Improving pharmacovigilance and the role of the pharmacist
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Introduction
Chapter 1.1

The world of pharmacovigilance

In 1953, as a result of a storm that happened to coincide with a spring tide, a large number of dykes in the south-western coastal area of the Netherlands gave way. Vast areas of the two provinces of Zeeland and Zuid-Holland were inundated and more than 200 people were drowned. This disaster not only prompted the decision to raise the dykes but also led to the formulation of the so-called Delta plan or Deltaworks, a comprehensive project designed to guarantee the safety of the south-western regions of the Netherlands. The scheme comprised closing off estuaries and inlets, raising the dykes and the construction of many other sophisticated civil engineering works. Its completion lasted several decades. This chain of events, a calamity followed by large-scale safety measures to minimise the risk of a recurrence, can also be said to characterise the development of drug safety monitoring. There are striking parallels between this and the thalidomide tragedy in the 1960s when thousands of babies were born with serious congenital malformations as a result of the maternal use of thalidomide (also marketed as Softenon®). A part from causing the quality standards for the composition of drugs to be raised and more stringent criteria for the safety and efficacy of drugs to be formulated, the catastrophe also triggered the formation of an extensive system of post-marketing surveillance, which ultimately led to the creation of a new scientific discipline: pharmacovigilance.

Tragic events like the ‘Softenon drama’ could easily lead to the idea that drugs are hazardous. This would be a misperception. After all, drugs are remarkably safe.(1) As the director-general of the Dutch Ministry of Public Health Muntendam remarked in 1964: ‘The recent events have caused some panic over the new drugs. Quite understandable, but, by and large, unjustified’. (2) A new level of equilibrium needed to be found in which the blessings of the many new drugs that were released and the potential risks associated with and inherent to the use of these new medications would be given proportional attention.

The rapid advances that have been made in the synthesis of new drugs since the 1930s have drastically changed the nature of health care. The introduction of antibiotics has meant that bacterial infections are now relatively easy to treat, even specific infections like tuberculosis. Often fatal in the first half of the previous century, today pneumonia only rarely leads to mortality, and then usually only in the elderly patient. The nature of psychiatric care has also been notably transformed due to the introduction of
psychopharmaca. Psychiatric hospitals, formerly often closed and isolated institutions, turned into open centres situated in parklands, which are now increasingly being closed because the improvements due to new drug make ambulant care facilities possible. An important, more recent development is the medicinal treatment of gastric complaints with H2-receptor antagonists or proton pump inhibitors, virtually making surgical interventions for non-malignant gastric disorders a thing of the past.

Despite the many benefits we have derived from the development of new medication we always need to keep in mind that, whereas at the individual level drugs are of course a care product, by and large at the societal level they are mainly commercial products. This implies that for millions, perhaps even billions of people medication is not available: for them the cost of drugs is prohibitive simply because they happen to live in a ‘low income country’ or, if they do live in an affluent country, belong to the underprivileged classes. By far the largest quantity of drugs is used in the USA, with Europe and Japan at some distance. Africa hardly features in this story and here, each day thousands of people, mostly children, die from illnesses like malaria and the measles or the simplest of infections that are all highly treatable elsewhere in the world. Clearly, there is no relationship between the burden of illness in a country and its drug consumption, but there is between prosperity and the demand for medication. This was unambiguously illustrated by the recent events in Argentina where in 2002 drug use plummeted with 67% due to the country’s economic crisis, which is, however, likely to increase the demand for medical care.

1.1.1 Drug safety

As mentioned earlier, it is essential to recognise that, apart from the blessings of our modern medicinal resources, there is a downside too. In his inaugural speech in 1969 Meyler already indicated that basically there is no difference between drugs and toxins. Not only are many remedies traditionally derivatives of toxic substances, the distinction between the therapeutic effect and the toxic effect of a drug is mainly determined by its dose. Adverse reactions to drugs (ADR) are thus defined as ‘a response to a drug which is noxious and unintended and which occurs at doses normally used in man’.

