Summary
This thesis bears the title: ‘Improving pharmacovigilance and the role of the pharmacist’. The main theme is: How can the safety of medicinal drugs be monitored in a better way? Specific attention is paid to the role the pharmacist can play in this process.

Since the ‘Softonon tragedy’ in the early 1960s there is the awareness that drugs are not always be a blessing, but can also mean a risk. At that time, over 10,000 children were born with congenital malformations resulting from the maternal use of thalidomide (Softonon®) during pregnancy. This is why today drugs are examined before they are approved to be applied in the daily, clinical practice. They need to meet the highest standards with regard to their efficacy, safety and quality. In the Netherlands drugs are granted their marketing authorisation by the ‘College ter Beoordeling van Geneesmiddelen’ (Medicines Evaluation Board, MEB), frequently in European context.

Since the 1960s doctors and pharmacists are also requested to report suspected side effects or adverse drug reactions (ADRs) in order to prevent a disaster like the Softonon tragedy from occurring again. Under the authority of the MEB the Netherlands Pharmacovigilance Centre Lareb collects and analyses the reports on possible adverse events and reports back to the MEB. Drug safety monitoring, by a close surveillance of the risks associated with the use of drugs, is essential because at the time when a drug is granted a marketing authorisation the practical experiences with the product are still limited. Only when it is used by many and under all kinds of different circumstances is it possible to determine whether it is safe or unsafe. Worldwide, drug safety monitoring under the practical conditions of clinical usage is called pharmacovigilance.

In Part 1 the abovementioned aspects are explained in more detail and it is described that pharmacovigilance is a distinct discipline with its own reasoning, methods and development. The role of the pharmacist in drug safety monitoring is also discussed and it is noted that, remarkably, in the Netherlands it is the community pharmacist whose contribution is most substantial. In other countries the community pharmacist plays a less significant role and here in some countries it is the hospital pharmacist who contributes most.

Part 2 describes the distinctive position of pharmacovigilance as a scientific discipline and thus lays the foundation for the remainder of the thesis. In chapter 2.1 an overview is presented in which the attention adverse reactions to drugs have received in history. Professor Meyler of the Dutch University of Groningen was one of the first to pay systematic attention to adverse drug reactions. Chapter 2.2 is dedicated to the remarkable story behind his, still renowned, book entitled ‘Side effects of drugs’.
Chapter 2.3 describes the way pharmacovigilance is organised in the Netherlands. Special attention is paid to the activities of the Netherlands Pharmacovigilance Centre Lareb, which has a key role in its implementation. This chapter is also essential because it describes the background of and the circumstances in which the pharmacist functions in the Netherlands, as will be described in more detail in Chapter 3.

The discussion of the concept of underreporting in chapter 2.4 underscores the uniqueness of pharmacovigilance as a separate discipline. The term underreporting refers to the fact that by no means all adverse reactions are reported. Underreporting is often used to challenge pharmacovigilance's main methodology: the spontaneous reporting system (SRS). We explain that it is the more epidemiological perspective of the reporting system that accounts for this bias. It is demonstrated that from a pharmacovigilance standpoint underreporting is in actual fact desirable.

**Part 3** discusses the contribution of the pharmacist in the reporting of adverse drug reactions. In chapter 3.1 we look at the contribution of these health professionals in the various countries participating in the worldwide collaborative programme of the World Health Organisation. It is found that the pharmacist is particularly appreciated in those countries that have been operating an effective reporting system for some length of time and where the pharmacist is authorised to participate.

It is explored why the (community) pharmacist plays such an important role in the Netherlands. To this end, the attitude of the Dutch community pharmacists was assessed by means of a survey. They proved to regard ADR reporting as an integral part of their professional duties, inherent to the pharmaceutical care they wish to provide.

To determine the extent of the actual contribution the pharmacists make in the Netherlands, the reports they submitted in the period between 1995 up and including 1999 were compared with those sent in by doctors during the same period. This showed that 40% of the reports Lareb had received originated from pharmacists. Overall, their reports were of good quality. Pharmacists tended to report more eye and skin complaints. Doctors more frequently reported serious adverse events and the clinical information they provided tended to be more detailed.

