiry date) and (3a)restock medications fulfilling quality criteria or (3b)dispose of medications not fulfilling criteria. Total time required for all steps up to restock one medication package was on average 5.3 (SD ±0.3) and 6.8 (SD ±0.3) minutes for medications stored at room-temperature and under refrigeration, respectively, and associated costs were €5.54 and €7.61. Similar outcomes were found if a medication package would ultimately be disposed of. The price level primarily dependent upon the proportion of dispensed packages returned unused to the pharmacy and fulfilling the quality criteria: if 5% is returned, of which 60% fulfils quality criteria, the price level was €101 per package for medications requiring room-temperature storage and €215 per package for those requiring refrigeration. However, if 10% is returned, of which 60% fulfils the quality criteria, the price level decreases to €53 and €109, respectively.

Conclusions
Redispensing unused medications in the pharmacy is at least cost-beneficial if applied to expensive medications. This price level will decrease if either the proportion of medication returned to the pharmacy or the proportion of medication fulfilling the quality criteria for redispensing increases.

Introduction

Pharmaceutical care, including both prescription and over-the-counter medications, represents a substantial proportion of the global healthcare budget[1]. However, up to one-third of patients do, for various reasons, not use all medication dispensed to them[2,3]. It is difficult to precisely estimate the extent and costs of unused medications because disposal occurs at various moments in time, such as during therapy, months hereafter or even after patient's death, and through multiple routes, including returning unused medications to the pharmacy, disposing of them as household waste or flushing them down the toilet[4]. Conservative estimates suggest that around $5 billion and £300 million is annually wasted in the US and UK, respectively[2,5]. These numbers indicate that substantial resources are wasted in the form of unused medications, which highlights the need for the implementation of interventions effectively reducing unnecessary medication waste.

Some packages that are returned to the pharmacy still are completely unopened and intact[6,7]. These medications could theoretically be redispensed in the pharmacy if they are still of good quality, thereby reducing medication waste and optimising the use of healthcare resources. The discussion on the potential of redispensing unused medications as a waste-reducing intervention is not new[6,8–10]. However, redispensing is currently not implemented in pharmacies (*Bekker, submitted*), mainly because of legal restrictions, uncertainty about the quality of the returned medications, lack of knowledge regarding patient support for such an approach and uncertainty about the cost-benefits of the redispensing process[11,12].

To determine whether the implementation of the redispensing of unused medications in the pharmacy is cost-beneficial, a better understanding of the costs associated with this process is required. Such an assessment will facilitate the identification of the types of medications that are eligible for redispensing. This study therefore aimed to assess the costs associated with redispensing unused medications in the pharmacy. Furthermore, an attempt was made to define the price level at which redispensing becomes cost-beneficial.

Methods

Study design and setting
A micro-costing study was performed in four hospital-based outpatient pharmacies in the Netherlands between February and June 2016. Micro-costing studies comprise the detailed identification and measurement of all process steps and resources used for an intervention, in this case redispensing, which are subsequently quantified into costs[13]. In this study, a healthcare provider's perspective was used, for which only the provider's (pharmacy) costs in the redispensing process were considered. The economic analysis was performed according to Dutch pharmacoeconomic guidelines[14].

An important prerequisite for redispensing unused medications is a guaranteed product quality. To ensure proper storage of medications at patients' homes, various criteria should be monitored, such as storage temperature, light and humidity exposure and package integrity (unopened, intact). In addition, the medication should have a sufficient long shelf life (here, an expiry date at least six months in the future)[10]. It was assumed that an additional

outer package (i.e. transparent sealbag) combined with manufacturer's original primary and secondary packaging would be sufficient to ensure proper storage in terms of light and humidity exposure. This would also facilitate the assessment of the package integrity if the seal is unbroken, ensuring that the package remains unopened and undamaged.

Two types of medications were distinguished based on their storage recommendations; medications requiring storage at room-temperature (15-25°C) and medications requiring refrigeration at (2–8°C). Previous research has shown that medications requiring room-temperature storage are generally stored at an appropriate temperature, whereas medications requiring refrigeration are often stored outside the recommended temperature range, including below 0°C[15,16]. Therefore, for medications requiring refrigeration detailed temperature information is needed to assess proper storage. It was assumed that a digital temperature measurement logger system would be needed to measure temperature constantly for these medications, but that a simple indicator that indicates out-of-range temperatures (for example, by changing colour) would be sufficient for monitoring storage temperature of medications requiring room-temperature storage.

Process identification and time measurements

To identify all the additional process steps and resources on top of standard pharmacy practice needed to redispense unused medications, pharmacy staff from the participating four pharmacies were interviewed. The researchers composed a list of the expected process steps and materials required, which was sent to the pharmacists prior to the interview, and the pharmacy staff was asked to adjust the list, adding or excluding steps and materials, and to identify the type of pharmacy staff (e.g. technician or pharmacist) involved in each step.

The identified process steps were simulated in each pharmacy by staff and a researcher recorded the time taken for each step. The simulation was performed three times in each pharmacy. The last simulation in each of the four pharmacies was considered most accurate and therefore used in the analysis (see Table 1 for the process steps and time). Process steps that differed between medications stored at room-temperature or under refrigeration were simulated separately.

Cost estimation

Direct and indirect costs were calculated for all additional process steps and resources. Direct costs were defined as the pharmacy's additional costs made during the redispensing process, including labour and materials. Labour costs were calculated for each process step by multiplying the mean time by the costs of the type of pharmacy staff involved, based on the median annual salary reported by the Royal Dutch Pharmacists Association[17]. Salary scales were converted to a per-minute rate based on 1558 working hours per year and a 36-hour working week[18]. The salary was increased with 39% to account for social charges[18]. Material costs were calculated using purchase prices. For medications requiring refrigeration, the purchase prices of the digital recording system were included, assuming a life span of three years and six uses of the logger. Indirect costs were defined as the pharmacy's overhead costs made through the employment of staff, the operating activities of the facility and the quality assurance. The overhead costs were valued at 44% of the direct costs[18]. All costs are reported in Euros (2016) and were adjusted using inflation rates where needed[19]. Detailed information on the source of cost information is presented in Table 1.

Table 1: Unit cost of labour and materials.

Resources	Unit cost (€, 2016)	Source
Pharmacy technician	0.32	Royal Dutch Pharmacists Association
Pharmacist	0.55	Royal Dutch Pharmacists Association
Sealbag	0.42	Transposafe sealbag
Temperature sensor	0.86	Telatemp warmmark time temperature indicator
Temperature logger	10.00	Safe-Rx, Confrerie Clinique
Software and licence for logger	4700.00	Safe-Rx, Confrerie Clinique
Tablet	499.00	Dell-venue 11 pro 7000
Printed paper	0.02	Staples
Printed label	0.01	Zebra Z-select 2000D label
Return envelope	0.72	Dutch post

Price level

To determine the price level that indicates the price of a single medication package that would be financially eligible for redispensing, a general model was constructed for different scenarios. This model was based on the following assumptions: fixed calculated labour- material- and overhead costs (Table 2), variation in the proportion of medication packages that are returned to the pharmacy (between 1-10%) and variation in the proportion of returned medication packages that fulfil all quality criteria (between 20-80%). For medications requiring refrigeration, the proportion of loggers that were returned as normal care was set as 77%, the proportion returned by post as 4.0% and 19% of the dispensed loggers were assumed not to be returned and lost that should be extra purchased (based on personal communication with Vlieland et.al.). To define a base case, the number of medication packages for one therapeutic class dispensed in one pharmacy in one year was in this study set as 10,000 (100%). Total costs were calculated and divided by the proportion of returned medication packages that were assumed to fulfil all quality criteria, and as follows the price level for the price of a single medication package was estimated (Appendix A for example). For estimating the price level the following formula was used:

$$\textit{Price level} = \frac{\textit{(Total costs in one year)}}{\textit{(Proportion of returned medication packages that fulfils quality criteria*100\%)}}$$

*Total costs in one year=(cost step1*100% of dispensed packages)+(cost step2*proportion of returned packages*100%)+(cost step3a*proportion of returned packages that fulfils quality criteria*proportion returned*100%)+(cost step3b*proportion of returned packages that not fulfils quality criteria*proportion returned*100%)**

**Additional for medications requiring refrigeration:+(cost step4a*proportion of loggers returned by post*(100%-proportion returned))+(costs step4b*dispensed loggers returned as normal care*(100%-proportion returned))+(cost of loggers lost [cost logger-cost of dispensed logger]*proportion of loggers lost*(100%-proportion returned))+cost measuring system for one year*

In addition, the number needed to redispense (i.e. the number of dispensed medication packages that are needed in order to restock one medication package) was calculated for each scenario. Therefore, the number of dispensed medication packages was divided by the number of medication packages that returned to stock.

Data analysis

Data were entered into Microsoft Excel 2010 and descriptively analysed. Averages were expressed as means with standard deviations (SD) or their minimum and maximum values, and proportions were reported as percentages.

Results

Process identification and time measurements

To identify the additional process steps and resources required to redispense unused medications in the pharmacy, six interviews were held with eight pharmacists and one pharmacy technician (three interviews were held with two employees). During the sixth interview, no new process steps were identified and the composed list was therefore considered comprehensive. Overall, three main process steps were identified in redispensing unused medications in the pharmacy: (1) add materials required for monitoring home storage during the initial dispensing process; (2) assess the quality of the medications returned to the pharmacy in terms of temperature storage, package integrity and expiry date; and either (3a) place medications that fulfils all quality criteria into the pharmacy stock or (3b) dispose of medications that not fulfils the quality criteria. As a fourth step for refrigerated medications, patients that use their full medication course would be requested to return the temperature loggers by post (4a) or during their regular pharmacy visit (4b) for reuse. For a general overview of the redispensing process see Figure 1, and for the process steps see Table 2.

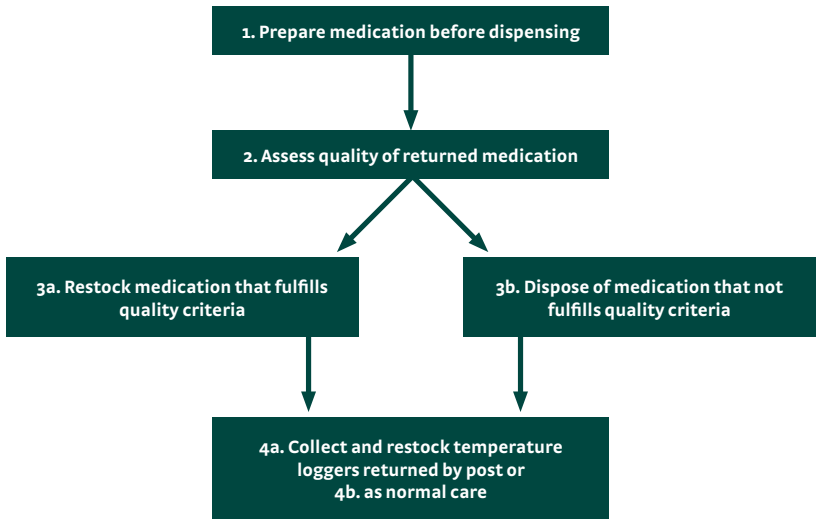

Figure 1: Flowchart of the additional process steps required to redispense unused medications in the pharmacy.

The total time required to perform all process steps up to restocking one medication package was on average 5.3 (SD ±0.3) minutes if requiring room-temperature storage and 6.8 (SD ±0.3) minutes if requiring refrigeration (Table 2). Similar outcomes were found if a medication package would ultimately be disposed of, respectively 5.2 (SD ±0.4) minutes and 6.7 (SD ±0.5) minutes. Time differences between room-temperature stored medications and those requiring refrigeration were a result of time required for temperature logger activation and assessment compared to the temperature sensor. For both medication types, more than half of the time was spent on the quality assessment of returned medications.

Cost estimation

The costs associated with all process steps and resources, including direct labour- and material costs and indirect overhead costs, required to ultimately return one medication package to stock was €5.54 if requiring room-temperature storage, while these costs were €7.61 for a package requiring refrigeration (Table 2). Similar costs were found if the package would ultimately be disposed of.

Price level estimation

The price level of a single returned medication package making redispensing cost-beneficial varied strongly for the different scenarios and decreased when more medications that met the quality criteria would be returned to the pharmacy (Figure 2). For instance, if 5% of the dispensed medication packages would be returned to the pharmacy, of which 60% would fulfil the quality criteria, the price level would be €101.00 per package for medications requiring room-temperature storage and €215.00 for those requiring refrigeration. However, if 10% would return to the pharmacy, of which 60% would fulfil the quality criteria, the price level decreases to €53.00 and €109.00, respectively. Overall, the price level is lower for medications that require room-temperature storage compared to those that require refrigeration.

The number needed to redispense decreased if more medications would return to the pharmacy (Figure 3). As an example, if 5% would be returned to the pharmacy, of which 60% would fulfil the quality criteria, 33 medication packages would need to be dispensed to allow for restocking of one package.

Table 2: Process steps required to redispense unused medications in the pharmacy, the mean time spent on each step and the associated costs. All process steps could be performed by a pharmacy technician unless stated otherwise.

Process steps	Medication requiring room-temperature storage		Medication requiring refrigeration	
	Mean time (minutes; min-max)	Cost (€)	Mean time (minutes; min-max)	Cost (€)
Step 1. Prepare medication before dispensing Register patient information and medication intended for dispensing in PHIS[a] Collect a sealbag and temperature-measuring device Activate temperature-measuring device Place medication with temperature-measuring device in sealbag Inform the patient about the redispensing process	1.6 (1.4–1.7)	2.90	2.0 (1.8–2.3)	4.30
Step 2. Assess quality of returned medication Register returned medication in PHIS Place medication in a storage location if not assessed directly Determine the quality of the medication and register temperature storage, package integrity and expiry date Place medication in storage location Review and sign off checklist by pharmacist	2.9 (2.4–3.6)	2.14	3.9 (3.5–4.2)	2.73
Step 3a. Restock medication that fulfil all quality criteria Collect medication from storage location Remove old patient label from medication package Document the restocking in PHIS Place medication in pharmacy stock[b]	0.8 (0.6–1.0)	0.50	0.9 (0.8–0.9)	0.58
Step 3b. Dispose of medication that not fulfil quality criteria Collect medication from storage location Document the disposal in PHIS Place medication in disposal bin	0.7 (0.7–0.8)	0.48	0.8 (0.7–1.0)	0.53
Step 4a. Collect and restock temperature loggers returned by post	-	-	0.4 (0.3–0.4)	1.28
Step 4b. Collect and restock temperature loggers returned as normal care Take logger from envelope (paid by pharmacy) Deactivate logger Place logger in stock			0.4 (0.3–0.4)	0.25
Total				
Medication that returns to stock (step 1,2,3a)	5.3 (SD ±0.3)	5.54	6.8 (SD ±0.3)	7.61
Medication that is disposed of (step 1,2,3b)	5.2 (SD ±0.4)	5.52	6.7 (SD ±0.5)	7.56

[a]Pharmacy's information system, [b]Stock adjustments and communication with the financial department could not be simulated

