5
General discussion and perspectives
In this concluding chapter we shift our attention from the more specific aspects of pharmacovigilance to the broader, contextual picture with particular emphasis on future developments and the role of the pharmacist in all this. In the literature the generation of signals is commonly seen as pharmacovigilance's core task. This indeed has long been the main activity of the professionals working in this field. Once new signals of adverse drug reactions (ADRs) had been identified, sometimes confirmed by additional (epidemiological) research, they could be weighed against the benefits of the treatment and, if necessary, measures could be taken. However, pharmacovigilance is far more than mere signal generation and it is these other facets of pharmacovigilance that are even more likely to prevent harmful effects to patients and the economy.

1. By continuously drawing attention to (the possibility of) adverse reactions to drugs, physicians are also induce to include suspected ADRs in their differential diagnoses at an early stage, thus expediting an appropriate response, which frequently implies that the treatment is discontinued. In this way unnecessary and expensive diagnostic tests can be avoided and the time patients spend in the hospital could be shorter. The physicians’ and pharmacists’ awareness of adverse events is raised.

2. Raising the awareness of ADRs also is an important instrument to promote rational and safe prescription practices. Again, pharmacovigilance can help to prevent detrimental health effects and control public health expenditure. Given that only a limited number of new drugs is released every year and that today there is every reason to be conscious and economical when prescribing drugs. Apart from the drug’s effects, the profile of its adverse reactions can be an important consideration for doctors in their choice of drug therapy.

In other words: awareness of adverse drug reactions may significantly contribute to prudent and sensible prescription practices. This is all the more relevant since it has been shown that about half of all adverse events are avoidable.(1,2) The points mentioned above, i.e. enhancement of the status of ADRs in differential diagnoses and promotion of ADRs as the foundation for a rational and careful prescription of drugs, illustrate that the impact of pharmacovigilance on a prudent and safe use of drugs is much greater and that its scope is far wider than the mere detection of unknown adverse events.
It was also the premise that awareness of and a deeper insight into ADRs, specifically by the enhancement of doctor-pharmacist interactions, would positively affect pharmacotherapy, that lay at the heart of the decision to found the Netherlands Pharmacovigilance Centre Lareb.(3)

Developing pharmacovigilance
The safety of drugs, and thus pharmacovigilance as the scientific and practical environment for the implementation of drug surveillance, did not receive systematic attention until the disastrous thalidomide episode in the early 1960s. We now have the third generation of scientists that is dedicated to this field. To prevent any new tragedies from occurring, and within a short space of time, its pioneers were able to develop a methodology that, based on the daily experiences of the medical practice, made it possible to detect ADRs that had not come to light during the pre-marketing clinical trials, which tests have since been made compulsory. The method was founded on a spontaneous reporting system (SRS), which in several countries was supplemented by a system of Intensive Monitoring. In addition to the practical implementation, as formulated in the WHO Technical Report in 1972, which had from an organisational point of view already taken shape in the collaboration of ten countries participating in the WHO International Drug Monitoring Programme launched in 1968, the scientific underpinning of the activities has also received due attention. Finney specifically pointed to the significance of individual cases and their statistical relevance.(4) Inman has specified practical solutions for the implementation of the concept of Intensive Monitoring.(5)

In the various reports it has issued, the Council for International Organisations of Medical Sciences (CIOMS) and the International Conference on Harmonization (ICH) have laid down the regulatory terms the pharmaceutical industry needs to comply with. The knowledge about ADRs has increased markedly over the years, which is for a large part due to the significant contribution of clinical pharmacologists and to a lesser degree clinical pharmacists. Pharmacoepidemiology has been the main forum for the theoretical underpinning of the importance of databases in which international organisations like the International Society of Pharmacoepidemiology and the International Society of Pharmacovigilance have played a major role. Noteworthy in this context is that in a number of countries, among which the Netherlands, toxicology and teratology, both essential fields for effective drug safety monitoring, have evolved separately from pharmacovigilance and have remained independent from the ADR surveillance systems.

Advances in pharmacovigilance are made at a fast pace and concern both the delineation of its field of knowledge and methodologies as well as their practical implementation. Especially with respect to the applications of related disciplines
such as clinical pharmacology, (pharmaco)epidemiology, toxicology and teratology, areas like pharmacy and health sciences are increasingly gaining in influence.