To illustrate the importance of well-documented pharmacist reports in chapter 3.4 a female patient is described who died from thrombosis while on a new oral contraceptive. Based on, among other indications, this report doctors and pharmacists could be warned that as far as the risk of thrombosis is concerned this new pill did not seem to be any different from the more established widely used pills.
‘How to improve pharmacovigilance’ is the theme of **Part 4.** In pharmacovigilance it is crucial to gain insight into the as yet unknown risks associated with new drugs when they are used by large numbers of patients in the clinical practice as soon as possible. In chapter 4.1 a study is reported in which, based on the data generated by the computer systems of pharmacies, doctors are requested to report to Lareb hitherto unknown and serious adverse drug reactions associated with new drugs. Although a small-scale trial, we found that with this method it is possible to encourage the submission of reports soon after a drug has been introduced to the market. In addition, pharmacists and doctors were found to be motivated to participate.

It is not only the doctors and pharmacists that have questions and concerns regarding adverse reactions to drugs. Evidently, these are also shared by those using the drugs: the patients. For answers, many patients turn to the ‘Geneesmiddelen Infolijn’, a drug helpline operated by pharmacists. In chapter 4.2 these queries are compared to the reports pharmacists submitted to Lareb. Although the conclusions are tentative because the information on the questions patients had posed was limited, the pharmacist reports tended to adequately reflect the complaints about side effects the patients had expressed to the helpline.

The next logical step would be for patients to report side effects direct to the national reporting centre. Worldwide, there is little experience with such a system. A common objection raised in this context is that such reports are likely to contain insufficient information to allow conclusions to be drawn about the relationship between the complaint and the drug mentioned. In chapter 4.3 we describe the pros and cons of direct patient reporting based on a review of the available literature.

It is the primary objective of pharmacovigilance to uncover new information on adverse drug reactions. It goes without saying that this also means that doctors and pharmacists should apply this new knowledge in their daily practice. In chapter 4.4 four examples are given that shows this latter aspect is badly in need of improvement. The drastic measure of taking a drug off the market in reaction to its adverse effects could be avoided in some cases. The main challenge for the future is to ensure that, by exploiting the most recent knowledge; drugs are prescribed and dispensed in such a way that the risk of adverse events is reduced. Several recommendations to achieve this goal are given.

**Part 5** of the thesis is a synthesis of the issues described in the preceding chapters. By raising their awareness of adverse drug reactions doctors and pharmacists can help prevent much harm, both in terms of health and costs. They can contribute by adhering to careful prescription practices and by more readily considering adverse reactions as a possible cause of complaints. Awareness of adverse events can thus become the foundation for a more effective pharmacotherapy.
Suggestions are provided to further improve pharmacovigilance. By encouraging doctors and pharmacists, and possibly also patients, to submit more and well-documented reports we may add to our knowledge about the incidence of adverse drug reactions. It is essential to take the concern the reporter raises in his or her report seriously and to provide him or her with proper feedback. In pharmacovigilance automated systems are becoming increasingly important, also in international context. Another significant development is the so-called pro-active surveillance of drugs, which has been given more weight of late. This method entails that when marketing approval of a new product is applied, the manufacturer needs to indicate which risks of adverse reactions he anticipates, which, among other sources, should also be based on the data generated by the pre-marketing trials. In this way, extra measures to monitor these likely risks can be taken.

In the last part of this thesis the desirability of an autonomous pharmacovigilance is stressed, that is independent of both the pharmaceutical industry and the national authorities, as well as of other parties involved. Independent scientific analysis is the best guarantee of an effective drug safety surveillance aimed to protect the interests of the patient.

It is evident that the pharmacist needs to be given an important role in the further development of pharmacovigilance. In those countries where he is not yet authorised to report or where his contribution is still limited, it is essential to give the pharmacist, as an expert on medication and as an ADR reporter, the status that has proven so valuable in the Netherlands. On the other hand, the contribution of the Dutch hospital pharmacist needs to be enhanced by awarding him a coordinating role in the promotion of proper drug use, of which ADR reporting forms part.

In the final chapter of the thesis the distinctive character of pharmacovigilance is underpinned once again and it is emphasised that the acquisition of knowledge as derived from the experiences of individual patients is ultimately aimed at improving the pharmacotherapy to individual patients. Evidently, drug safety is pivotal in this process. An alternative interpretation of the risk aspects of new drugs is advocated: a drug can only be used safely if its safety has been effectively proven.