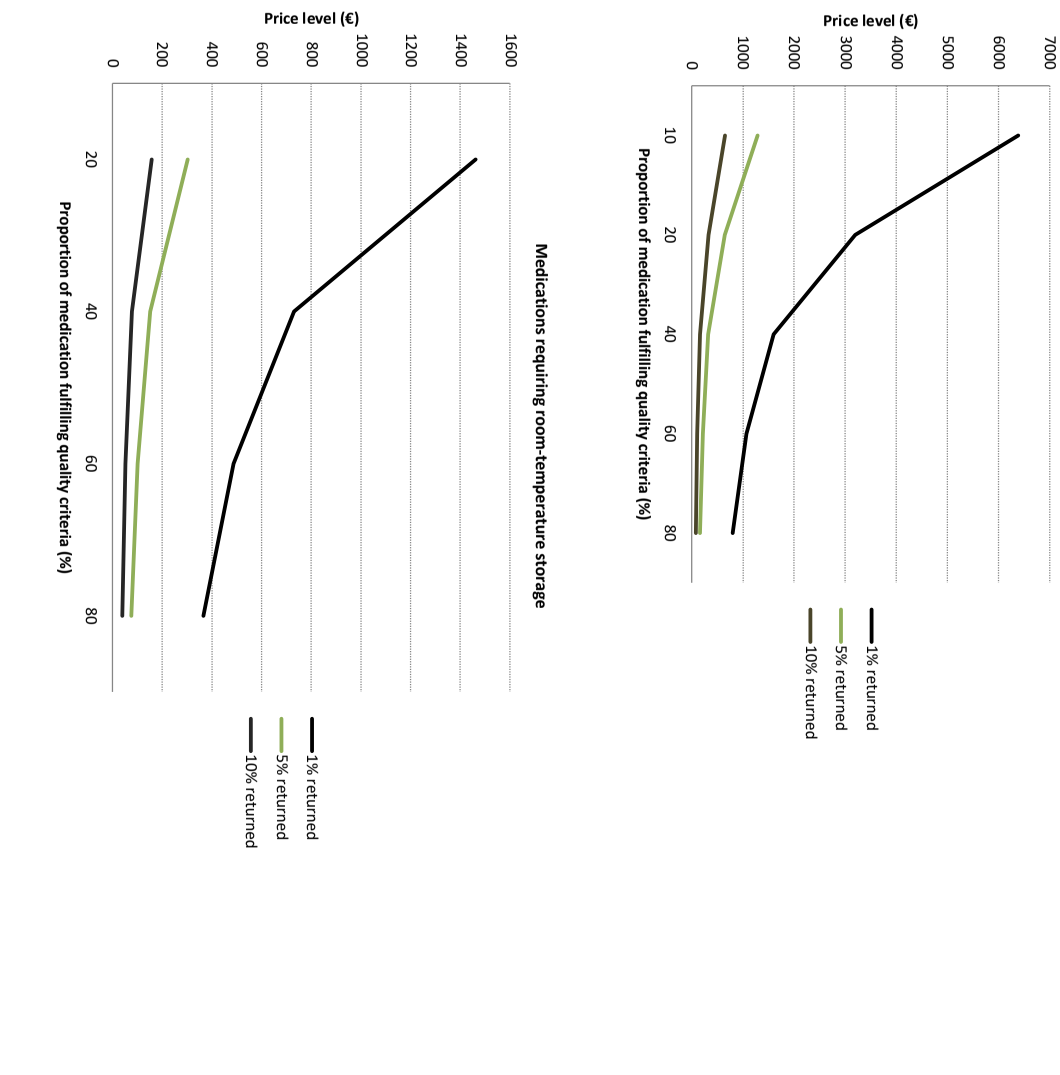

Figure 2: The price level for cost-beneficial redispensing for medications requiring room-temperature storage and refrigeration. *The threshold depends on the proportion of dispensed medication packages that are returned to the pharmacy and its proportion that fulfils quality criteria and can be redispensed.*

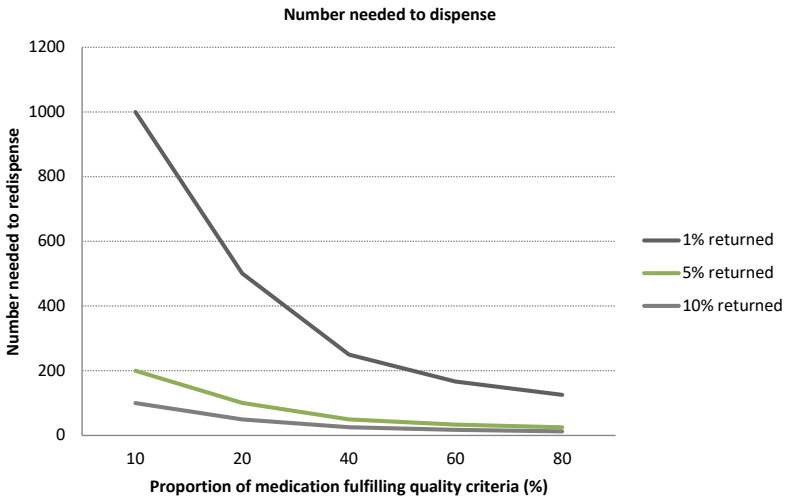

Figure 3: Number of medication packages needed to redispense, which is equally for medications requiring room temperature storage or refrigeration.

4.1

Discussion

In this micro-costing study, all additional process steps and resources required to redispense unused medications in the pharmacy were explicitly identified and quantified, and the costs associated with these were assessed. The price-level at which redispensing unused medications becomes cost-beneficial was identified and found to vary strongly depending on the proportion of dispensed packages that is returned unused to the pharmacy that fulfil the quality criteria.

Most studies that address the potential cost savings related to redispensing unused medications include solely the cost of the medications that remain unused[7,20–23] and do not take into account the associated pharmacy costs. Glanville et al assessed the pharmacy's operational costs for redispensing medications donated by patients to patients who lack health insurance and financial means to obtain medication. Their analysis was based on the cost of the donated medications, minus the pharmacy costs needed for the quality assessment, resulting in a total net cost of the redispensed medications[24]. In contrast, this study provides detailed information on the pharmacy costs of the redispensing process when implemented as normal care.

Most costs that enable redispensing would already be made during the initial dispensing of medications to the patient, which requires additional materials to protect the original packaging and to measure home storage temperature conditions. To cover all pharmacy costs associated with redispensing, the price level identified from the analysis indicates that implementation is most likely to be cost-beneficial for expensive medications. The price level was estimated for one therapeutic class of which it was assumed that 10.000 medication packages would be dispensed in a year (base case). However, this may not be feasible to

dispense for a small pharmacy. Therefore, a general model was created that can be used for multiple scenarios. Varying the quantity of dispensed medication packages would not impact the determined price levels for medications that require room-temperature storage. However, for medications that require refrigeration, the determined price levels are likely to decrease or increase, due to costs related to the logger system that is needed for monitoring temperature storage. For these reasons also, the price level for cost-beneficial redispensing is higher for medications requiring refrigeration compared to those requiring room-temperature storage. The price level will decrease if more unused medications that fulfil the quality criteria are returned to the pharmacy. However, many patients do not return their unused medications to the pharmacy and dispose of them through, for instance, the household waste system instead[3,4]. National awareness campaigns could be implemented to increase the proportion of unused medicines that are returned to the pharmacies, which is likely to increase the quantity eligible for redispensing. Increasing patient awareness on proper home storage could also increase the proportion of medications returned to the pharmacy that meet the quality criteria. Campaign costs were not included in this study, and if such awareness programmes were developed, this may affect the estimated process costs if these should be covered by the pharmacy. Overall, the estimated price levels indicate at which price redispensing becomes cost-beneficial and all costs that the pharmacy makes for this process are covered. In general, large-scale implementation involving more therapeutic classes may decrease the direct and indirect costs of the pharmacy investments per package and could provide further economic benefits.

4.1

In this study, the pharmacy's process costs associated with redispensing unused medications were estimated. If a redispensing system would be implemented in practice as normal care, one should consider how the monetary benefits are shared among all involved stakeholders. It can be argued that patients are less willing to return their unused medications to the pharmacy when only pharmacists financially benefit from redispensing. On the other hand, pharmacists are less likely to redispense medications if the additional costs are not covered. According to stakeholders, the financial benefits can be shared among patients, pharmacists and health insurance companies or used for research[10].

By redispensing unused medications that are currently disposed of, waste can potentially be avoided. In a previous study many stakeholders including pharmacists expressed concerns about the feasibility of implementation of redispensing in current clinical practice (*Bekker, submitted*). On the other hand, multiple stakeholders highlighted that, in order to realise successful implementation of redispensing, several requirements should be met, such as extensive public engagement, quality assurance of returned medications and an evaluated cost-benefit ratio[10,12]. Other studies have confirmed that the majority of patients and professionals support redispensing if their concerns about medication safety and quality are addressed[25,26]. Redispensing is prohibited in some countries under current legislation, mainly due to uncertainty about the quality of unused medications and a fear of counterfeit medications entering the supply chain. The latter is currently being tackled by the European Union Directives 2011/62/EU and EU2016/161, which demand that manufacturers add tamper indicators and unique identification codes to their outer packaging. Furthermore, if these medications are dispensed in a closed seal bag by the pharmacy and only eligible for redispensing when returned unopened this risk is minimised. In terms of quality assurance, medications should be dispensed to patients in the manufacturer's original outer packaging

with tamper-evident seals and thermal devices[12,27]. Based on these outcomes, one can assume that most requirements to enable the successful implementation of redispensing in practice can be fulfilled.

Strengths and limitations

The main strength of this study is the use of a micro-costing approach, which is the most comprehensive and precise method to estimate the costs of an intervention[13]. The study also has some limitations. Primarily, this is a simulation study and the process steps that were identified may differ if redispensing is implemented in real practice. However, redispensing is not routinely performed in the pharmacy and therefore these simulations enabled a detailed estimation of the time and resources involved, which was required to calculate the costs. Furthermore, pharmacy staff was not experienced in simulating the process steps, which may have resulted in increased times. Most process steps were similar to the normal pharmacy practice, and three consecutive simulations were performed to increase their experience, of which the last was considered most accurate. It can be assumed that the number of simulations performed by the pharmacy technicians was sufficient to simulate real practice. It was not possible to simulate stock adjustments and communication with the financial department, and no training of the pharmacy staff was included in the analysis. This may have resulted in lower estimations of the time and cost, and ultimately in an underestimation of the price level. However, this would not have altered our general findings that only expensive medication packages are eligible for redispensing. In addition, a healthcare provider's perspective was used for the cost estimates, and no societal costs were taken into account. In our view, redispensing requires limited effort from society, other than the patients returning their unused medications to the pharmacy. Most patients visit their pharmacy regularly and one can assume that returning unused medication would not result in additional visits. Finally, this study was performed in a Dutch outpatient pharmacy setting and as such, the outcomes may be less generalizable to other countries. We believe that the identified process steps will be similar between countries, however, the unit costs that were included in the analysis may vary. The proportion of dispensed packages that remain unused and are returned to the pharmacy may depend on national prescribing and dispensing policies. Therefore, a general model with various scenarios was build that can be used in different settings as an indicator to determine the price level of medications eligible for redispensing.

Conclusions

This study demonstrates that the redispensing of unused medications in the pharmacy is cost-beneficial if applied to expensive medications. This threshold can lower if more unused medications are returned to the pharmacy and have been properly stored at patients' homes of which the quality can thus be guaranteed.

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Ethics approval and consent to participate

Participating pharmacy employees gave oral consent prior to participation. The study was reviewed and approved by the UPPER institutional review board of the Utrecht University (no.1604)[28].

Conflicts of Interests

All authors declare they have no conflicts of interest.

4.1

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Appendix A: The model to calculate the break-even point, *italic* variables were varied among the scenarios. *In this case, 10% of dispensed medication is returned to the pharmacy of which 60% would meet the quality criteria.*

		Medication requiring room-temperature storage		Medication requiring refrigeration	
	Packages	Cost (€)	Total cost (€)	Cost (€)	Total cost (€)
Step 1.	10,000	2.90	28,978	4.30	43,046
Step 2.	*1000 (10%)*	*2.14*	*2138*	*2.73*	*2727*
Step 3a.	*600 (60%)*	*0.50*	*298*	*0.58*	*345*
Step 3b.	*400 (40%)*	*0.48*	*193*	*0.53*	*210*
Step 4. Loggers	*Of 9000*	-	-		
a. Returned by post	360 (4%)			1.28	462
b. Returned as normal care	6930 (77%)			0.25	1704
c. Lost	1710 (19%)			8.33	14,244
d. Logger system 1 year	1			2496	2496
Total			31,608		65,233
Price level per single package (Total/3a units)			53		109

Chapter 4.2

Redispensing of unused HIV post-exposure prophylaxis for medical students

Charlotte L Bekker
Raween L Kalicharan
Eward J Melis
Helga Gardarsdottir
Bart JF van den Bemt
Marcel L Bouvy
Erik M van Maarseveen
Antoine CG Egberts

Submitted

Abstract

Introduction
Many medical schools provide post-exposure prophylaxis (PEP) kits to students who temporarily study abroad to minimise the risk of acquiring a human immunodeficiency virus (HIV) infection after occupational exposure. Most PEP kits remain fortunately unused and are destroyed upon return to the pharmacy. Redispensing of this unused medication, conditional of guaranteed quality, could reduce costs.

Objectives
To assess the proportion PEP (Kaletra® and Combivir®) that is redispensed after being returned unused by medical students, and the potential cost savings thereof.

Methods
This retrospective follow-up study included medical students who received a PEP kit from the outpatient pharmacy of the University Medical Center Utrecht between March 2014 and December 2017. The PEP kit consisted of lopinavir/ritonavir (Kaletra®) and lamivudine/zidovudine (Combivir®) wrapped in a sealed bag with a temperature logger. Redispensing of Kaletra® and Combivir® returned to the pharmacy was permitted as long as: 1) the sealed bag was returned unopened, 2) the medication's primary and secondary packaging materials were undamaged, 3) the expiry date was ≥6 months after the return date, and 4) the medication had been continuously stored below 35° Celsius. Cost savings were estimated as the total value of redispensed medication packages minus the pharmacy's additional processing costs to enable redispensing. Cost savings were compared with the medication costs that would incur without redispensing.

Results
A total of 379 medical students received a PEP kit during the study period of which 370 (97.6%) returned these unused to the pharmacy. From the 379 dispensed kits, 80.3% of the Kaletra® and 76.6% of the Combivir® packages had been previously dispensed one or more times to medical students. The most common reason for the medication not being redispensed was because the remaining time to expiry was too short. The PEP had an average value of €805 and the total value of all dispensed medication was €305,095. Medication that was redispensed had a total value of €240,714. When adjusting for the additional processing costs of redispensing (€15,037 per +/- four years) the net cost savings obtained from redispensing were €225,677 over the study period. Redispensing resulted in 74% cost savings in comparison with no redispensing.

Conclusions
The majority of Kaletra® and Combivir® can be redispensed after being returned unused by medical students. Redispensing PEP can result in substantial cost savings.

Introduction

Healthcare workers are at particular risk of acquiring a Human Immunodeficiency Virus (HIV) infection attributable to occupational exposure to infected body fluids[1,2]. The same holds for medical students, whose relative inexperience and sometimes lack of adequate safety precautions place them at increased risk of occupational injuries. Studies reported that 20%-60% of medical students experienced at least one needle stick injury while in medical school[3–9]. Administration of post-exposure prophylaxis (PEP) is widely recommended and has shown to substantially decrease the likelihood of becoming infected with HIV after (occupational) exposure[10]. The PEP usually consists of two or more antiretroviral drugs and should be administered as soon as possible after (potential) HIV exposure[11–13].

A substantial proportion of medical students (and nurses in training) in the Netherlands acquire work experience abroad and frequently choose a resource-limited country. The prevalence of HIV is relatively high in many of these countries and the availability and access to PEP is low. Therefore, many medical schools provide PEP kits to these students via the pharmacy. PEP is then readily available in case of potential HIV exposure, enabling rapid administration which reduces the risk of becoming infected and gives the students sufficient time to seek medical advice. Fortunately, most PEP kits are not needed by the students and thus these are destroyed upon return to the pharmacy. Since PEP is expensive, the disposal of this unused medication results in substantial financial waste.