Issues likely to determine pharmacovigilance in the immediate future are:
- Increasing the volume and enhancing the quality of ADR reports
- The role of computerisation
- Prospective planning
- Applying new knowledge

These issues will be discussed in the next sections.

**Increasing the volume and enhancing the quality of ADR reports**

In the light of the arguments made in Chapter 2.4 in reference to Underreporting we wish to stress once again that, especially in countries in which the pharmacovigilance system has been firmly rooted, inviting more reports is not the ultimate goal. What is important is to gather a sufficient amount of qualitatively sound signals that will allow a reliable surveillance of the safety of drugs. A part from a continuous monitoring of all marketed drugs it is essential to obtain information on the possible risks of newly marketed drugs during normal use as quickly as possible. In our description of Intensive Monitoring (Chapter 4.1) we outlined a practical method that, by making use of pharmacists’ computerised systems, may provide a fast and accurate first impression of prescription practices, the indications for which the drug has been prescribed and, if implemented on a larger scale, possible or likely adverse events.

- The role of the National Pharmacovigilance Centre

The thesis by Lindquist shows that, on a global scale, the countries which have operated a SRS for some length of time contribute most to pharmacovigilance. A prerequisite for effective pharmacovigilance is continuity. Potential contributors need to be continuously made aware of the importance of reporting suspected ADRs. Moreover, they need to be (made) familiar with the national reporting system, which implies that systems should not be subjected to continuous changes. National pharmacovigilance centres sometimes underestimate the importance of public relations and the vital role these play in supporting their other activities. Only if the system’s goals and relevance are advocated systematically and over long periods of time it will be possible to raise the number and quality of ADR reports. Rather than promoting the centre itself campaigns should be aimed at raising the awareness of ADRs and stress the relevance of systematic attention for ADRs in the day-to-day practice of physicians and pharmacists.

- Promoting and enhancing ADR reporting

As detailed in Chapter 3.2 ample research has been conducted into the motives underlying the physician’s and pharmacist’s decision whether or not to report,
if indeed reporting is even considered as an option. Here it is essential to exploit the professional expertise and to link with the scientific interest potential contributors may have.\(^7\) In addition to motivation practical considerations also play an important role.\(^8\) The format of the reporting form should elicit a response and accommodate for easy completion. Alternative ways to report ADRs should also be taken into account. One could, for instance, allow the correspondence between health professionals, detailing the required information, to be submitted. Apart from facilities to report via e-mail and websites, the computer systems of general practitioners, pharmacists and hospitals can be supplemented with an electronic report module. Implementation, however, may pose problems. The Netherlands Pharmacovigilance Centre Lareb has had ample experience with such integrated modules and found that particularly the lack of uniformity in hospital systems proved a major obstacle. Still, both in terms of volume and quality of ADR reports as well as in terms of efficiency the system looks promising.

- Reporting by patients

In Chapter 4.3 on Consumer Reporting we discussed direct reporting by patients. Although at international level the merits of patient reports are being considered, to date the literature does not yet provide any actual results in relation to the detecting of adverse drug reactions. Patient interest in the safety aspects of drugs is great as the reactions to the side effects of Diethylstilbestrol (DES) and the discussions about negative experiences with benzodiazepines and antidepressants have shown. The Netherlands Pharmacovigilance Centre Lareb has recently added a special page to its website, inviting patients who prefer to do so to report their suspicions of adverse reactions direct to Lareb (www.meldpuntbijwerkingen.nl). However, this does require them to provide full details to allow Lareb to make a well-founded evaluation of the relationship between the suspected ADR and the drug mentioned. Patients are also requested to send in (post-paid) a signed print-out of their report, giving Lareb their consent to make further enquiries with their doctor(s) or pharmacist, if necessary. This pilot project is aimed at exploring, by assessing their quality, whether patient reports may indeed add to the existing knowledge of ADRs or may help to accelerate the detection process. Since also direct patient reporting pharmacovigilance is about enhancing the existing knowledge, other objectives such as patient empowerment fall outside the scope of pharmacovigilance.