That unforeseen negative effects of drugs can occur even at normal doses is a critical theme in pharmacotherapy. When selecting a drug for prescription its safety profile often is the deciding factor. The awareness that drugs are not by definition safe also largely determines the way people in general perceive drugs. The large array of side effects mentioned in the Summary of Product Characteristics (SPC) and the Patient Package Insert (PPI) acts as a deterrent for both the prescriber and the user. The concern over drug safety is a concern that is shared by all those involved in their use. The main reasons why a drug's safety profile cannot be all-inclusive prior to
marketing, necessitating post-marketing surveillance, are presented in Table 1. Also the pharmaceutical industry is increasingly focusing more of their attention on the safety aspect of their products. This is partly brought on by the intensified national and international rules and regulations, but also partly induced by the fact that in the past few years a relatively large number of drugs were withdrawn from the market because of their adverse effects. (7) Also pharmaceutical companies have come to realise that it is in their own interest to give more attention to the safety aspects of drugs.

Although they fall outside the scope of this thesis, there are many other aspects that are all highly relevant for the safety and safe use of drugs. We would like to mention thorough registration procedures, prescriptions that are consistent with the indication, drugs that are dispensed at the right dose, a proper use of the prescribed drug (compliance), but also meticulous manufacturing and drug synthesis procedures based on high-quality components. These matters all seem self-evident but, as experience has shown, they not always are. (8)

1.1.2 Pharmacovigilance

According to the definition in a recent WHO publication pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem. (9) This is a more detailed definition than the one Rawlins used in his often-cited lecture for

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<td>Reasons why drug safety issues may not be indentified until the post-marketing periode</td>
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<td>1. The adverse reaction is rare and therefore undetectable until large number of patients have been exposed to the drug</td>
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<td>2. There is a long latency between starting the drug and development of the adverse reaction</td>
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<tr>
<td>3. The drug has not been studies in normal clinical practice:</td>
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<td>- patients treated in clinical practice are likely to have different characteristics to trial patients (e.g. demography, other diseases, other medication);</td>
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<tr>
<td>- in clinical practice a drug is less likely to be used strictly in accordance with the recommendations by both doctors and patients, and with less monitoring</td>
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Pharmacovigilance is the process of identifying, and then responding to, safety issues about marketed drugs. This latter characterisation came from a report by the Committee on Safety of Medicines and the Medicines Control Agency in the UK, which explains the emphasis on the practical implementation of the concept. In the literature pharmacovigilance is frequently put on a par with Post Marketing Surveillance. This approach highlights pharmacovigilance's most visible method, viz. the spontaneous reporting system (SRS). In their latest textbook Mann and Andrews define pharmacovigilance as 'the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities'. But this includes more as only collecting reports of possible ADRs and looking for signals of new ADRS. In a recent overview Edwards, looking ahead, mentions five activities that are essential to pharmacovigilance. (Table 2).

### Table 2
Activities that are essential to pharmacovigilance according to Edwards

- suspected ADR signal generation and formation of hypothesis
- analysis of all issues around the signal, particularly confirmation (of refutation) of hypotheses, estimation of the size of the risk and whether susceptible patients exist
- consideration of possible changed benefit-to-risk issues in therapy
- communication of information to health professionals and patients in a useful way and possible regulatory action
- consequence evaluation.


#### 1.1.3 The circle of knowledge and practice
Pharmacovigilance is characterised by the fact that it derives its knowledge about the safety of drugs from the clinical usage of drugs in daily practice. By systematically recording and analysing the most recent empirical data on clinical drug usage new knowledge is obtained. It is especially this latter aspect that has received much attention, both in the literature and in the legislation or other rules regulating drug surveillance. However, pharmacovigilance is a two-way system, which is represented by the circle of knowledge and practice as depicted in Figure 1. The upper half of the circle represents the aforementioned aspect but the lower half
1.1.4 The science of pharmacovigilance

Pharmacovigilance is the science dedicated to the safety of drugs as used in the clinical practice, based on experiences from the clinical practice, thus generating knowledge on the harmful effects of drugs, both at the individual and the population level, that will eventually be applied in the clinical practice and thus lead to a safer use of drugs.