The Faculty of Medicine of the Utrecht University has, in collaboration with the outpatient pharmacy of the University Medical Center Utrecht (UMCU), implemented a waste-minimising measure in which unused PEP returned by medical students is redispensed. One of the main requirements for safe redispensing, which is also included in the UMCU redispensing protocol, is guaranteed product quality[14,15]. Improper storage, for instance at high temperatures, may affect the product stability and thereby the clinical efficacy and safety. The product quality of returned PEP is therefore established by measuring the storage temperature abroad and assessing the medication's packaging material quality and the medication's expiry date. This study aims to assess the proportion of PEP, consisting of Kaletra® and Combivir®, that are redispensed after being returned unused by medical students who had internships in countries with a high prevalence of HIV, and to estimate the potential cost savings thereof.

Methods

Design, setting, and study population
This retrospective follow-up study was conducted in the outpatient pharmacy of the UMCU in the Netherlands. Medical students who received a PEP kit from the outpatient pharmacy between March 2014 and December 2017 were included in this study.

Ethics
The study was reviewed by the Medical Research and Ethics Committee of the UMCU (protocol reference number 18-280/C), which deemed that the Medical Research Involving Human Subjects Act (WMO) was not applicable to this study.

4.2

Procedure

Medical students who had planned an internship in a country with a high prevalence of HIV were provided with a prescription for a four-week PEP course by the Faculty of Medicine and the hospital's occupational health department. This PEP could only be dispensed by the outpatient pharmacy of the UMCU. PEP consisted of lopinavir/ritonavir (Kaletra®, 200/50 mg, 120 tablets, shelf life three years) and lamivudine/zidovudine (Combivir®, 300/150 mg, 60 tablets, shelf life two years) and included either new medication packages or packages which had previously been dispensed to another student. Medical students received the PEP wrapped in a sealed bag with a temperature logger that measured and registered the surrounding temperature continuously on an hourly basis (range -40° Celsius to +50° Celsius, Icespy®, Re5al, the Netherlands), see Figure 1 for the PEP kit. The medication was dispensed in the original manufacturer's primary and secondary packaging materials that were designed to sufficiently protect it from light and moisture. The pharmacy provided the students with oral and written storage instructions and requested that the PEP kit be returned to the pharmacy with the seal unopened if the medication had not been used. Although the PEP kit was provided for free by the Faculty of Medicine, the students were required to pay a fee if the medication was not returned or if returned damaged.

Pharmacy staff assessed whether the returned Kaletra® and Combivir® could be redispensed. All of the following criteria had to be met for redispensing: 1) the sealed bag was returned unopened by the student, 2) the primary and secondary packaging materials were undamaged, 3) the expiry date was at least six months after the date of the medication being returned, and 4) the medication had been continuously stored below 35° Celsius. If the storage temperature exceeded 35° Celsius, the expiry date was shortened by one month per excursion above this temperature.

Figure 1: PEP kit. PEP dispensed in a sealed bag with a temperature logger.

Outcomes

Study outcomes included the proportion of Kaletra® and Combivir® that fulfilled all criteria and were redispensed, as well as the potential cost savings derived from redispensing this medication. At the beginning of the current study some medication had been previously dispensed, meaning that the baseline included new and redispensed medication packages. The cost savings were therefore assessed by calculating the total economic value of the redispensed medication packages using Dutch medication prices[16] (including the pharmacy's dispensing fee and value-added tax) minus the pharmacy's additional processing costs that were required to enable redispensing. In addition, the cost savings were compared with the total value of all dispensed medication packages to the medical students, which would have been made when the redispensing process was had not been implemented. The additional processing costs were based on the results from a previous micro-costing study that assessed costs associated with redispensing unused medication in the pharmacy (Chapter 4.1). In short, the micro-costing study identified the additional processing steps required for redispensing and quantified these into costs by calculating direct costs (labour and materials) and indirect costs (overhead). For the current study, the labour costs were based on the time required to perform the process which was derived from discussions with pharmacy staff. The material costs were adjusted to account for the material used for redispensing PEP (see Table 1 for the labour and material costs and Table 2 for the additional steps and their costs). All costs were based on 2016. Total processing costs were calculated by multiplying the costs of each step by the number of medication packages involved in each step, for which the following formula was used:

*Total processing costs=(cost step1*dispensed packages)+(cost step2*returned packages)+(cost step3a*returned packages that fulfils quality criteria)+(cost step3b*returned packages that not fulfils quality criteria*)+(cost step4*loggers returned without medication)+(cost of loggers lost [cost logger-cost of dispensed logger]* loggers not returned)+cost temperature software*

Table 1: Unit cost of labour and materials.

Resources	Unit cost (€, 2016)	Source
Kaletra®	500.00	Pharmacy's information system
Combivir®	305.00	Pharmacy's information system
Pharmacy technician	0.30 (per minute)	Royal Dutch Pharmacists Association
Pharmacist	0.55 (per minute)	Royal Dutch Pharmacists Association
Seal bag	0.41	Eaglepac 10x15
Temperature logger	9.72	Icespy
Temperature software	97.76	Icespy
Printed paper	0.02	Staples
Printed label	0.01	Zebra Z-select 2000D label

Table 2: Additional processing steps required for redispensing PEP, the average time spent on each step, and the associated costs, which include labour, material, and overhead costs.

Process steps	Pharmacy staff	Average time (minutes)	Cost (€)
1. Preparation of PEP kits before dispensing: adding temperature logger and sealed bag*	Technician Pharmacists	18.0	26.22
2. Assess quality of returned medication	Technician Pharmacist	7.0 5.0	9.74
3a. Restock medication that meet all criteria	Technician	0.75	0.45
3b. Dispose of medication that does not meet criteria	Technician	0.73	0.44
4. Collect loggers returned without medication	Technician	5.0	3.00
Total steps 1, 2, 3a		**30.75**	**36.41**

*32 kits were prepared but not dispensed to students that resulted in costs of €12.61 per kit for the total processing costs

Data analysis

The data were descriptively analysed and presented as percentages or medians with interquartile ranges (IQR). Outcomes were stratified for the type of PEP (Kaletra® and Combivir®). Temperature measurements were exported to the statistical package SAS version 9.2 (SAS Institute, Cary, NC, USA) to calculate the storage time per PEP kit above 35° Celsius and the mean kinetic temperature, which is generally higher than the mean temperature and takes into account temperature fluctuations[17]. Potential cost savings were determined for a worst-, average-, and best-case scenario. A model was therefore constructed that included the following variables:

- Number of times PEP could be redispensed, derived from the duration students went abroad and the medications' duration until expiry.
- Variation in the proportion of PEP that met the criteria for redispensing (between 0-100%).
- Fixed variables: number of PEP kits dispensed to students (fixed at n=100), proportion of returned PEP kits (based on study results), calculated medication prices, and additional processing costs.

The worst case was defined as the least number of times PEP could be redispensed. This scenario was based on the 90th percentile of the measured duration students went abroad and the 10th percentile of the duration until expiry of the new medication packages that were received from the manufacturer. The best case was defined as the greatest number of times PEP could be redispensed. This scenario included the 10th percentile of the measured duration abroad and the 90th percentile of the duration to expiry. The average case included the median measured duration abroad and the median duration to expiry. Total cost savings for each scenario were calculated taking the pharmacy's additional processing costs into account. Analyses were conducted in Microsoft Excel 2010.

Results

A total of 379 PEP kits were dispensed to an equal number of medical students by the outpatient pharmacy during the study period. Of these, 19.7% of the Kaletra® packages and 23.4% of the Combivir® packages were new and 80.3% of the Kaletra® packages and 76.6% of the Combivir® packages were redispensed (i.e. had been previously dispensed one or more times).

Of the dispensed PEP kits, 370 (97.6%) were returned to the pharmacy. The most common reason for disposing of the returned medication was "remaining time to expiry date too short", followed by "temperature logger defect" (Table 3).

Of all returned PEP kits, 288 (77.8%) were continuously stored below 35° Celsius. The lowest and highest storage temperatures measured were -5.9° Celsius and 54.9° Celsius. The median storage time above 35° Celsius for the PEP kits that exceeded this temperature was 4 hours (IQR 2-9). Although some PEP kits were temporarily stored above 35° Celsius, adjusting for temperature fluctuations showed that all PEP kits had been stored at a mean kinetic temperature below 30.0° Celsius.

Table 3: Reasons for disposing of PEP that was returned. *These were based on PEP kits that were dispensed during the study period and subsequently returned.*

	Kaletra® n (%)	Combivir® n (%)
Dispensed	379	379
Returned to pharmacy	370 (97.6)	370 (97.6)
Packages disposed of*	154 (43.0)	169 (47.0)
-Expiry date too short	111 (72.1)	112 (66.3)
-Temperature logger defect	31 (20.1)**	30 (17.8)**
-Damaged primary and secondary packaging materials	9 (5.8)	21 (12.4)
-Temperature data accidently removed in pharmacy/other	3 (1.9)	3 (1.8)
-Seal opened	3 (1.9)**	5 (3.0)**
-Unknown	6 (3.9)	11 (6.5)

*Multiple reasons could be reported
**Numbers are not corresponding due to incorrect information registered

Cost savings

Providing a PEP kit to the medical students using the redispensing process costed on average €841 per kit; €805 for the medication and €36 for additional processing costs, including labour, material and overhead costs (see Table 2). The total value of the redispensed medication packages (80.3% of the Kaletra® packages and 76.6% of the Combivir® packages) was estimated at €240,714. When adjusting for the pharmacy's total additional processing costs, which were estimated at €15,037 over the +/- four year study period, the cost savings achieved from redispensing were valued at €225,677. The total value of all medication packages dispensed during the study period, which would have been made when the redispensing process had not been implemented, was estimated at €305,095. Redispensing thus resulted in savings of 74% of the total medication costs.

On average, students went abroad for 5.2 months (10th percentile 3.3, 90th percentile 7.4). The new medication packages had an average time of 16 months to expiry (10th percentile 8.2, 90th percentile 19.9). The most optimal scenario would allow PEP to be redispensed five times, resulting in cost savings of around €300,000 when 80% of the returned medication would be eligible for redispensing (Figure 2). In the worst case, PEP could not be redispensed, incurring a financial loss due to the additional processing costs for redispensing. In general, cost savings increase when a higher proportion of PEP is eligible for more frequent redispensing.

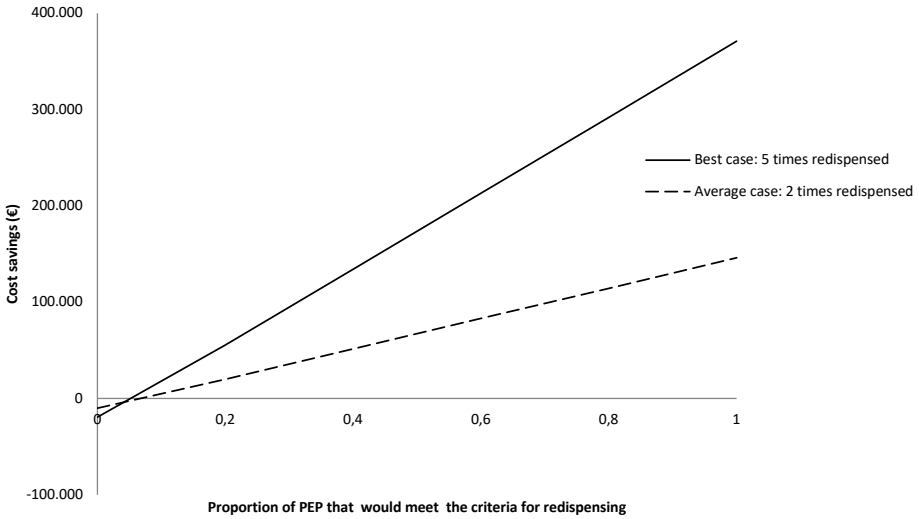

Figure 2: Cost savings of redispensing PEP for an average- and best-case scenario. *In the worst case, PEP could not be redispensed and a financial loss would occur (not shown). Scenarios are based on 100 dispensed PEP kits, of which 97.6% would be returned, with redispensing processing costs of €3,906 for 100 kits.*

Discussion

This study shows that the majority of Kaletra® and Combivir® returned unused by medical students who had internships in countries with a high prevalence of HIV fulfilled all predefined quality criteria and, thus, was eligible for redispensing. Redispensing resulted in 74% savings of the total value of dispensed PEP (€305,000) that would have been made when the redispensing process had not been implemented.

The criteria used to determine if the returned medication could be redispensed are in line with those used by others[18–21]. These studies showed that around 15-90% of medication returned unused to pharmacies was potentially eligible for redispensing, which is comparable with our findings. Most of these studies contained a hypothetical approach regarding the possibility of redispensing. Only one study redispensed returned medication in actual practice by donating these to the poor[21]. To our knowledge, this is the first study that evaluated the redispensing process for PEP that is implemented in clinical practice.

Research shows that the benefits acquired through redispensing are most strongly affected by the proportion of medication that is returned to the pharmacy and the proportion of medication that meets the criteria to allow for redispensing (Bekker, submitted). In the current study, nearly all PEP kits remained unused and were returned to the pharmacy. As a result, the current cost saving estimation strongly depends on the duration of time which the students spend abroad and the expiry date of the medication itself. It was shown that the optimal scenario with the highest cost savings would include a combination of a short time spent abroad by students and medication with a long time to expiry. This would enable the redispensing of PEP for multiple times. In the worst case, students would spend a long time abroad and the medication would have a short time to expiry, thus meaning that the PEP could not be redispensed. In this case, a financial loss would occur due to the additional costs incurred for the redispensing process in the pharmacy. The model that is provided in this study can be used to estimate the cost savings that can be achieved by redispensing. For clinical practice, this indicates that medication that has a long time to expiry is more likely to be redispensed.

One of the major concerns with redispensing unused medication is uncertainty regarding the quality of the returned medication. In certain regions of the world, ambient temperatures often exceed 30° Celsius. Medication storage outside the recommended temperature as stated in the Summary of Product Characteristics (SmPC) may induce product instability. SmPC storage conditions are based on standardised stability tests of the International Conference on Harmonisation (ICH) guideline for new products[17]. According to the SmPC, Kaletra® does not require any specific storage conditions and is therefore considered stable when stored at temperature conditions up to 40° Celsius for 6 months. Combivir® is light sensitive and should be stored below 30° Celsius, indicating stability for 6 months when stored below this temperature. In this study, the redispensing requirement included a threshold of 35° Celsius to determine if the medication was properly stored. This could have resulted in the redispensing of Combivir® packages that were unjustifiably deemed to be of good quality. However, only short excursions of a few hours above 35° Celsius were observed and, furthermore, all PEP kits had been stored below a MKT of 30° Celsius. The MKT is higher than the mean temperature and, based on the Arrhenius law, includes temperature variations, related storage duration, and their influence on the medication. Therefore, it was assumed that the product quality had not been affected. But it is unclear if short excursions above the recommended temperature directly affect the quality.

Protecting health and safety of medical students who gain work experience abroad is the responsibility of medical schools. Medical students have a higher risk of occupational needle stick injuries, thereby requiring additional safety precautions when working in countries where the prevalence of HIV is high. To reduce the risk of students becoming infected with HIV, institutional protocols have been developed that include the provision of PEP kits, educational training, and post-exposure follow-up[22–24]. However, some students may not carry PEP kits with them since PEP is expensive and institutions may not be able to provide this expensive medication free of charge. Also, students may not be aware of the potential risk of HIV infection or may not be willing to pay for the medication themselves. The UMCU invested in total around €80,000 on new PEP and the additional redispensing process during the almost four years. Our study results show that a small investment is needed to enable the provision of free PEP kits to students following a redispensing protocol, while the cost savings are substantial.

4.2

This could enable institutions to consider providing PEP kits at no cost to students and other travelling healthcare workers, making PEP more accessible.

Several limitations of this study should be acknowledged. Firstly, the reason for which some students did not return their PEP kit, and whether this PEP was used because of potential HIV exposure, was unknown. If PEP indeed prevented students from acquiring HIV infection, this would emphasize that the provision is desired. Moreover, humidity and light exposure was not measured and PEP kits may have been stored at a humid location that could potentially have affected the product quality. However, the medication was dispensed in the original manufacturer's primary and secondary packaging materials that were assumed to sufficiently protect it from light and moisture. Thirdly, most discarded medication had a time to expiry of less than six months. Most likely these medication packages had been redispensed, however, how often is unknown. Although this may underestimate the cost savings, which depend on the number of times medication packages are redispensed, it still enabled us to show that this redispensing result in substantial cost savings. Finally, this is a single-centre study performed in the Netherlands and generalisability of the outcomes to other settings may be challenging. Cost savings strongly depend on the duration of the students' time abroad and the type of PEP that is dispensed, specifically regarding costs, expiry date, and storage recommendations. Nevertheless, it still enabled us to report on the substantial economic benefits that can be obtained from redispensing medication that remains unused, which could be of potential interest in other sectors, such as for the military field as well as for expensive medication therapies in normal patient care.

Conclusions

The majority of Kaletra® and Combivir® that was returned unused by medical students who had internships in countries with high a prevalence of HIV could be redispensed, if properly stored. The additional cost investments for the redispensing process were relatively low in comparison to the medication costs that were saved. Overall, the redispensing of PEP resulted in cost savings of 74% in comparison with no redispensing.

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Disclosure of Interest
All authors declare that they have no conflicts of interest.

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Chapter 5

General discussion

Introduction

Studies have shown that many patients do not (entirely) use all pharmacy-dispensed prescription medication[1–3], often because they are oversupplied with medication or they discontinue therapy at an early stage due to unsatisfactorily response or because of non-adherence. Medication waste is considered a financial loss of healthcare resources, with estimates indicating that at least 3-6% of total pharmaceutical spending is wasted[4,5]. In addition, it leads to environmental pollution when disposed of by patients directly in the environment through, for instance, the toilet or sink. Dutch estimates indicate that only 54% of the patients return their unused medication to the pharmacy[1]. Prevention of medication waste may significantly contribute to cost containment in healthcare, a sustainable use of healthcare resources and reduction of environmental pollution. Despite the consequences of medication waste, not much is known about the extent of waste within the community and outpatient pharmacy setting or the potential to prevent medication waste among specific patient or medication groups.

A significant proportion (20–90%) of the medication that has been dispensed by pharmacies and were not used by patients remain unopened in their intact outer packaging[5–7]. This unused medication could potentially be redispensed to other patients. However, this is not a standard pharmacy practice, primarily due to uncertainties regarding the quality of the medication and legal constraints. Storage and distribution of medication within the pharmaceutical supply and use chain should comply with international guidelines on Good Distribution Practice (GDP) (EU Directive 2013/C 343/01). Medication that is dispensed to patients is no longer supervised following GDP guidelines for which thus quality cannot be guaranteed when returned unused to the pharmacy. Moreover, the feasibility of implementing redispensing and the cost savings that could be achieved have not been thoroughly investigated.

The objectives of this thesis were therefore to investigate medication waste among patients in terms of quantity, cost, preventability, and currently implemented waste-reducing measures. In addition, the feasibility of redispensing medication that remains unused by patients will be investigated. The studies presented in this thesis show that patients frequently have unused medication, which are mainly of low-cost in the community pharmacy and of high-value in the outpatient pharmacy. Around 40% of the medication waste is preventable and as such indicate the need for waste-preventive measures. Patients and other stakeholders support the redispensing of unused medication given that several requirements, especially a guaranteed product quality, are met. However, considering the pharmacy's additional processing costs of redispensing this strategy is most cost beneficial if applied to expensive medication.

In this general discussion, the studies presented in this thesis will be put in a broader perspective by addressing three themes. First, the potential waste-minimising measures that could be undertaken by stakeholders in the pharmaceutical supply and use chain will be discussed. Next, the feasibility of redispensing unused medication in clinical practice will be addressed, with a special focus on barriers to and facilitators of implementation. Finally, methodological considerations of studies on medication waste and redispensing will be addressed.

Potential waste-minimising measures

The societal impact of medication waste in terms of its economic and environmental consequences is globally increasingly recognised. The International Pharmaceutical Federation (FIP), for example, advocates for "green (pharmacy) practices" among all stakeholders involved in the pharmaceutical supply and use chain, including awareness of the environmental burden of medication waste[8]. In addition, in 2013 the Dutch Ministry of Health carried out a survey among 16,000 people, including both professionals and the public, regarding waste in healthcare[9]. Most of the respondents commented specifically on medication waste and advocated for redispensing. As a result, the Ministry identified possibilities for waste reduction in healthcare, including limiting prescribing, redispensing unused medication and continuity of home medication during hospitalisation[10].

The studies described in this thesis show that medication waste occurs among all types of patients and medications in various settings, and that it is a multifactorial problem. It was found that patients often have multiple medication packages that remain unused. While in the community pharmacy these were generally low-cost medications, with an average value of €1.75 (**Chapter 2.1**), high-value medications were also wasted in the outpatient pharmacy for expensive therapies (e.g. oral anti-cancer and biological disease-modifying anti-rheumatic drugs), with an average value of €826 (**Chapter 2.2**). In **Chapter 2.1**, it was demonstrated that around 40% of the medication waste is preventable. This is in line with estimates from the UK, which also reported that less than half of the medication waste is avoidable[2]. These findings underline that a substantial proportion of medication waste and thus unnecessary spending can be minimised.

The multiple causes of medication waste (e.g. adverse effects, insufficient effect, patient's death, condition resolved, passed expiry date) imply that no single intervention will sufficiently combat the problem and thus a multitude of approaches is needed. Medication waste minimisation can be achieved by various strategies in all stages of the pharmaceutical supply and use chain (Figure 1). Prevention of waste in the prescribing and dispensing stage is the most preferable, followed by the redispensing of unused medication and the recycling of wasted materials after the medication has been dispensed to patients (Figure 2). For maximum success, waste minimisation also requires a joint responsibility of all stakeholders involved. In the next paragraphs, the different measures that can be taken by each stakeholder will be discussed in more detail. These measures focus on minimising medication waste that occurs at the prescriber, pharmacist and patient level.

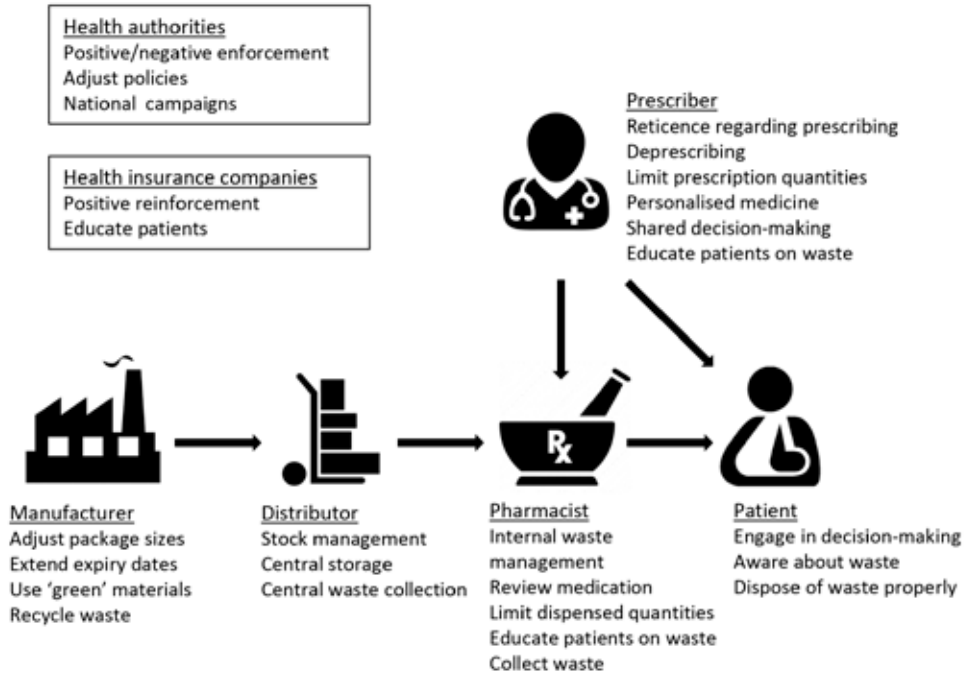

Figure 1: Examples of waste-minimising measures for stakeholders involved in the pharmaceutical supply and use chain.

Manufacturers

Manufacturers are at the origin of the pharmaceutical supply and use chain and determine the manner in which the pharmaceutical product is manufactured and provided. For waste minimisation at the patient level, the four main actions recommended for manufacturers are adjusting package sizes, extending expiry dates, using environmentally friendly materials and recycling of waste.

Medication packages produced by manufacturers do not always match with the appropriate dose and quantity required for the patient's prescription. In **Chapter 2.3**, half of the participating pharmacists working in Western countries reported that they are by law not allowed to split medication packages into smaller quantities. As a result, pharmacists can only dispense complete medication packages as produced by the manufacturer, which can result in an excessive supply of medication to patients. To prevent medication waste, a variety of smaller or even unit-dose package sizes should be available to enable pharmacists to dispense the appropriate size for the patient's prescription. However, this may not fit with the manufacturer's business model, as supplying smaller packages could imply less money per patient. Most likely this would have to be regulated or linked to a specific incentive.

Many patients return unused, expired medication to community pharmacies for disposal (**Chapter 2.1**). Although patients also keep unused packages at home for potential further use, these are often disposed of only after the expiry date has passed. Expiry dates are an assurance of product quality, and in general indicate that the medication should contain 90–110% of

their active pharmaceutical ingredients given storage as stated in the Summary of Product Characteristics. Research has shown that over 80% of medications retain their potency for decades beyond their expiry dates if properly stored, with pharmaceutical ingredient concentrations at least 90% of their labelled amount[11]. Based on stability data, the expiry dates of almost 90% of the 112 different medications tested could have been extended[12]. These findings indicate the potential of extending expiry dates. In the pre-authorisation phase, International Council for Harmonisation (ICH) guidelines for stability testing could be adapted and additional tests for expiry date extension could be performed. Patients thereby would not have to dispose of unused medication so quickly or the unused medication could potentially be redispensed when having a sufficient long time to expiry (**Chapter 4.2**).

To reduce the environmental consequences of medication waste, environmentally friendly packages that are easy to recycle or produced from recycled materials could be introduced ('green' materials). The outer cardboard packaging could be fully biodegradable. For instance, carbon that is produced from agriculture waste, such as harvested leaves that remain unused, could serve as outer packaging[13]. Inner packaging, such as blister packs that often consist of paperboard, plastic and aluminium foil layers, is often difficult to recycle. Blister packs could be replaced with layers made from biodegradable material.

Another important waste-minimising measure includes recycling of wasted medication themselves. In analogy with the recycling of, for instance, glass and paper, active pharmaceutical ingredients could be extracted from wasted medication and used to produce new medication. Excipients, which ensure tablet stabilisation, could be used for production of animal feed. The potential of this theoretical approach in practice should be further explored.

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Distributors

Distributors can minimise waste by optimal stock management. Pharmacies could, for example, be advised on first-in-first-out principles and on stock volume, particularly for medication that is not frequently dispensed to patients and therefore has a greater likelihood to expire. In addition, distributors could act as the regional storage location for medication with a short expiry date or medication that is rarely used in order to prevent these from expiring and being wasted. This medication could subsequently be distributed to the pharmacy when needed for a specific patient. Further, distributors could collect unused medication that is returned to pharmacies by patients, separating the wasted products and the inner and outer packaging to enable efficient recycling.

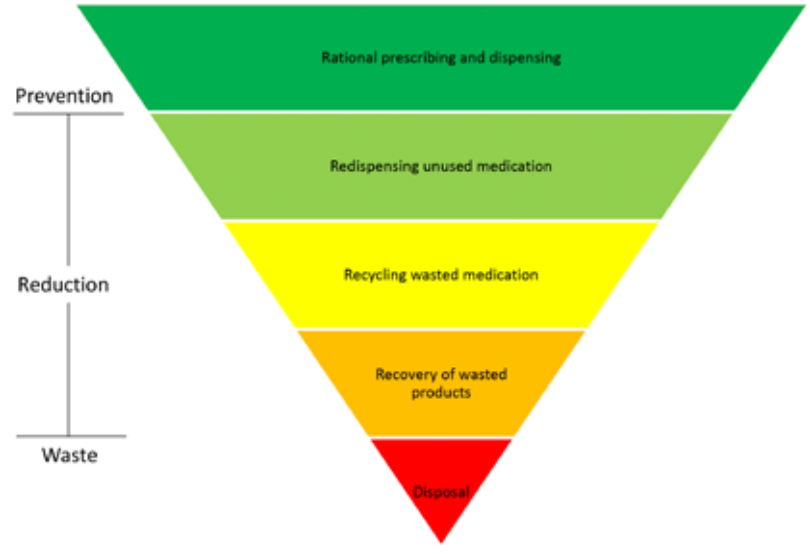

Figure 2: Overall waste management hierarchy, indicating the order of preference that starts with prevention, followed by reduction, and handling of waste.

Prescribers

Prescribers are among others responsible for the medical diagnosis and, together with the patient, for the decision to initiate pharmacotherapy. Multiple measures are conceivable at the prescriber level to minimise medication waste: increasing the general reticence regarding prescribing medication, regular evaluation of prescribed medication, and deprescribing if possible. Furthermore, if prescribing is necessary measures include considering prescription quantities, incorporating personalised medicine and shared decision-making, increasing patient awareness about medication waste, and prescribing for short durations.

Medication that is not prescribed cannot be wasted thus stimulating reticence when prescribing is important. This reticence can include a more thoughtful decision on therapy initiation as well as on discontinuation. Patients in need of long-term pharmacotherapies often have repeat prescriptions that enable them to collect their medication directly from the pharmacy without consulting the prescriber. While this is implemented to reduce prescriber costs and increase patient access to medication, this also facilitates the provision of excessive medication to patients that are no longer needed. One measure could be to periodically review the different medications prescribed for each patient and discontinue unnecessary therapies. Over the past year, increased attention has been paid to this so called deprescribing[14].

When a prescription is considered necessary there are other measures that can be taken to minimise medication waste. The studies described in **Chapter 2.1** and **2.2** show that a substantial proportion of medication remains unused because of early discontinuation of therapy, either following a spontaneous resolution of the condition or because the therapies have insufficient benefit or adverse effects (especially at start of therapy). Moreover, multiple medications often remain unused when patients have passed away (**Chapter 2.1**). As example

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thereof, one family member returned 24 different types of medications to the community pharmacy because the patient had died. These reasons for medication waste have also been reported in a systematic review[3]. Early discontinuation is frequently unpredictable, meaning that medication waste is to some extent inevitable. It is therefore recommended that special attention should be paid to medication quantities that are prescribed for each patient and the potential of some remaining unused. For example, by prescribing smaller quantities to patients in the end-of-life phase and to patients who start new therapies.

During prescribing, shared decision-making between prescribers and patients could help to tailor pharmacotherapy to patient's individual preferences. Shared decision-making significantly improves patient's adherence to pharmacotherapy[15], and may therefore also reduce medication waste arising from non-adherence. Moreover, quantities that patients have at home from previous prescriptions could be identified. In such cases, smaller quantities could be prescribed. Moreover, information could be provided to patients during consultation to improve their knowledge and awareness about medication waste and its negative consequences.

There are advances in the field of pharmacogenetics that can lead to more personalised medicine. Some medication is only effective for specific patients because of their genetic profile. For instance, tamoxifen is commonly prescribed to women with breast cancer but has shown wide variability in effective treatment outcomes. Women with a mutation in their CYP2D6 gene do not benefit from tamoxifen treatment[16]. Screening on genetic profiles prior to pharmacotherapy initiation could tailor therapies to the individual patient, resulting in less discontinuation of ineffective therapies and potentially less medication waste.