As in most applied sciences the field of pharmacovigilance is an amalgam of numerous other scientific domains, each contributing their own expertise to the field, which combined knowledge fosters drug safety reasoning. Pharmacovigilance is essentially a clinical science. To allow a sound judgment of any adverse effects of drugs we need clinical knowledge at the level of the individual patient. It takes extensive general medical knowledge, preferably supported by direct experience with patient care, to be able to make an accurate assessment of the impact pharmacotherapy is likely to have, which becomes even more urgent when unintended adverse events occur. Clinical pharmacologists have been instrumental in the development of the field and are still indispensable, as are the pharmaceutical sciences. By profession, pharmacists are the experts when it comes to drugs. An in-depth knowledge of the mechanisms and behaviour of drugs in the human body are often crucial to gain insight into the actual effects a drug has, and may also help explain a (suspected) adverse drug reaction.

Similarly, the field of toxicology is, by its very nature, closely related to pharmacovigilance and, from an organisational point of view, has been fully integrated in many countries. Many of the insights on adverse effects to drugs were provided by toxicologists. Also teratology has played a significant role in this respect. Pharmacoepidemiology, the science concerned with the effects of drugs in large populations, has been another key contributor and, among other contributions, has helped establish the basis for the statistical analysis techniques and risk assessments in pharmacovigilance.

Finally, with respect to the implementation of the knowledge pharmacovigilance has helped to acquire, it is now increasingly recognised that the existing means to communicate and implement this knowledge need to be improved.

Regulatory pharmacovigilance

Some parties have been crucial to the development of pharmacovigilance. It has been the authorities, both at the national and increasingly at the international level, that have initially helped foster the field. Labeled as regulatory pharmacovigilance by Waller et al., they define pharmacovigilance as ‘the process of evaluating and improving the safety of marketed medicines’. They underlined the responsibilities the various governments have in the monitoring of drug safety, which task many national governments took firmly in hand following the
thalidomide tragedy.(19,20) It is undeniable that in several countries, most notably in the USA and UK, legislation has significantly contributed to the advance of pharmacovigilance as a specialised field of knowledge. The role of the World Health Organisation stands out here. The collaborative programme launched under the auspices of the WHO by ten countries in 1968 was the start of an historic international cooperative effort, resulting in the WHO International Drug Monitoring Programme.(21) The Technical Report entitled ‘International Drug Monitoring: The Role of National Centres’ published as the proceedings of one of the WHO meetings in 1972, laid the theoretical and practical foundation for the further development of pharmacovigilance.(5) The programme has also resulted in the WHO Collaborating Centre for Drug Monitoring (the Uppsala Monitoring Centre) which maintains the international ADR database and fulfils an important role particularly by the support it offers to the pharmacovigilance centres in low-income countries.

The role of the pharmaceutical industry
The second great influence on the development of pharmacovigilance is the pharmaceutical industry. This is not surprising since it is their product, a product they themselves have both developed and manufactured, that is the object of study. From their circles great influence has been exerted to come to international agreements, many of which have since been formalised in the various reports the Council for International Organisations of Medical Sciences (CIOMS) and the International Conference on Harmonisation (ICH) have issued. Initially, the sector’s main interest lay in the epidemiological approach and causality assessment, but nowadays aspects of risk management are also given due attention.

International societies
Lastly, it has been the international scientific societies that have been vital in furthering pharmacovigilance as a discipline in its own right. The International Society of Pharmacoepidemiology, founded in 1984, has helped formulate the epidemiological underpinning of the safety aspects of drugs. The International Society of Pharmacovigilance (founded as the European Society of Pharmacovigilance in 1992) has promoted the field’s clinical and communication aspects.

1.1.5 The need for numbers
Both the regulatory authorities and the pharmaceutical industry want hard facts, preferably concrete numbers. This has meant that the epidemiological approach has long dominated drug safety. Pharmacoepidemiology is the science dedicated to the use of and the effects of drugs in large numbers of people.(22) It evolved as a sub-
discipline of epidemiology in the 1970s and 1980s. The debate on the safety of drugs following the thalidomide affair in the early 1960s played a role here and post marketing surveillance, the research of the usage and safety of marketed drugs, became one of its key tasks. Methodology, statistics and rates are the foundation of pharmacoepidemiological reasoning aimed to provide (numerical) conclusions on group level.