Furthermore, prescriptions for durations of at least three months are associated with preventable waste (**Chapter 2.1**). Several studies have also concluded that the quantity of medication wasted per prescription is lower when dispensing a one-month supply compared with a three-month supply[17–21]. These findings suggest that prescribers should prescribe for a short duration for every patient to minimise waste. However, when accounting for the additional costs associated with more frequent refills for smaller prescription quantities, this will only lead to overall cost savings for expensive medication. An important issue that arises when implementing a shorter prescription duration is that patients are not always satisfied with receiving 28-day supplies because of inconvenience and costs of picking up medication more frequently[22]. To overcome this barrier, pick-up services such as a continuously accessible locker system or direct delivery to patients' homes could be considered.

Pharmacists

Pharmacists have a central role in the pharmaceutical supply and use chain. As discussed in **Chapter 2.3**, pharmacists can undertake a variety of waste-minimising measures such as to reduce internal waste, to evaluate and limit medication being dispensed, to educate patients about waste, and to collect unused medication.

For internal waste management, pharmacists could minimise medication kept in stock. Medication nearly to expire could be transferred to other pharmacies that are able to dispense these to patients in time. A helpful tool would be an online database in which pharmacies can register medication close to expire as well as requests for medication not in stock. Furthermore, medication with a short expiry date could be stored at a central storage facility that regulates the distribution to pharmacies. Waste of medication compounded in the pharmacy due to inappropriate vial sizes could, besides adjusting package sizes, be solved by scheduling patients requiring parenteral medication on the same day.

Patients often have unused medication due to being oversupplied, which may be attributable to a lack of evaluation of their medication. Patients with chronic conditions often receive automatic refills prior to running out of stock. Although this optimises pharmacy workflow and improves supply service, some patients receive medication refills without a clear therapeutic index. Evaluation of such dispensing services is therefore highly recommended. An example of a waste-minimising measure is to conduct medication reviews to reduce the number of medications being unnecessarily dispensed to patients. Another example is applying a split-fill supply for new long-term prescription medication, providing a trial quantity at the start of treatment and supplying the remainder when the medication is well-tolerated. Paterson et al. showed that a split-fill supply could reduce the cost of medication waste in Canada[23]. In the Netherlands, this initiative has already been implemented for decades; however, no studies have evaluated its effectiveness on waste reduction. To further reduce quantities supplied to patients, medication combinations could be compounded that include all active pharmaceutical ingredients a patient needs combined in one dosage form. Such a polypil has been developed for cardiovascular diseases and it significantly improves medication adherence[24]. In addition, it reduces the amount of packaging materials needed and thereby the environmental burden if therapy is discontinued.

Understanding patient needs and experiences with taking their medication could help to reduce the amount of unnecessary medication collected by patients[25]. However, only 22% of pharmacists reported to discuss medication quantities with patients (**Chapter 2.3**). Guidelines and professional standards could be adjusted to ensure that these discussions are incorporated during medication supply to patients. Thereby also patient awareness about medication waste and its negative consequences could be increased.

When medication waste occurs despite preventative measures, it is important that patients dispose of medication properly to reduce the environmental burden and potential abuse by others. To influence patient behaviour regarding disposal, pharmacists could regularly provide information to increase awareness about proper disposal routes; either verbally or by using supportive materials. Tai et al. found that two-third of pharmacists do not regularly give disposal education because of a lack of patient requests for such information, a focus on other content during counselling, and workforce issues[26]. To overcome this barrier, informative tools could be made available such as information leaflets or stickers placed on medication packages that request any unused medication to be returned to the pharmacy. Furthermore, as motivational approach pharmacies (and other facilities) could provide disposal bins to enable patients to easily return their unused medication. Recently, a waste-minimising initiative was launched in the Netherlands, providing disposal bins in pharmacies[27]. To facilitate efficient recycling of unused medication, disposal bins could include separate boxes for medication's inner and outer packaging. It is important that pharmacists still discuss patient's reasons for disposing of unused medication to identify potential problems, such as non-adherence. Since many patients keep their unused medication at home, pharmacy staff could also collect these during a medication management consultation or medication review at patients' homes.

Patients

Reducing medication waste should certainly be perceived as a primary responsibility by patients as well. They can take measures to minimise waste that include actively engaging in pharmacotherapy decision-making, becoming more healthcare cost aware, and disposing of medication properly.

To prevent medication waste patients ideally receive medication just prior to administration. A potential measure could include the direct production of medication at patients' homes. 3D printers are increasingly applied to print any product, from organs to food, and medication also belongs to the possibilities. Personalised production could ensure that only medication that is needed is compounded, preventing the occurrence of medication waste. A similar approach has recently been piloted in the Netherlands, were a machine enables pharmacists to produce biological medication tailored to the individual patient directly in the hospital[28]. It should be taken into account, however, that 3D printing at patients' homes is heavily subjected to regulatory constraints.

Waste minimisation should be accompanied by patient engagement in pharmacotherapy decision-making. This includes discussing sufficient medication quantities that match their needs and informing the prescriber about personal preferences regarding pharmacotherapy, such as intention (not) to start pharmacotherapy. Moreover, patients should be aware about the cost of pharmacotherapy and should take responsibility for a sustainable healthcare. For instance, patients using expensive medication could be provided with a one-month supply to reduce waste if therapy is discontinued. This is beneficial from a waste perspective even though it requires more pharmacy visits for patients. Discussions about medication waste should be carefully conducted to prevent patients feeling guilty about receiving medication in the first place.

Almost half of patients who ever had unused medication has returned this to the pharmacy (**Chapter 3.2**, data unpublished). For those who discontinued expensive medication therapy, over half reported to keep the unused medication at home (**Chapter 2.2**). These practices have been confirmed by others[1,29] and emphasize that patients often do not properly dispose of unused medication. Literature shows that approximately 80% of patients receive no or insufficient information on proper disposal routes from their healthcare providers[30–32]. Furthermore, only 43% of patients are aware of the environmental consequences of medication waste[33]. To reduce the negative consequences arising from medication waste, patients should be aware. The National Health Service of the UK has chosen to display medication costs over £20 on dispensing labels to increase patient awareness about the costs of medication and waste[34]. In contrast to the intended effect, this information is perceived negatively by the public. They either feel guilty for needing medication or do not care about costs because medication was perceived as necessary[35]. The effectiveness of this strategy on waste reduction has not yet been evaluated. Further, an educational programme consisting of providing informative materials and healthcare counselling led to improved medication disposal among cancer patients[36]. Another study found that counselling about disposal practices positively influenced patient beliefs about disposal[31]. Of patients who received information about proper disposal from their healthcare provider, 75% was likely to dispose of their unused medication in an appropriate manner[30]. Providing counselling and education regarding medication waste to patients is therefore recommended. Moreover, patients call for information can facilitate education on reducing medication waste.

Patients can also be motivated to properly dispose of unused medication. In general, behavioural change in patients is more likely to succeed if they are intrinsically motivated or rewarded. To maintain behavioural changes, positive effects should be communicated with patients. Patients' environmental concerns associated with inappropriate disposal are the main drivers for returning medication to pharmacies[37]. Many people dispose of empty batteries in special collection bins available in stores. More patients might return their unused medication if disposal bins are widely available and easily accessible. In other sustainability initiatives, small financial incentives have substantially changed people's behaviour to environmentally friendly actions. For instance, establishing a deposit for returning empty soda bottles has significantly increased the amount of plastic being recycled, and almost 80% of the general Dutch population felt positively about the use of deposits to stimulate the return of empty soda cans as well[38]. Similar incentives for returning unused medication packages would likely increase proper disposal and reduce the environmental pollution.

Health authorities

Measures at the health authority level include installing regulations aimed at minimising medication waste through positive or negative enforcement and national campaigns.

Regulators of pharmaceutical market authorisation primarily focus on scientific evaluation of efficacy and safety, with little attention paid to the potential occurrence of medication waste. There is a lack of clear guidance on package sizes or additional stability tests required for the extension of expiry dates. Adjustments to the market authorisation application that include measures undertaken to reduce medication waste are highly recommended. For instance, the European Medical Agency (EMA) could decide not to authorise medication that is unavailable in small size packages adapted to expected use of patients. Other waste-minimising measures include requiring healthcare providers to prescribe and dispense appropriate quantities of medication. In many European countries, medication can be prescribed for up to three months at a time[39]. Although this somewhat restricts the supply of medication, large quantities of medication could still remain unused in the case of early therapy discontinuation. As stated before, it is recommended to restrict expensive medication to a one-month supply in order to reduce waste and save costs. The Netherlands serves as an example where the first six months of expensive medication therapies is supplied on a monthly basis. In **Chapter 2.3**, half of the included countries reported that pharmacists are not allowed to adjust prescription quantities by splitting medication packages, resulting in the obligation to dispense an oversupply to patients. Based on these findings, it is recommended that prescribing and dispensing policies are reconsidered.

Waste minimisation could also be achieved through positive reinforcement; for example, by providing a financial support for disposal or stimulus for rational (de)prescribing and dispensing. In some countries pharmacists are responsible for disposal of returned medication and thus costs[40], and as a consequence, some refuse to collect these packages. Health authorities could cover these costs to limit the environmental pollution from improper disposal by patients due to a lack of available disposal locations.

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Finally, for successful waste minimisation, awareness about medication waste and minimisation measures among the public and professionals should be increased. The development of national awareness campaigns is strongly encouraged. In addition, take-back programmes could be promoted for the collection of unused medication by pharmacies. In many countries, public campaigns and take-back events have been effective in collecting unused medication[41–43]. In the Netherlands, the government recently launched a camping and provides posters to all pharmacies to raise patient awareness on the environmental burden of improperly disposing of unused medication[44]. Such initiatives will hopefully contribute to improved disposal and less environmental pollution.

Health insurers

Health insurance companies in the Netherlands and many other countries regulate access to healthcare. In general, little attention is paid to medication waste and sustainable use of medication. Dutch health insurance companies recently discussed implementing a one-year supply for most medications to limit pharmacy dispensing costs. However, this will likely increase the extent of medication waste, which in turn increases unnecessary pharmaceutical spending. Health insurers could instead financially stimulate waste-minimising behaviour among healthcare providers. In many healthcare systems business models stimulate dispensing larger medication quantities because of an increase in profit. Also reimbursement systems stimulate the supply of large packages to patients because these are sometimes cheaper compared with smaller packages. Business models could be adjusted so that rational prescribing and dispensing, including deprescribing, is also rewarded. Insurers could also increase reimbursements for smaller packages. Furthermore, insured patients can be easily approached with newsletters raising awareness of medication waste.

5

Further directions for sustainable use of medication

The multiple causes of medication waste imply that no single intervention will sufficiently minimise the problem and thus a multitude of approaches throughout the entire pharmaceutical supply and use chain is needed. For maximum success of waste minimisation, also a joint responsibility of all stakeholders involved is necessary. Multiple waste-minimising opportunities for each individual stakeholder have been addressed. Most of these measures require effort of several stakeholders (Table 1). For instance, measures are regulated at the health authority level (e.g. policies), implemented at the healthcare provider's level (e.g. rational prescribing), and involve the patient (e.g. engagement in decision-making). Stakeholders should therefore enhance their co-operation for minimising medication waste.
Although some of the suggested measures may not be cost-effective, these are still important to reduce the environmental burden and aim for a sustainable use of medication. It is therefore also proposed that new initiatives should focus on the development of a circular economy to foster a sustainable pharmaceutical supply and use chain. This system aims at completely minimising waste using multiple approaches. Prevention is the preferred approach, which could be achieved through rational prescribing and dispensing. As some waste is inevitable, unused medication could be redispensed to maximise their potential for use. When redispensing is not possible, wasted medication could be recycled into similar products. The inner and outer packaging could be reprocessed, as could the active pharmaceutical ingredients of the medication. As a last resort, the waste could be recovered as materials to be used in other products. Furthermore, medication that is excreted by the patient after intake could be removed from the sewer system by using for example, toilet paper can be used for

active coal which in turn absorbs active pharmaceutical ingredients[45]. A recent example of such an circular economy initiative is found in the Dutch food sector, where several institutes, organisations, companies and the government have developed a joint initiative to decrease food waste by 50% by the year of 2030[46]. They focus on the optimal use of products, followed by the reuse and recycling of wasted products. For instance, soup is produced from vegetables that are not visually attractive for sale. Moreover, waste reduction strategies are presented to the public through awareness campaigns. The exploration of similar possibilities for the sustainable use of medication is strongly encouraged.

Table 1: Potential waste-minimising measures aimed at prevention, reduction and optimal waste disposal and the stakeholders involved

	Manufacturer	Distributor	Prescriber	Pharmacist	Patient	Health authorities	Health insurers
Prevention							
Rational prescribing			X	X	X	X	X
Rational dispensing				X	X	X	X
Adjusting package sizes	X			X		X	
Extend expiry dates	X					X	
Pharmacy's stock management		X		X			
Awareness about medication waste	X	X	X	X	X	X	X
Reduction							
Redispensing unused medication			X	X	X	X	X
Recycling wasted medication	X	X		X	X	X	
Recovery of wasted medication	X	X		X	X	X	
Waste							
Proper disposal of waste	X	X	X	X	X	X	X
Use 'green materials'	X					X	

5

Feasibility of redispensing unused medication in clinical practice

Although the redispensing of medication returned unused to pharmacies has frequently been mentioned as a possibility to reduce medication waste and efficient use healthcare budgets, this has not been extensively investigated. In this thesis, the feasibility of implementing redispensing unused medication in clinical practice was comprehensively assessed. Many factors play a role when considering the feasibility of a redispensing process. These include amongst others support of key stakeholders, preparedness of patients to return unused medication, a positive cost-benefit ratio, and possibility to assure product quality. One of the most important aspects of a sustainable redispensing process is stakeholder support. Over half of Dutch patients are willing to use medication returned unused by another patient if quality is guaranteed (**Chapter 3.2**)[47]. Moreover, other Dutch stakeholders are generally positive towards the implementation of redispensing (**Chapter 3.1**). Studies from the UK reported similar findings for patients and other stakeholders such as pharmacists, general practitioners and nurses[48–51]. Furthermore, redispensing becomes more feasible when unused medication is returned to pharmacies or at other repositories. Research from the UK and Singapore has shown that a substantial proportion of unused medication returned to pharmacies remain unopened, with intact outer packaging, and could potentially be redispensed[6,7]. This is in line with the results described in **Chapter 2.1** and **2.2**. Moreover, implementation of redispensing is preferably cost-beneficial. Considering the pharmacy's additional processing costs of redispensing, it is most beneficial for expensive medication (**Chapter 4.1**). In this thesis it was found that over half of patients who had discontinued expensive medication therapies, such as oral anti-cancer drugs or biological disease-modifying anti-rheumatic drugs (bDMARDs), had unused medication (**Chapter 2.2**), the majority of which remained in an unopened outer packaging and thus could potentially be redispensed. In **Chapter 4.2**, redispensing resulted in savings of 74% of the medication costs compared with no redispensing for expensive post-exposure prophylaxis (PEP) that was to travelling medical students. A targeted redispensing process applied to more expensive therapies could thus substantially save costs and contribute to sustainable use of medication.

One of the main requirements to enable redispensing is that the product quality should be guaranteed (**Chapter 3.1**). Medication that requires refrigeration, such as bDMARDs, are often not stored within the recommended temperature range by patients and are therefore not suitable for redispensing[47,52]. Moreover, such medication would require extra precaution measures to ascertain proper storage if included in the redispensing process. These include a logger that continuously measures temperature and clear storage instructions to patients with each dispensed medication. Both aspects would increase the cost-benefit threshold for redispensing. Expensive medication that requires room-temperature storage, such as the oral anti-cancer drugs, are often properly stored[53]. Medication that requires room-storage would require a simple and less-costly temperature indicator to measure out-of-range temperatures and as such seem most cost-beneficial. The study described in **Chapter 4.2** showed that the majority of PEP returned by students who visited countries with in general more extreme climates had been properly stored and was therefore suitable for redispensing. These findings indicate that medication that requires no specific storage conditions are most eligible for redispensing.

To our knowledge, no studies have evaluated the implementation of redispensing unused medication returned to pharmacies in clinical practice as part of patient care. To promote effective implementation of redispensing and to prolong its sustainability, one should consider which barriers may arise at the various levels of healthcare (e.g., the patient level, the pharmacy level, the healthcare system level or the regulatory level) and how they can be overcome. Multiple theories advocate the effective implementation of an intervention in clinical practice. These often translate research findings into practice by guiding how such implementations should be conducted, and can be a useful tool. From a comparison of a broad range of theories, Damschroder et al. developed a comprehensive framework that consolidates constructs which are potentially relevant to a particular intervention and its context[54]. This Consolidated Framework for Implementation Research (CFIR) guides the identification of constructs, key factors most likely to influence the implementation of interventions. The CFIR describes five major domains, each with several constructs that can influence the effectiveness of an implementation, including (1) the intervention characteristics, (2) the inner setting, comprising the features of the implementing organisation, (3) the outer setting, comprising the features of the external context in which an organisation resides, (4) the characteristics of the individuals involved and (5) the process of the implementation. Following the first four CFIR domains, potential barriers that may arise prior to the implementation of a redispensing process are discussed below (Figure 3). In addition, potential facilitators that may be considered to overcome these barriers are suggested. The fifth domain should be considered during the implementation itself and is outside of the scope of this general discussion.

Intervention characteristics

The first domain is related to the characteristics of the redispensing process. The requirements of a sustainable redispensing process from a stakeholder's point of view were identified in **Chapter 3.1**. These included a guaranteed product quality, patient willingness to participate, financial aspects (cost-benefit ratio, financial handling), legal aspects (feasibility, responsibility) and stakeholder involvement (commitment). Similar prerequisites have been discussed by others[51,55–57]. A set of criteria that can be used to guarantee product quality and thus eligibility for redispensing was introduced in this thesis, including that the medication should: (1) be returned in its unopened and intact manufacturer's packaging, (2) be stored following the storage conditions stated in the Summary of Product Characteristics and (3) have an expiry date at range of at least six months. This range for the expiry date is assumed to be sufficient as most medication is dispensed for three months and are expected to be used within six months when redispensed to a patient. To assess if returned medication meets the other quality criteria, temperature-measuring devices and seals (bags) should be added during dispensing. Additionally, more subjective criteria may be taken into account to assess a medication's eligibility for redispensing, such as smell (e.g. cigarette smoke) and the general appearance of the package.

Other potential intervention determinants include the (improper) handling of the financial benefits obtained through redispensing unused medication. Stakeholders reported that patients are less likely to be supportive of redispensing if the cost-savings only flow back to pharmacies or other stakeholders (**Chapter 3.1**), and instead feel that redispensing should be beneficial to society as a whole. It is therefore important that financial matters are arranged prior to implementation. Cost savings of redispensing could be shared among patients through, for instance, lower healthcare premiums, or used for research that benefits society.

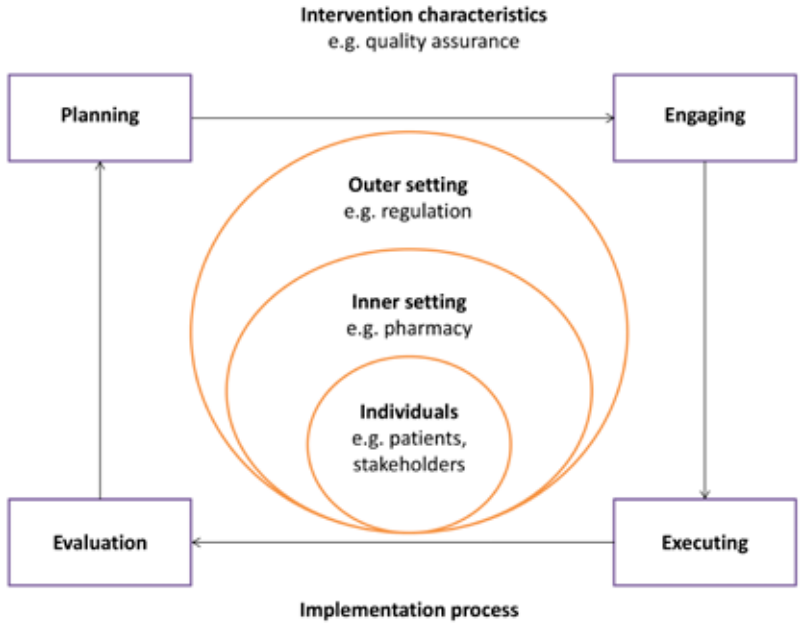

Figure 3: Schematic presentation of domains that could influence the implementation of redispensing in clinical practice.

5

Inner setting

This domain includes the features of the organisation in which the redispensing process will be implemented. Stakeholders suggested that unused medication should be redispensed by pharmacies (**Chapter 3.1**). The barriers to such an implementation at the pharmacy level could include a lack of resources to execute redispensing, including workforce, materials and financial resources. Prior to implementation, it should be clear how these could be overcome; for instance, pharmacies should be compensated for the additional costs they incur during redispensing. Furthermore, patients should be able to easily return their unused medication to pharmacies. However, this may also increase the return of medication that is not eligible for redispensing and thereby disposal costs. In general, redispensing requires support from all stakeholders involved in the process, including the healthcare facilities, professional organisations and health authorities. Although it can be concluded from the qualitative study that the stakeholders were positive towards redispensing (**Chapter 3.1**), only a small sample was interviewed, and their views may not reflect the majority of their fields.

Outer setting

The outer setting domain refers to the context within which an organisation resides, including any external policies and regulations that may hamper the implementation of a new process. One of the major barriers mentioned in the studies described in this thesis is the possible existence of legal prohibitions to redispense unused medication. Some pharmacists reported that they are not allowed to redispense unused medication (**Chapter 2.3**), as it is prohibited by law in many countries[58]. While this is not the case in the Netherlands, the government addressed recently that prevention of unused medication is on favour of redispensing

because quality cannot be guaranteed[59]. This thesis shows that several quality criteria can be used to guarantee the product quality, which is presumably not affected if the medication has been stored at patients' homes following the Summary of Product Characteristics. Pharmacy practices in the Netherlands are based on the Dutch Medicines Act that refers to the European GDP, which states that medication can be returned to stock if several factors concerning quality control are confirmed and the medication is returned within acceptable time limit (EU Directive 2013/C 343/01). Although this gives potential for redispensing, prior to implementation, regulatory guidelines should be adjusted to allow pharmacists to redispense unused medication. When redispensing is considered for other countries, one should first assess their specific regulatory constraints.

Concerns exist about increased risk of counterfeit medication entering the pharmaceutical supply and use chain during redispensing (**Chapter 3.1**)[48]. This will be tackled by the European Union directives 2011/62/EU and EU2016/161, which demand that manufacturers add tamper indicators and unique identification codes to the outer packaging of medication from 2019 to minimise the risk of falsification. Each unique package will be registered in a large repository, then during the dispensing to the patient its authenticity will be verified and the package will be unsubscribed from the database. Unfortunately, this directive will likely hamper redispensing, as returned medication cannot re-enter the database and thus cannot be verified during the subsequent redispensing. How to tackle this barrier should be further explored. For example, authorised persons such as pharmacists may be able to re-subscribe returned medication into the database.

Other concerns related to the outer-setting domain include communication to patients, and the issue of whether patients should be (individually) informed if their dispensed medication has been previously dispensed. Medication packages are only eligible for redispensing if they fulfil all quality criteria and should thus be identical to new packages. Patients should not be able to tell whether their dispensed medication package has been returned by another patient. The provision of general information about redispensing may therefore be considered sufficient, for instance, through the use of information campaigns and pharmacy information leaflets.

5

Individual characteristics

This domain covers the knowledge and beliefs of individuals, which includes all stakeholders but especially patients, regarding redispensing. Any organisational change starts with individual behaviour change. One of the core components and potential barriers to redispensing would be a lack of support and participation by patients (**Chapter 3.1**). Patients would be required to return their unused medication to the pharmacy and should be willing to use medication that has been returned unused by another patient. The study described in **Chapter 3.2** showed that over half of patients would be willing to use medication returned unused to the pharmacy if their quality could be guaranteed. Patients who were less willing to use redispensed medication had a non-Dutch cultural background and lower levels of education. To increase patient support, their barriers to redispensing should be identified and considered in depth, as should their motivations for participation. One-to-one or focus group interviews will be vital for gathering this information. To successfully implement redispensing, support from healthcare providers is also needed. Healthcare providers should be able to inform and convince patients to engage in redispensing, and must therefore be well-informed prior to implementation.

In the cost analysis, it was found that the proportion of dispensed medication returned unused to pharmacies strongly influences the cost savings generated through redispensing (**Chapter 4.1, Chapter 4.2**). Studies show that a significant proportion of patients do not return their unused medication to the pharmacy for safe disposal[29]. Previously, it was discussed that the provision of information and education by healthcare providers on the proper disposal of unused medication will likely increase the number of patients returning their medication. In addition, patients could be motivated to return their unused medication by influencing their behaviour using various motivational methods. Throughout society, a variety of effective financial rewards are used to encourage the return of (un)used products. One example is the separate collection of plastic waste in the Netherlands, for which no disposal costs are charged. During interviews with stakeholders, it was suggested that incentives could be considered to stimulate patient participation (**Chapter 3.1**), including financial rewards for each returned medication package or a lowering of patient's health premium. However, these rewards may stimulate patient non-adherence to their therapy regimen. Other motivational approaches could also be considered. Many people are willing to participate in recycling programmes without any direct personal (financial) reward if it benefits the environment or others. For example, people donate old clothes in special boxes for charity organisations. A similar approach for redispensing is preferable to providing a financial reward for returning medication.

In conclusion, redispensing could likely be implemented in clinical practice for expensive medication therapies that have no specific storage recommendations. A thoughtful approach should be used, including the quality assurance of medication returned unused to pharmacies as well as extensive communication with all stakeholders. An implementation study should be performed that includes the assessment of patients' barriers to and facilitators of redispensing in depth, preferably using qualitative research methods. In addition, the cost savings that can be achieved through redispensing expensive medication in clinical practice should be determined.

Methodological considerations

Applying the most appropriate methodology to answer a specific pharmacy practice research question is often challenging. Considering the (mostly observational) studies on medication waste and redispensing presented in this thesis, different methodological issues were encountered. These were related to the study design, the selection and sampling of the study population and setting, and the measurements. These methodological issues will be discussed below.

Study design

Most studies presented in this thesis on medication waste had a cross-sectional study design. Although this enabled a rapid collection of substantial information, cross-sectional studies are primarily explorative. Cross-sectional studies give insight into potential associations between determinants and an outcome, but it is difficult to establish causality and the direction thereof because determinants and outcomes are measured at the same point in time. In addition, the cross-sectional study design involves the collection of data at a single point in time and does not account for fluctuations in responses of data. Point measurements can over- or underestimate the prevalence of some of the study variables. For example, in **Chapter 2.1**, prescription medications that were returned during one week were collected. The extent of this medication waste may fluctuate in time depending on the day of the week, the month, or the season. Measurements should include a sufficient long period (e.g. one year) to account for potential fluctuations. Future research on the extent of medication waste and associated determinants ideally includes data on prescribed and dispensed medication to assess the proportion of prescribed medication that remains unused. Medication could be dispensed with a temperature logger and a GPS system to measure home storage temperature and where medication is stored or transferred by patients as well as disposal routes (e.g. through household garbage). This information, accompanied by detailed patient socio-demographic and health data could be used to identify specific patient groups that highly likely have medication waste. As follows, patients could be interviewed about the reason for having unused medication and how waste can be minimised, making them more aware of the problem as well as involving them in finding a solution.

In this thesis, an extensive feasibility assessment on redispensing was made. Although a simulation study on redispensing in pharmacy practice was conducted in **Chapter 4.1**, redispensing in real life will probably be influenced by environmental factors like the healthcare settings, legal systems and cultures (individual beliefs). In **Chapter 4.2**, an implemented redispensing process was retrospectively evaluated but this was no part of standard patient care (medical students received medication as a preventive measure that in most cases remained used). As a consequence, this thesis did not provide information on the support from stakeholders in real practice, the barriers to and facilitators of implementation in real practice, or the experiences of patients that receive medication that has been previously dispensed to another patient. Patients could perceive barriers towards redispensing and may therefore not be willing to participate. In addition, pharmacist may not be compensated for the required additional activities or do not have sufficient manpower and could be therefore less likely to implement redispensing. It is therefore recommended that future research on redispensing include prospective multicentre implementation studies embedded in standard patient care to identify the barriers to and facilitators of redispensing in practice and how these can be overcome.

Study population and setting

Inclusion of participants in any study can be challenging as participating study subjects may not be representative of the general population. This hampers the external validity, meaning that the outcomes generated are not generalizable to other populations due to selection bias. The surveys that were performed as part of this thesis were conducted in the community and outpatient pharmacy settings; **Chapter 3.2** included pharmacy visitors. However, pharmacy visitors may differ from people who do not visit the pharmacy. Pharmacy visitors may have a closer relationship with the pharmacy and are therefore more supportive for new initiatives. In addition, they may be more familiar with medication use, costs, and waste compared with people who do not visits the pharmacy. Populations may differ in their views on a certain domain (e.g. redispensing). In addition, medication waste was assessed in terms of medication that was returned to community pharmacies (**Chapter 2.1**) or quantities of unused medication reported by patients (**Chapter 2.2**). These studies did not give insight into the amount of unused medication kept at patient's home. Moreover, medication waste that occurs within healthcare facilities, such as hospitals or nursing homes, where patients often use multiple types of medications, was not taken into account. In the Netherlands, during hospitalisation patients home medication is often discontinued and substituted by medication prescribed by a medical specialist and as a consequence, the home medication remains unused and is wasted. It is therefore preferred that future studies on medication waste and redispensing are conducted in those settings as well. Studies could also include visits of healthcare providers at patients' homes to identify potential unused medication kept at home and to provide patients with information on proper disposal.

The studies presented in this thesis were conducted in community and outpatient pharmacies. In the Netherlands, outpatient pharmacies dispense more expensive medication therapies that are prescribed by medical specialists whereas community pharmacies generally dispense more generic medications. These types of pharmacy and differences in types of medication dispensed are rather unique for the Netherlands and therefore lack generalisability to other countries. However, the cost of the waste of expensive medication was found to be extensive. **Chapter 2.3** showed that patients discontinuing expensive medication therapies often have medication that remains unused, leading to a substantial financial loss. It is expected that expensive medication therapies in the Netherlands, for which frequently no generic (lower-cost) variant is available, are also expensive in other countries. Most likely the highest financial waste also occurs among expensive therapies in other countries. It is therefore suggested that, regardless the type of pharmacy, waste minimising interventions that aim at reducing unnecessary pharmaceutical spending should focus on expensive medication.

The studies of this thesis were primarily conducted in the Dutch healthcare setting and this hampers generalisability to other countries. National healthcare regulations may largely influence the allowed prescription quantities that are dispensed to patients and thus the quantities that remain potentially unused. Furthermore, medication prices differ between countries and the financial consequences of waste might therefore vary. In addition, some national reimbursement systems require patients to (partially) pay for their medication themselves. As such, the overall size of the problem of medication waste and feasibility of redispensing for other countries may not be comparable with the Dutch healthcare setting and the findings of this thesis. It is therefore recommended that specific issues on, for instance, how reimbursement systems influence the extent of waste, are investigated for multiple countries.

Measurements

Some outcome measures have no clear criteria for their definition. In this thesis, medication waste was defined as 'any medication that remains unused throughout the pharmaceutical supply and use chain'[60]. Although this implies that all unused medication is wasted, this interpretation is questionable. In **Chapter 2.1**, the outcome measure waste was further classified into preventable and non-preventable medication waste. It could be argued that the amount of excess medication dispensed to patients is sometimes inevitable. This amount of unused medication could therefore not necessarily be classified as wasted that would influence the study outcomes. A clear definition of preventable waste is needed for assessing the effect of interventions. This could be obtained, for instance, from a Delphi-study among (international) stakeholders involved in the pharmaceutical supply and use chain.