The relationship between pharmacoepidemiology and pharmacovigilance may be characterised as follows: pharmacoepidemiology, by studying large populations, aims at deriving facts that may also be of relevance to the individual, whereas pharmacovigilance studies the clinical experiences of individuals in order to be able to draw conclusions that may also be valid for larger sections of the population. Epidemiological and pharmacoepidemiological reasoning have long stood in the way of a full appreciation of pharmacovigilance's distinctive qualities. Their approach based on numerical reasoning, caused attention to be shifted from thinking in terms of clinical observations (clinical reasoning) to thinking in terms of large numbers and averages.(23) Claude Bernard, who did not believe in ‘the average patient’, was the first to criticise this approach. He was a strong advocate of causal and deterministic reasoning based on clinical observations in the individual patient. Recently, there has been a broad renewed appreciation of the relevance of the individual case as the basis for scientific thinking.(24) Also where pharmacovigilance relies on data derived from large datasets it is essential to always weigh these findings against the underlying individual case histories before any conclusions are drawn.(25,26)

Apparently it is mostly cases and case series on which the regulatory authorities base their final conclusions and measures; only rarely are their decisions supported by pharmacoepidemiological research.(27) Moreover, most often the signals underlying their decisions are confirmed in the literature eventually.(28) In the light of these facts it is obvious that pharmacovigilance cannot provide a quantitative risk assessment, although its data may in some cases provide an indication. This is a task for the pharmacoepidemiologists since pharmacovigilance has other objectives. Similar to all clinical disciplines the field of pharmacovigilance has to deal with countless uncertainties. In this thesis the concept of underreporting is used to illustrate the distinctiveness of pharmacovigilance in relation to pharmacoepidemiology.

1.1.6 Spontaneous reporting as the main source of signals

The signals of adverse drug reactions derived from the experiences with patients using the drugs as reported by doctors and pharmacists lie at the heart of pharmacovigilance. Meyboom defined a signal as a set of data constituting a hypothesis that is relevant to the rational and safe use of a drug in humans.(29) It is
pharmacovigilance’s key task to try and underpin this hypothesis, thus confirming its validity. As stated earlier, the data on which the signal is based originate from the daily experiences of physicians and pharmacists and have manifested themselves in individual patients. It is therefore of the utmost importance that appropriate methods are available to facilitate the collection of these experiences and observations. In the past few decades several such methods have been developed. The most widely used method is the so-called Spontaneous Reporting System (SRS). A SRS is especially effective for detecting rare and serious adverse drug reactions. All drugs during their whole lifetime are subject to a SRS. It invites health professionals and increasingly also patients to report their observations or information to a pharmacovigilance centre. These reports need to contain sufficient information to allow an accurate evaluation and a well-founded assessment of the relationship between the suspected ADR and the drug in question (causality assessment). This implies that a limited number of qualitatively sound reports is preferred to large quantities of poorly specified reports.

The hallmarks of an effective spontaneous reporting system are listed in Table 3.

In addition to the SRS pharmacovigilance has several other sources at its disposal. It can make use of the findings generated by the various (pharmaco)epidemiological research methods; data that may help confirm earlier suspicions. This thesis will also expand on methods of Intensive Monitoring like Prescription Event Monitoring which has been successfully applied in the UK and New Zealand for many years.

Publications of case reports are also an important source of information and may facilitate the detection of a signal or strengthen earlier signals. And finally, there are the quantitative methods of signal detection in extensive ADR datasets with which studies have been conducted worldwide. However, this approach should be seen as an additional source of information and not as a panacea for the clinical assessment of cases.

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<td>Hallmarks for an effective spontaneous reporting system (SRS):</td>
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<td>- Vigilant users</td>
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<td>- Creative and competent doctors, pharmacists and other health professionals, who, when they uncover a likely adverse event, are prepared to report their suspicion and do so as fully documented as possible</td>
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<tr>
<td>- Efficient reporting procedures facilitating smooth reporting</td>
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<td>- A pharmacovigilance centre fully equipped to detect signals</td>
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Large sections of this thesis are dedicated to the enhancement of these facets of pharmacovigilance, hopefully leading to both better and more reports on suspected adverse drug events.
Chapter 1.2

The role of the pharmacist

The motivation for this thesis was the observation that the pharmacist’s share in the total volume of ADR reports submitted in the Netherlands was considerable, especially when compared to the rest of the world. Dutch pharmacists are well-acquainted with the spontaneous reporting system and they submit roughly 40% of the reports the Netherlands Pharmacovigilance Centre Lareb receives. As such this is not surprising because from its start it has been Lareb’s aim to promote ADR reporting as a collaborative effort of doctors and pharmacists. The rationale was that a closer cooperation would improve pharmacotherapy since an increased awareness of adverse effects would not only boost the number and quality of reports but would at the same time encourage these health professionals to become more actively engaged in the prevention of adverse events, thus encouraging more judicious prescription practices. A recent study shows that in the twelve months preceding the survey 43% of Dutch community pharmacists had reported at least one or more ADRs to Lareb.

Lareb has always been a testing ground for the cooperation between doctors and pharmacists. In both the General Board and the Scientific Advisory Board as well as at the staff level doctors and pharmacists have always had an equal input. The Royal Netherlands Society for the Advancement of Pharmacy and the Netherlands Society of Hospital Pharmacists are both represented in the General Board of Lareb. With their respective clinical and pharmaceutical expertise clinicians and pharmacists each make their own specific contribution to the knowledge on adverse drug reactions.

1.2.1 The changing role of the pharmacist

The position of the pharmacist within the health care system has continually been subject to change. With respect to drug dispensing several tasks can be distinguished. The pharmacist’s primary mission is to dispense drugs as prescribed by the physician and to ensure these drugs meet the required standards. Nowadays the pharmacist also frequently acts as a consultant on pharmacotherapy and in the UK and USA pharmacists are, to a degree, also authorised to write out prescriptions, which, incidentally, has been a long-standing practice in many countries where doctors are in short supply. The changing role of the pharmacist is most noticeable in The Netherlands. Whereas initially the emphasis was on the chemical analysis of drugs and its raw materials, the local production of medicines and the dispensing role, today the pharmacist’s role has shifted more
towards the prevention of adverse drug reactions and interactions, information and instruction about good use of drugs and is he a consultant on drug therapy, both for physicians and patients. In the N etherlands a bill is being prepared to award the pharmacist the official status of co-consultant, thus making him jointly responsible for pharmacotherapy. Nevertheless, the fundamental role of the pharmacist will always be to ensure that medicines are used safely.

The role the pharmacist plays or is given to play also depends on the circumstances in which he exercises his profession. In Chapter 3.1 we will elaborate on this issue. The term pharmaceutical care is often used to describe the more comprehensive interpretation of the occupation, although the term is given different meanings and often thought to be too vague.

In the literature several other ways in which the pharmacist can contribute to the safe use of drugs are mentioned. In addition to their responsibilities relating to drug dispensing and compliance and their role in ADR reporting, which we will discuss in the next section, record keeping, education and their role regarding over-the-counter (OTC) products, both conventional and alternative drugs, are areas where they can play a prominent role.

Since in pharmacy monitoring and consequently also in drug safety more and more use is made of automated systems, the pharmacist’s role, both as a user and in his capacity of system manager, is also becoming more and more important.

1.2.2 The pharmacist as a reporter of adverse drug reactions

This thesis specifically focuses on the significance of the pharmacist as a reporter of adverse drug reactions. As mentioned above, in the Netherlands their contribution is substantial, which cannot be said for the rest of the world. Not only are pharmacists not authorised to report everywhere, even where they are, their contribution is often still relatively small.