Studies of this thesis measured the extent of medication waste for one disposal route at a time (**Chapter 2.1, Chapter 2.2**). It is known that patients often use various disposal routes for their unused medication, so it was not possible to adequately determine the absolute magnitude of medication waste in the community. Ideally, each disposal route should be investigated, including disposal at pharmacies, chemical waste depots, household garbage, toilets, sinks and those that remain stored at home and used by others. A large patient cohort that is followed prospectively is therefore ideally suitable. Measures could include medication dispensed to patients, dispensed medication that remains unused and their reasons thereof, disposal routes of unused medication patients (e.g. measuring pharmaceutical ingredients disposed of through toilet and sink, medication ending up in household garbage). Furthermore, the studies described in this thesis primarily focus on the financial consequences of medication waste. Future research should investigate the environmental burden due to improper disposal practices and potential to remove pharmaceutical ingredients from the environment.

In **Chapter 3.1**, a qualitative study was used to identify stakeholders' views on the redispensing of unused medication. The major strengths of qualitative research include the provision of detailed information on a given domain, with in-depth understanding of individual's experiences and perspectives (e.g. meaning, motives and beliefs), and the opportunity for flexibility in the data collection[61]. Weaknesses of qualitative approaches include lack of rigour, reproducibility, generalisability, and potential influence of the researcher during the data collection and analysis[61,62]. Guidelines on conducting and reporting of qualitative research (like the COREQ) could increase rigour and reproducibility[62]. Researcher bias could be reduced by allowing the interviewees to check the data collected through the interview and to provide feedback on the researcher's interpretations. This thesis used checklists, like the COREQ, to ensure comprehensive reporting and enabled participants to comment on the data (**Chapter 3.1**). Interviewees were asked to represent their organisation but may not be representative of all stakeholders in the field. Qualitative studies therefore often lack generalisability. However, no new themes emerged during the final interviews and the data was considered to be comprehensive.

In multiple studies in this thesis, questionnaires were used to collect the data. Although this is a relatively easy and cheap method to collect data from a large sample, this may lack in-depth information from respondents[63]. In **Chapter 3.2**, over 2,200 patients completed a short questionnaire regarding their willingness to use medication returned to the pharmacy by another patient. The questionnaire did not include in-depth questions that would allow for

a deeper understanding of why they are willing or unwilling to use returned medication. Qualitative studies can provide in-depth information, but include often only a limited number of participants and therefore lack generalisability. This was seen in **Chapter 3.1**, where 19 stakeholders were interviewed regarding their views on redispensing. Both methods answer different research questions (qualitative versus quantitative) and choosing the appropriate design depends on the nature of the project, the type of information needed, and availability of resources.

Finally, the quality of medication eligible for redispensing was determined using criteria on the medication's packaging, expiry date, and storage temperature (**Chapter 4.2**). It can be assumed that medication that has been stored according to instructions of the Summary of Product Characteristics, with an intact packaging and sufficient time to expiry, is still of good quality. However, validation to ensure that the product quality and stability remains unaffected could be performed. Future research could assess the chemical composition and product stability of returned medication and certify that this medication is safe to use.

Concluding remarks

Medication waste is substantial among all types of patients and has considerable consequences economically and environmentally. Medication waste is often preventable and for a sustainable use of medication, minimisation is needed. For maximum success all stakeholders involved in the pharmaceutical supply and use chain, including manufacturers, distributors, prescribers, pharmacists, patients, and health authorities must be engaged. This includes being aware about the consequences of medication waste and the methods by which it can be reduced. The multiple causes of medication waste imply that a single intervention will not sufficiently minimise waste and thus a multitude of approaches is needed, which should include preventive measures. A substantial proportion of medication waste comprises unopened medication packages that are presumably of good quality. This thesis provides a comprehensive assessment on the feasibility of redispensing unused medication, revealing support from both patients and other stakeholders. Redispensing requires a thoughtful implementation strategy with comprehensive communication to all stakeholders, paying particular attention to product quality assurance, financial handling, and legal aspects. Considering the additional processing costs of redispensing, its implementation would likely be most feasible for expensive medication therapies without specific storage conditions.

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Chapter 6

Summary

The objectives of this thesis were to investigate medication waste among patients in terms of quantity, cost, preventability, and currently implemented waste-reducing measures. In addition, the feasibility of redispensing medication that remains unused by patients was investigated. **Chapter 2** focused on medication waste in terms of medication that remained unused by patients. Additionally, activities that community and hospital pharmacists presently undertake to minimise medication waste were inventoried. **Chapter 3** addressed the feasibility of redispensing unused medication returned to pharmacies by patients in terms of stakeholders' views. In **Chapter 4**, the economic considerations of redispensing were discussed. Finally, in **Chapter 5**, the overall findings of this thesis were discussed from a broader perspective.

In **Chapter 2.1** we assessed patient and medication related factors that were associated with preventable medication waste and possibilities for redispensing unused medication. In 41 community pharmacies medication that was returned by persons during one week was collected. Returned medication was classified as preventable waste if the remaining amount could have been prevented and as eligible for redispensing if the package was unopened, undamaged, and had at least six months until the expiry date. In total 279 persons returned 759 (low-cost) medications. We found that 39.3% of the returned medication was classified as preventable waste. Factors that were associated with preventable medication waste included male users, older patients, and medication dispensed for at least one month. These factors might act as possible targets for waste-minimising interventions. Furthermore, we found that one-fifth of the returned medication could potentially be redispensed. However, most returned medication was of low cost, 80% of these were below €25, and therefore, we concluded that redispensing is less interesting to implement in the community pharmacy from an economical point of view. A substantial proportion can, however, be prevented and therefore waste-preventive measures are needed.

To assess medication waste among expensive therapies, the proportion of patients who had unused oral anti-cancer drug (OACD) and biological disease-modifying anti-rheumatic drug (bDMARD) after therapy discontinuation, and the quantity and economic value of these unused medications were retrospectively investigated in **Chapter 2.2**. Over a four-month period in one outpatient pharmacy, 48 OACD and 23 bDMARD users had discontinued therapy and were shortly interviewed by phone regarding the quantity of medication that had remained unused. The results showed more than half of these patients discontinuing OACD or bDMARD therapies had unused medication. High costs were thereby wasted, around €1100 per patient. These outcomes emphasize the need for waste-minimising measures to save costs.

Activities that community and hospital pharmacists undertake to minimise medication waste were identified in a two-phase international survey in **Chapter 2.3**. Fourteen main waste-reducing activities in the pharmaceutical supply chain were identified in the first phase using an exploratory questionnaire, which applied to the prescribing, dispensing (pharmacy/patient-related), and leftover stage. These main activities were subsequently used to create a new questionnaire for the second phase. This questionnaire was disseminated among a new set of pharmacists. Most activities were undertaken by a minority of pharmacists. Pharmacists considered most activities as important for waste reduction but were less certain about the feasibility of broadly implementing these activities in daily practice. It seems that there may be barriers that hamper implementation, such as legislation, and that there is a need for feasible waste reducing measures.

During a qualitative study in **Chapter 3.1**, 19 stakeholders were interviewed regarding their views on the redispensing of unused medication. The stakeholders included healthcare professionals, health authorities, health insurance companies, patient- and consumer organisation, pharmaceutical industry representatives and wholesalers. Various requirements that need to be met to enable redispensing were discussed. The stakeholders were in general positive towards redispensing if several requirements were met. These included quality assurance of redispensed medication, the willingness of patients to use and trust redispensed medication redispensing, legal feasibility, assessment of the cost-benefit ratio to determine which medication is eligible for redispensing, and involvement of all stakeholders in the process to succeed. These results give insight into the requirements that should be fulfilled to enable implementation of redispensing in clinical practice.

The willingness of patients to use medication returned unused to the pharmacy by another patient was assessed in a survey **Chapter 3.2**. A total of 2,215 adult community and outpatient pharmacy visitors completed therefore a questionnaire regarding their willingness to use returned medication. In total, 61.2% was willing to use redispensed medication, primarily because it is a shame to destroy good quality medication. This indicates that a substantial proportion of patients seem to support redispensing if implemented in practice. However, the barriers of patients who were not willing to use redispensed medication should be further explored in depth.

To determine if the implementation of the redispensing of unused medication is economically feasible, **Chapter 4.1** described a micro-costing study. In this study, a detailed overview of all pharmacy's additional process steps that are associated with redispensing was obtained that were subsequently simulated in four outpatient pharmacies. Direct and indirect costs were calculated for the required labour and materials for each additional process step. We found that, taking the additional costs for redispensing into account, redispensing is most cost-beneficial if applied to expensive medication. This threshold can be lower if more unused medication is returned to the pharmacy that have been properly stored at patients' homes of which thus the quality can be guaranteed. Based on these results we concluded that redispensing could be implemented for expensive medication.

To evaluate an implemented redispensing process in clinical practice, **Chapter 4.2** described the cost savings that were generated from redispensing unused HIV post-exposure prophylaxis (PEP) for medical students. In almost four years, 379 students who studied abroad received PEP as a preventive measure against potential HIV infection from the outpatient pharmacy. Of the dispensed PEP, over 75% of the medication had been previously dispensed one or more times to other medical students. The additional cost investments for redispensing process were relatively low in comparison to the medication costs that were saved (€225,000), and the redispensing of PEP resulted in 74% cost savings in comparison with no redispensing. Based on these findings, we concluded that it is feasible to implement a redispensing process in practice and that for expensive medication substantial costs can be saved if the medication has been stored properly and is returned unused to the pharmacy.

In **Chapter 5** the studies presented in this thesis were put in a broader perspective. Potential waste-minimising measures that each stakeholder involved in the pharmaceutical supply chain were discussed. Hereafter, the feasibility of redispensing unused medication in clinical practice was addressed by specifically focussing on barriers to and facilitators of implementation. The main conclusions of this thesis are that medication waste is substantial among all types of patients and has considerable consequences economically and environmentally. Medication waste is often preventable and for a sustainable use of medication, minimisation is needed. For maximum success, all stakeholders involved in the pharmaceutical supply and use chain must be engaged. A multitude of measures is needed that should include preventive measures. This thesis provides a comprehensive assessment on the feasibility of redispensing unused medication, revealing support from both patients and other stakeholders. Redispensing requires a thoughtful implementation strategy with comprehensive communication to all stakeholders. Considering the additional processing costs of redispensing, implementation would likely be most feasible for expensive medication therapies.

6

Nederlandse samenvatting

Geneesmiddelen worden veelvuldig gebruikt voor het voorkomen en behandelen van symptomen en ziektes. Uit verschillende onderzoeken blijkt echter dat een groot deel van de patiënten niet al hun geneesmiddelen gebruikt die zij van de apotheek ontvangen, wat leidt tot verspilling. Immers, geneesmiddelen die eenmaal bij de patiënt zijn geweest, worden niet meer aan andere patiënten verstrekt maar vernietigd. De oorzaken van medicijnverspilling zitten in de gehele geneesmiddelen distributie- en gebruiksketen, van fabrikant tot patiënt. Dit zijn onder andere te grote verpakkingen die zijn geproduceerd door de fabrikant, het teveel voorschrijven door artsen en het teveel meegeven van geneesmiddelen door apothekers. Daarnaast stoppen sommige patiënten eerder met hun geneesmiddelen omdat de klachten soms over zijn nog voordat het geneesmiddel op is, sommige patiënten ernstige bijwerkingen ervaren en sommige patiënten soms minder geneesmiddelen innemen dan de arts voorgeschreven heeft (therapieontrouw). In dit proefschrift is gekeken naar de geneesmiddelenverspilling die op patiëntniveau optreedt. Omdat voor deze geneesmiddelen reeds is betaald en ongebruikte geneesmiddelen niet opnieuw worden verstrekt kost dit de maatschappij geld. Onderzoek heeft aangetoond dat minstens 3-6% van de uitgaven aan farmaceutische zorg hierdoor wordt verspild. Schattingen op nationaal niveau gaven aan dat in Nederland ongeveer 100 miljoen euro wordt verspild, in Groot Brittannië 300 miljoen pond en in de Verenigde Staten ongeveer bijna 6 miljard dollar. Daarnaast brengen niet alle patiënten de ongebruikte geneesmiddelen terug naar de apotheek, maar gooien ze deze weg via het huisafval of het riool wat leidt tot milieuvervuiling. Om kosten te besparen en de milieuvervuiling te verminderen is het belangrijk dat de geneesmiddelenverspilling zo veel mogelijk wordt verminderd.

Een deel van de verspilling betreft geneesmiddelen die in een nog volledig onaangebroken en intacte verpakkingen terug worden gebracht in de apotheek. Voor duurzaam gebruik van geneesmiddelen zouden deze, na een kwaliteitscontrole, heruitgegeven kunnen worden aan een andere patiënt. Het heruitgeven van geneesmiddelen gebeurt nog niet. Dit is voornamelijk omdat de kwaliteit van teruggebrachte geneesmiddelen door een patiënt niet gewaarborgd kan worden. Ook stelt wetgeving in sommige landen dat een apotheker een retour gebracht geneesmiddel niet voor een tweede keer mag uitgeven. Toch is er de laatste jaren aanzienlijk meer interesse gekomen voor deze benadering om de geneesmiddelenverspilling te verminderen. Zo bleek uit een peiling van het Ministerie van Volksgezondheid over verspilling in de zorg dat de meeste meldingen gingen over het heruitgeven van geneesmiddelen als oplossing. Om te beoordelen of het heruitgeven van ongebruikte geneesmiddelen in de klinische praktijk daadwerkelijk mogelijk is, is een uitvoerige bepaling van de haalbaarheid nodig. Dit betreft zowel inventarisatie van draagvlak onder stakeholders en patiënten evenals het vaststellen van de kosten en baten. Het doel van dit proefschrift is om de geneesmiddelenverspilling onder patiënten te bepalen in termen van hoeveelheid, kosten, preventie en reeds geïmplementeerde acties tegen verspilling. Daarnaast heeft het als doel om de haalbaarheid van het heruitgeven van geneesmiddelen die door patiënten niet worden gebruikt te onderzoeken.

Dit proefschrift bestaat uit drie hoofdthema's gevolgd door een algemene discussie. **Hoofdstuk 2** richt zich op de verspilling van geneesmiddelen. **Hoofdstuk 3** gaat over de haalbaarheid van het heruitgeven van geneesmiddelen gezien vanuit betrokken stakeholders, inclusief de patiënt. **Hoofdstuk 4** richt zich op de economische aspecten van heruitgifte. Tot slot worden in **hoofdstuk 5** de bevindingen van dit proefschrift in een breder perspectief geplaatst en

worden er aanbevelingen gegeven van het verminderen van verspilling.

In **hoofdstuk 2.1** hebben we onderzocht welke patiënt- en geneesmiddelenkenmerken zijn geassocieerd met onnodige geneesmiddelenverspilling en mogelijkheden voor heruitgifte. In 41 openbare apotheken zijn gedurende één week alle receptgeneesmiddelen die door mensen werden teruggebracht geregistreerd. In totaal brachten 279 personen 759 geneesmiddelen terug. Van de teruggebrachte geneesmiddelen werd 39.3% beoordeeld als onnodige verspilling. We zagen dat deze onnodig verspilde geneesmiddelen vaker waren gebruikt door mannen en ouderen en vaker waren meegegeven voor een langdurige periode. Hiernaast hebben we ook onderzocht welk deel van de teruggebrachte geneesmiddelen theoretisch heruitgegeven kon worden. Opnieuw uitgeven werd door ons mogelijk bevonden indien de verpakking onaangebroken en onbeschadigd was en de periode tot verloop van de houdbaarheidsdatum meer dan zes maanden bedroeg. Uiteindelijk bleek dat 19.1% van de teruggebrachte geneesmiddelen aan al deze voorwaarden voldeed. Echter, 80% van deze geneesmiddelen had een prijs had onder €25 waardoor het niet rendabel lijkt om deze opnieuw uit te geven. Deze resultaten laten zien dat een groot deel van de teruggebrachte geneesmiddelen voorkomen had kunnen worden en dat het wenselijk is om te onderzoeken welke preventieve maatregelen daartoe zouden kunnen helpen.