In an international review, Griffin notes that in 1986 many countries have accepted pharmacists’ reporting ADRs as standard practice. In 1989 Fincham comments: ‘Exclusion of pharmacists simply does not make sense’. In their article in 1993 on the differences between European countries Lindquist and Edwards remark: ‘Pharmacists who advise patients directly... are the most likely to detect adverse reactions’. Roberts et al. conclude in 1994: ‘It is hoped that pharmacists in other countries will also be encouraged to participate in ADR reporting, a procedure that could only lead to better patient care’. The Uppsala Monitoring Centre (UMC) regularly publishes an overview of the ways the national reporting systems in the various countries are operated, in which the volume of pharmacist reports are also listed. The literature on the actual contribution of pharmacists in ADR reporting often relates to the hospital pharmacist in the USA, Canada and the UK.
The majority of publications concern the ongoing debate in the UK where, for the past ten years, the desirability of direct reporting by pharmacists has been discussed. (43,57)

In the various textbooks on pharmacoepidemiology and pharmacovigilance the pharmacist receives little attention, with the exception of Inman who, as early as in 1986, devoted a chapter to the role of the pharmacist. (46) The authors examine their contribution in relation to non-prescription drugs and also point to the medication history pharmacies keep and the edge pharmacists have through the use of computer technology. They conclude by stating: ‘It is to be hoped that protection of professional territories will not prejudice such a contribution’.

What is important here is that there is mutual respect and acknowledgement of professional expertise. In the literature it has been widely reported that doctors fully subscribe to a prominent role for pharmacists in drug policies. (58) In Chapter 3.1 the role of the pharmacist in relation to ADR reporting is discussed from an international perspective. In Chapters 3.2 and 3.3 we focus on the pharmacists’ attitude towards and their actual contribution to ADR reporting.

1.2.3 The contribution of the hospital pharmacist

Hospital pharmacists can also play a significant role in ADR reporting. It is in their work environment that the most serious adverse drug events can be seen to occur. Several recent publications have underlined the extent to which adverse drug events account for hospital admissions. In the US this was 6.7%, for France a percentage of 3.2 has been reported and for Sweden the most recent figure is 12%. (59,60,61) Evidently, there is every reason to make the prevention and recording of adverse events occurring in hospitals a priority, to control both their harmful effects and the costs resulting from these events. (62) This process could best be supervised by hospital pharmacists, particularly when they are directly involved in patient care. (62) Several articles have specifically highlighted this role and have suggested that hospital pharmacists could help reduce the ADR incidence rate substantially. (54,63) And yet, their potential in this context is not always recognised as two German studies have shown. Neither of the two studies, one on the detection of adverse drug reactions in hospitals and the other investigating the incidence of ADRs and the resultant costs, mention the hospital pharmacist. (64,65) Several prerequisites need to be fulfilled to ensure that their contribution will indeed help bring down the number of adverse events and improve ADR reporting: direct involvement in patient care and a functional, widely supported hospital reporting system in whose management the hospital pharmacist should have a key role. A part from their quantitative relevance, ADR reports from hospitals also raise the quality of ADR monitoring because of their high-quality
documentation. If hospitals were to report more, this would also enhance the surveillance of those drugs that are chiefly used in hospital settings. Moreover, hospital pharmacists also have more and more advanced means at their disposal to monitor drug safety, such as sophisticated computer systems and databases as well as the possibility to investigate deviant lab test results, which methods are not or less available elsewhere.

The contribution pharmacists make to ADR reporting is by far the largest in the U.S. Here the majority of the reports the Food and Drug Administration (FDA) receives direct from health professionals originate from hospital pharmacists. The FDA particularly encourages this professional group to report, also because of the high standard of their reports. The fact that they play such a key role is the direct result of a stipulation of the Joint Commission on Accreditation of Health Care Organizations (JCAHO) requiring hospitals to sustain an ADR monitoring programme. Evidently, they view such hospital reporting systems as a crucial element of the national reporting system. The same situation applies to Canada, although that here it was the Canadian Society of Hospital Pharmacists that took the initiative. The contribution of hospital pharmacists to their national system was also significantly augmented.

In the United Kingdom there has been a long lasting discussion over the position of the (hospital) pharmacist within the reporting system. As early as in 1982 Hardman and Lloyd proposed to grant the hospital pharmacist an active role in the monitoring of adverse drug reactions. A structural collaboration between clinicians and hospital pharmacists was proposed by Irvin et al. Winstanley et al. have demonstrated that the initiation of a pharmacy-based reporting scheme led to a substantial increase of the number of ADR reports, a finding that was later confirmed by Lee et al. Nevertheless, it was not until 1997 that the hospital pharmacist was officially allowed to report ADRs to the national SRS.

1.2.4 The contribution of the community pharmacist

This thesis specifically elaborates on the role of the community pharmacist in ADR reporting, which is not surprising since in the Netherlands it is particularly this group that contributes most to drug safety monitoring. From an international perspective this is quite remarkable because in most other countries this role is predominantly fulfilled by the hospital pharmacist, whereas in the Dutch system their share is relatively small. Both the community pharmacist’s attitude (Chapter 3.2) as his concrete contribution (Chapters 3.3 and 3.4) are discussed.
To date, little is known about their position or contribution in other countries and has only been described for Cuba. However, in the literature their potential role in relation to non-prescription medicines (‘over-the-counter drugs’) has received some attention. This not only concerns non-prescription drugs but also alternative medication; pharmacists are uniquely placed to learn of these ADRs and report them.

As regards the potential role of the pharmacist in relation to ADR reporting, Fincham stated: ‘Efforts must be expanded to include pharmacists in every ADR surveillance activity’. Also Kelly’s remark on the subject gets to the heart of the matter: ‘Pharmacovigilance: more a responsibility than a role!’
depicts the implementation of the knowledge into the clinical practice. This second aspect of pharmacovigilance has recently been given more weight. In the past pharmacovigilance was repeatedly criticised because once its activities had yielded a signal of an ADR this all too often meant that the licence of the drug concerned was suspended. Today it has become one of pharmacovigilance's priorities to try and find more creative and constructive ways to deal with these signals.(12,13) Ways to improve information and communication facilities are being considered but also the quite practical problems associated with the implementation of measures promoting the safe use of drugs are given appropriate attention. After all, a drug is never just safe or unsafe: it is only safe when it is applied in the proper dose in patients for whom the individual risk-benefit balance has proven positive. Mere prevalence rates of ADRs may be irrelevant for specific patient groups.(14) Pharmacovigilance concerns itself with all the aspects in the circle of knowledge and practice. Besides tracing and weighing risk factors, it tries to advise doctors and pharmacists on how best to deal with these risks and provide them with tools that will enable them to apply their newly acquired knowledge to the treatment of the individual patient. This approach permits pharmacovigilance to contribute to a safe and rational use of drugs for the benefit and well-being of those patients that are dependent on pharmacotherapy, as is supported in this thesis.
Chapter 1.3

Outline of the thesis

The present dissertation is about the safety of drugs, more specifically their surveillance after the regulatory authorities have judged their efficacy, quality, and safety sufficiently proven for the drugs to be applied in the clinical practice. After the thalidomide disaster in the early 1960s the awareness that drugs can constitute a serious risk was raised dramatically and, in addition to stringent approval procedures, a scheme was developed to monitor the safety of marketed drugs. Pharmacovigilance is responsible for both the scheme's theoretical underpinning and its practical implementation. For its implementation pharmacovigilance mainly relies on a (spontaneous) reporting system where clinicians and pharmacists can report their suspicions of any adverse drug reactions (ADRs), which are subsequently analysed. This thesis is about pharmacovigilance, what it entails and how it can be improved, with particular emphasis on the role pharmacists can play in this process, as is explained in Part 1.

Part 2 of the thesis provides the framework for the subsequent parts of it. Chapters 2.1 and 2.2 expand on various aspects of the history of drug safety monitoring, where Chapter 2.2 is a tribute to professor dr. L. Meyler, who with his book ‘Side effects of drugs’ paved the way for a systematic attention for adverse events associated with drug use in the clinical practice. Motivated by his personal experiences, he wrote down his observations at a time when this aspect of drugs was still very much underestimated.