In **hoofdstuk 2.2** beschrijven we geneesmiddelenverspilling bij twee dure therapieën, te weten orale oncolytica en biologische antireumatische geneesmiddelen. Gedurende vier maanden hebben we gebruik makend van een database met 1173 patiënten van een poliklinische apotheek retrospectief gekeken welke patiënten geen nieuwe uitgifte van het geneesmiddel hadden ontvangen en mogelijk gestopt waren met hun therapie. Deze patiënten werden telefonisch geïnterviewd of ze daadwerkelijk waren gestopt, en of het geneesmiddel (deels) was overgebleven. We vonden dat in totaal 71 patiënten waren gestopt met hun therapie, waarvan bijna 55% medicatie had overgehouden. Deze ongebruikte medicatie had een waarde van ruim €60.000, ongeveer €1100 per patiënt. Deze bevindingen laten zien dat ruim de helft van de patiënten die stoppen met orale oncolytica of biologische antireumatische geneesmiddelen medicatie overhouden, waarbij aanzienlijk hoge kosten worden verspild. Dit benadrukt dat interventies om deze verspilling te verminderen om zo kosten te besparen wenselijk zijn.

In **hoofdstuk 2.3** hebben we onderzocht wat apothekers doen om geneesmiddelenverspilling te verminderen, in hoeverre activiteiten om verspilling tegen te gaan geïmplementeerd zijn en hoe belangrijk en haalbaar deze activiteiten worden bevonden voor brede implementatie in de praktijk. Daartoe hebben we op internationaal niveau een vragenlijst onderzoek uitgezet welke bestond uit twee delen. In het eerste deel werd aan 53 openbare- en ziekenhuisapothekers gevraagd welke activiteiten zij ondernemen om verspilling te verminderen. Hieruit zijn 14 hoofdactiviteiten gekomen die werden onderverdeeld in de verschillende fasen van de geneesmiddelendistributieketen: tijdens voorschrijven, tijdens afgifte (apotheek/patiënt-gerelateerd) en op het moment dat er geneesmiddelen door de patiënt niet meer gebruikt worden. In het tweede deel werden deze activiteiten getoetst in een vragenlijst onder een nieuwe groep van 89 internationale apothekers. Hiervan laten de belangrijkste resultaten zien dat de meeste activiteiten door een minderheid van de apothekers wordt ondernomen, en dat er dus ruimte voor verbetering is. Ook bleek dat de apothekers de meeste activiteiten belangrijk vonden om verspilling te verminderen, maar dat deze implementatie in de praktijk minder haalbaar werd bevonden. Dit suggereert dat er mogelijke barrières zijn die de uitvoering van activiteiten om verspilling te verminderen belemmeren.

In een kwalitatief onderzoek hebben we in **hoofdstuk 3.1** de visie van 19 stakeholders op het heruitgeven van geneesmiddelen uitgevraagd. Semigestructureerde interviews werden gehouden met medewerkers van de volgende stakeholders: openbare apothekers, ziekenhuisapothekers, medisch specialisten, zorgautoriteiten, zorgverzekeraars, patiënt- en consumentenorganisaties, farmaceutische industrie en groothandelaren. Stakeholders hadden een positieve houding ten opzichte van het heruitgeven van ongebruikte medicatie, indien implementatie in de praktijk mogelijk is. Daarbij gaven stakeholders vijf hoofdrandvoorwaarden aan waaraan voldaan moet worden als medicatie heruitgegeven wordt: (1) gegarandeerde productkwaliteit, (2) positieve houding van de patiënt (bereidwilligheid en vertrouwen), (3) wettelijk mogelijk, (4) voordelen moeten opwegen tegen de kosten van heruitgifte en (5) samenwerking tussen stakeholders. Deze uitkomsten laten zien dat heruitgifte door stakeholders positief bevonden wordt, wat mogelijkheden biedt voor succesvolle implementatie mits aan de randvoorwaarden wordt voldaan.

Hoofdstuk 3.2 beschrijft expliciet de bereidheid van de patiënt om medicatie te gebruiken dat door een andere patiënt is teruggebracht naar de apotheek. In 41 openbare en 5 poliklinische apotheken is aan bezoekers gevraagd een korte vragenlijst in te vullen. In totaal vulden 2215 patiënten de vragenlijst in. Hiervan was 61.2% bereid om medicatie te gebruiken dat door een andere patiënt was teruggebracht. De voornaamste reden hiervan was dat het zonde is om goede geneesmiddelen te vernietigen. Patiënten die hiertoe niet bereid waren vonden dit voornamelijk riskant. Deze studie laat zien dat een substantieel deel van de patiënten bereid is om medicatie te gebruiken dat door een andere patiënt is teruggebracht wanneer de kwaliteit daarvan is gegarandeerd. Dit suggereert dat implementatie van heruitgifte mogelijk wordt ondersteund door patiënten.

Om de kosten van een heruitgifte systeem in de apotheek te bepalen en de drempelwaarde wanneer de baten hoger zijn dan de kosten, hebben we in **hoofdstuk 4.1** een micro-kosten studie opgezet. Allereerst hebben we alle handelingen die voor heruitgifte, naast de standaard apotheekhandelingen, geïdentificeerd. Vervolgens hebben we deze gesimuleerd in vier poliklinische apotheken, waarbij we de benodigde tijd hebben gemeten. Hieruit konden we de arbeids- en materiaalkosten bepalen, en dus de kosten van het proces. De belangrijkste resultaten laten zien dat heruitgifte in ieder geval economisch aantrekkelijk is als het wordt geïmplementeerd bij dure geneesmiddelen. Deze drempelwaarde kan naar beneden gaan als meer ongebruikte geneesmiddelen die worden teruggebracht naar de apotheek en nog van goede kwaliteit zijn.

In **hoofdstuk 4.2** hebben we een geïmplementeerd heruitgifte systeem voor geneesmiddelen geëvalueerd. Medische studenten die op stage gaan naar het buitenland krijgen van een poliklinische apotheek een post-expositie profylaxe pakket (PEP) om mogelijk HIV infectie te voorkomen. Deze geneesmiddelen zijn duur en worden door de meeste studenten niet gebruikt. Heruitgifte van deze geneesmiddelen zou tot kostenbesparingen kunnen leiden. PEP werd verstrekt in een gesealde zak met een temperatuurlogger om de bewaartemperatuur te registreren en kon opnieuw worden uitgegeven als (1) de gesealde zak ongeopend werd teruggebracht, (2) de omverpakking en blister onbeschadigd waren, (3) het geneesmiddel

nog minimaal 6 maanden houdbaar was en (4) het geneesmiddel onder de 35 °Celsius was bewaard. Over een periode van bijna vier jaar kregen 379 studenten een PEP pakket mee, waarvan ruim 75% al eerder was uitgegeven aan andere studenten. De kosten van alle PEP over de gehele studieperiode bedroeg ruim €240.000, en de additionele kosten van het heruitgifte systeem €15.000. De netto kosten die werden bespaard door heruitgifte bedroegen ruim €225.000. Heruitgifte leidde tot een kostenbesparing van 74% ten opzichte van wanneer geen heruitgifte had plaatsgevonden. Deze bevindingen laten zien dat de additionele kosten van een heruitgifte systeem relatief laag zijn, en dat heruitgifte van PEP tot substantiële kostenbesparingen kan leiden.

In het laatste hoofdstuk van dit proefschrift, **hoofdstuk 5**, hebben we de belangrijkste bevindingen in een breder perspectief geplaatst en zijn de methodologische aspecten bediscussieerd. We hebben beschreven welke maatregelen elke stakeholder in de geneesmiddelendistributie- en gebruiksketen kan ondernemen om verspilling te verminderen. Specifiek voor heruitgifte van geneesmiddelen, hebben we barrières besproken die mogelijk kunnen optreden bij implementatie in de praktijk. De belangrijkste conclusies van dit proefschrift zijn dat geneesmiddelenverspilling onder alle type patiënten voorkomt en aanzienlijke nadelige gevolgen op financieel gebied evenals voor het milieu heeft. De verspilling van geneesmiddelen is vaak te voorkomen en voor een duurzaam gebruik van geneesmiddelen, is het terugdringen wenselijk. Om dit tot een succes te laten komen, is betrokkenheid van alle stakeholders nodig. Het is belangrijk dat er bewustwording over de consequenties van verspilling komt en de mogelijkheden om verspilling aan te pakken. Omdat er meerdere oorzaken ten grondslag liggen aan de verspilling, is een enkele aanpak niet voldoende. Preventie is het meest belangrijke bij het verminderen van de geneesmiddelenverspilling, maar omdat dit niet altijd mogelijk hebben we uitvoerig de haalbaarheid van het heruitgeven van ongebruikte geneesmiddelen onderzocht. Zowel patiënten als andere stakeholders ondersteunen heruitgifte om verspilling te verminderen. Heruitgifte in de klinische praktijk vraagt om een goede implementatiestrategie met duidelijke communicatie naar alle stakeholders. Gezien de kosten van het heruitgifte proces, zal implementatie het meest haalbaar zijn voor dure geneesmiddelen.

Dankwoord

Daar is het dan, mijn proefschrift, het is gelukt. De afgelopen vier jaar die ik aan mijn promotie heb besteed waren een bijzonder traject waarin ik heel veel heb mogen leren over de wereld van de wetenschap, de farmacie, en het dagelijks functioneren van onderzoekers. Hoewel het niet altijd even makkelijk was, zijn er heel wat mooie momenten geweest die ik niet had willen missen. Nu ik terugkijk op het hele traject ben ik trots, dat ik met de onvoorwaardelijke hulp van anderen, tot dit eindresultaat ben gekomen. Een aantal mensen wil ik daarom in het bijzonder bedanken.

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List of publications

International publications

Within this thesis

Bekker CL, Gardarsdottir H, Egberts ACG, Bouvy ML, van den Bemt BJF. Redispensing of medicines unused by patients: a qualitative study among stakeholders. International Journal of Clinical Pharmacy 2017;39(1):196-204.

Bekker CL, van den Bemt BJF, Egberts ACG, Bouvy ML, Gardarsdottir. Patient and medication factors associated with preventable medication waste and possibilities for redispensing. International Journal of Clinical Pharmacy 2018;40(3):704-711.

Bekker CL, Melis EJ, Egberts ACG, Bouvy ML, Gardarsdottir H, van den Bemt BJF. Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy. Research in Social and Administrative Pharmacy 2018;6(3):1-14

Bekker CL, Gardarsdottir H, Egberts ACG, Bouvy ML, van den Bemt BJF. Pharmacists' activities to reduce medication waste: an international survey. Pharmacy 2018; "in press"

Outside this thesis

Vlieland, ND, van den Bemt BJF, **Bekker CL**, Bouvy ML, Egberts ACG, Gardarsdottir H. Older patients' compliance with drug storage recommendations. Drugs Aging 2018;35(3):233-241.

Other publications

Bekker CL, Gardarsdottir H, Egberts ACG, Bouvy ML, van den Bemt BJF. Heruitgifte van ongebruikte geneesmiddelen: een kwalitatief onderzoek onder stakeholders. Nederlands Platform voor Farmaceutisch Onderzoek 2017;2;A1653.

Conference proceedings

Abstracts

Bekker CL, Gardarsdottir H, Melis EJ, Egberts ACG, Bouvy ML, van den Bemt BJF. Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among patients who discontinue therapy. Conferences: ESCP Reykjavik, Iceland 2018 (oral presentation), ESCP Heidelberg, Germany 2017 (poster), NSPC Kuopio, Finland 2017 (oral presentation), PSWC Stockholm, Sweden 2017 (poster), Prisma Amersfoort, the Netherlands 2017 (oral presentation).

Bekker CL, van den Bemt BJF, Egberts ACG, Bouvy ML, Gardarsdottir. Patient and medication factors associated with preventable medication waste and possibilities for redispensing. Conferences: Green pharmacy conference Utrecht, the Netherlands 2017 (poster), ESCP Oslo, Norway 2016 (poster), Prisma Amersfoort, the Netherlands 2016 and 2017 (oral presentation), NSPC Kuopio, Finland 2017 (oral presentation), PSWC Stockholm, Sweden 2017 (poster).

Bekker CL, Gardarsdottir H, Egberts ACG, Bouvy ML, van den Bemt BJF. Redispensing of medicines unused by patients: a qualitative study among stakeholders. Conferences: WHO wintermeeting Utrecht, the Netherlands 2016 (oral presentation), ZFD 's-Hertogenbosch, the Netherlands 2016 (poster presentation), Prisma Amersfoort, the Netherlands 2015 (oral presentation), ESCP Lisbon, Portugal 2015 (poster), FIGON DMD Ede, the Netherlands 2015 (poster).

Bekker CL, Gardarsdottir H, Egberts ACG, Bouvy ML, van den Bemt BJF. Pharmacists' activities to reduce medication waste: an international survey. Conferences: NSPC Kuopio, Finland 2017 (oral presentation), PSWC Stockholm, Sweden 2017 (oral presentation), WHO wintermeeting Utrecht, the Netherlands 2017 (oral presentation), Prisma Amersfoort, the Netherlands 2015 and 2017 (oral presentation), ESCP Lisbon, Portugal 2015 and ESCP Heidelberg, Germany 2017 (poster), FIGON DMD Ede, the Netherlands 2015 (poster), ZFD 's-Hertogenbosch, the Netherlands 2016 (poster presentation).

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Bekker CL, West LM, Bouvy ML. "What can a clinical pharmacist do to reduce medication waste?" ESCP Oslo, Norway 2016.

List of co-authors

List of co-authors (in alphabetical order)

B.J.F. van den Bemt
Department of Pharmacy, Sint Maartenskliniek, Nijmgen, The Netherlands
Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands
Department of Pharmacy and Toxicology, Maastricht University Medical Center, The Netherlands

M.L. Bouvy
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

A.C.G. Egberts
Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

H. Gardarsdottir
Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland

A.M. Hövels
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

R. W. Kalicharan
Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

E.M. van Maarseveen
Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

E.J. Melis
Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

About the author

Charlotte Bekker was born on March 9th 1990 in Zevenaar, the Netherlands. After graduating from the secondary school in 2008 at the Driemark in Winterswijk she started studying Biomedical Sciences at the Radboud University in Nijmegen, the Netherlands. She completed her research internship at the Institute of Anatomy at the University of Zürich in Switzerland and obtained her master's degree in Biomedical Sciences in 2013 with a major in pathobiology and a minor in consultancy.

In 2014, Charlotte started her PhD at the department of Pharmacy at the Sint Maartenskliniek in collaboration with the department of Clinical Pharmacy of the University Medical Center Utrecht and the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht University, the Netherlands. Her PhD was supervised by Prof. Dr. Antoine CG Egberts, Prof. Dr. Marcel L Bouy, Dr. Bart JF van den Bemt, and Dr. Helga Gardarsdottir. Her PhD focussed on medication waste and the feasibility of redispensing unused medication. The results of her PhD are presented in this thesis and at several (inter)national conferences. In 2017, Charlotte was placed among the best three presentations at the Pharmaceutical Sciences World Congress in Stockholm, Sweden.

Since August 2018, Charlotte is working as a researcher at the Netherlands Institute for Health Services Research NIVEL in Utrecht and the department of Clinical Pharmacy of the Radboud University Medical Center in Nijmegen. Here, she is engaged in several pharmaceutical care research projects.