Chapter 2.3 provides an overview of the various ways in which pharmacovigilance is implemented in the Netherlands and the organisations that are involved. The special position of the pharmacist in the Dutch situation is also discussed. Chapter 2.4 is dedicated to the unique quality of pharmacovigilance as a scientific discipline, which is illustrated by the concept of ‘underreporting’. It is stressed that the view that underreporting is its major drawback does not do justice to the real basis and purpose of pharmacovigilance and that those who take this position do not appreciate what can and cannot be achieved with the data a reporting system generates.

Part 3 expands on the role the pharmacist has or should have in the detection and reporting of adverse drug reactions. Chapter 3.1 compares the situations in the various countries that participate in the
WHO Drug Monitoring Programme. In Chapter 3.2 we report the results of a survey held among Dutch community pharmacists on their attitude to ADR reporting. It is concluded that their knowledge and the conditions are such that their commitment to report is high. Several factors that may influence their commitment and actual reporting behaviour are also discussed. The contribution of Dutch pharmacists to the Netherlands Pharmacovigilance Centre Lareb between the years 1995 and 2000 is analysed in Chapter 3.3, both in quantitative and qualitative terms. During this period their share in the volume of reported ADRs was indeed substantial, i.e. 40%. The quality of the pharmacist reports is compared to that of the reports Lareb received from physicians. Chapter 3.4 demonstrates how a report Lareb received from a community pharmacist, containing high-quality information, resulted in a scientific paper published in an international journal. The paper warns clinicians and pharmacists that, similar to existing oral contraceptives, a newly introduced oral contraceptive also carries the risk of thrombosis.

Part 4 focuses on what can be done to improve pharmacovigilance, again with special reference to the pharmacist. In Chapter 4.1 a pilot study is described in which a method, allowing recently approved drugs to be monitored more intensively, is tested. This method is especially relevant given that the safety information for new drugs as based on their clinical usage is still limited. By making use of so-called first delivery signals generated by the automated systems of pharmacies, the doctor who has prescribed the drug in question is invited to anonymously report his or her experiences with its use. Wide-scale application of this method may mean that new insights into the clinical safety profile of newly marketed drugs can be obtained sooner. For questions relating to the safety of the drugs they have been prescribed patients will often turn to the pharmacist. In the Netherlands they have an additional source of information at their disposal, namely a national drug helpline (‘Geneesmiddelen Infolijn’), which service is also maintained by pharmacists. By comparing the patients’ queries the helpline received during one year to the pharmacist reports that were submitted to Lareb in the same period, we were able to assess whether the latter were an accurate representation of the concerns patients expressed. The findings of this comparative study are discussed in Chapter 4.2. An alternative way to do justice to the concerns drug users have, is by giving them the opportunity to report their concern directly to the national pharmacovigilance centre without mediation of their GP or pharmacist. Chapter 4.3 details the pros and cons of such a system of direct patient reporting. The primary aim of drug safety monitoring or pharmacovigilance is to acquire new
insights into the safety of (new) drugs based on the analysis of reports on suspected adverse events. Ultimately, this new knowledge needs to benefit those that use the drugs. To achieve this doctors and pharmacists need to be informed about any new risks or about earlier risks that have been substantiated. The most commonly applied method is to adjust the content of the Summary of Product Characteristics (SPC) and consequently the Patient Package Insert (PPI) where, among other aspects, the drug’s known adverse reactions are outlined, warnings and contraindications are specified and precautionary measures recommended. In exceptional cases clinicians and pharmacists may be alerted to a suspected risk by means of a ‘Dear Doctor Letter’. However, in practice these measures have been found to have little impact, which lack of response may sometimes lead to the drug’s approval being revoked or, alternatively, to the Marketing Authorisation Holder voluntarily taking the product off the market. If new insights were to be implemented better, drastic measures like these may be prevented. In Chapter 4.4 this dilemma is discussed in detail and several routes are proposed that may help to improve the practical implementation of the new knowledge on drug safety that we have derived from the clinical and practical experiences of both doctors and pharmacists, for the benefit of those for whom the medical and pharmaceutical care is intended: the patients.

**Part 5** gives a synthesis of this thesis and a perspective into the future.
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