- Feedback

The parties that have submitted the report, which, at present, usually concerns a doctor or pharmacist, also need to be informed that the report has been duly considered and should therefore be supplied with a prompt and expert assessment. This feedback also functions as éducation permanente for the sender. By no means
all reports lead to new ADR signals, nor is it possible to indicate precisely what type of reports will actually add to our knowledge. Sometimes it takes years before an unsubstantiated suspicion is corroborated. This is why all reports need to be taken seriously and why it is essential that the information they contain is documented properly. It is recommended to also inform those who have contributed to the detection of a new signal by submitting their report, for instance by sending them the publication, in which their information is used for such. New ways to communicate feedback and disseminate new information should be considered, e.g. via the Internet. During a debate in the European Parliament on the future of pharmacovigilance in Europe it has been stressed to make the collective data more accessible to the public. In a recent report the Heads of Agencies of the EMEA (European Medicines Evaluation Agency) have also expressed the desirability of a 'dialogue with reporters'.(9) Thus, any findings regarding the safety of drugs should be made accessible not only for those whose efforts have contributed to the detection of the signal but for all interested parties, including the users of drugs. In practice this implies that the data that are made available on the Internet should inform the public of the incidence of specific adverse reactions in such a way that their correct interpretation does not require any knowledge of the principles of causality assessment and statistics. Both at national and European level steps towards achieving this new information platform are being taken.

**The role of computerisation in pharmacovigilance**

It takes more than scientific expertise and ambition to make pharmacovigilance effective. Several preconditions, mainly at the managerial level, need to be fulfilled.(10) This includes an automation system that is constantly refined and kept up to date.

From its start pharmacovigilance has set great store by the use of computers. As early as 1972 it was stated that ‘adequate computer facilities are essential if a national monitoring centre is to reach full development’.(11) A number of applications that were first recommended 30 years ago, among which ‘rapid file retrieval for signalling potential new drug hazards’ and storage of first and follow-up reports, are still highly relevant today. Techniques for statistical analyses, specifically in relation to user rates, were proposed and the importance of international compatibility and standardisation of terminology stressed. Possibly, the advances in the field of automation are not as swift as often supposed. Next, some applications of advanced ICT technologies in pharmacovigilance will be discussed in brief.
- Quantitative signal detection
A promising technique to find new signals in large datasets that do not come to light in a case-by-case analysis is to look for the disproportionality of ADRs in relation to drugs. The size of today’s datasets and the periods covered now also allow us to find drug-drug interactions and associations between ADRs. Various statistical methods can be applied for this purpose. The Netherlands Pharmacovigilance Centre Lareb uses one of these methods in their weekly assessment meetings.

- Eudravigilance
The EMEA has given priority to drug safety for which setting up its own database of ADR reports, known as Eudravigilance, is seen as vital. Expectations are high since such a Eudravigilance environment will offer many advantages and will provide structure to the exchange of reports between EU member states. Nevertheless, the database is no more than a collection of reports and as such does not provide the much needed answers to the problems surrounding the detection of ADRs and the communication facilities that are required once an ADR has been discerned. Human intelligence, creativity and particularly expertise are indispensable to formulate the right questions and to evaluate likely solutions adequately. It is essential to always return to the individual cases on which the statistical findings are based.

And finally, it should be noted that the Eudravigilance databank is a subset of the WHO databank and consequently the sum total of national databanks and it questionable how much new information will come out of it. Promoting and collecting ADR reports and the analysis of the data and subsequent signal generation will always remain a task to be conducted at the national level.

- The use of health-care computer systems
Increasingly, use is made of the information contained in the various databanks of the national health care systems. An example is the GPRD (General Practitioners Research Database) in the UK, now managed by the Medicines Evaluation Agency, which is frequently consulted for information relating to the safety of a particular drug. In the Netherlands there are several databases available for epidemiological research, as there are PHARMO (Utrecht), IPCI (Rotterdam) and the InterActie Database (Groningen).

It is recommended that national pharmacovigilance centres promote the integration of report modules in the computer systems operated by general practitioners, pharmacists and hospitals. In this way it will be possible to link the data of these various systems to a suspected ADR and to pass the combined data to the pharmacovigilance centre.
Prospective surveillance and risk management

The raison d’être of a Post Marketing Surveillance System is the fact that the clinical pre-marketing trials of a drug generate a limited amount of information about the drug’s associated risks. Most of these findings are included in the Summary of Product Characterisation (SPC). However, there is safety information that does not make it to the SPC, even though it may be relevant for pharmacovigilance purposes. Until recently, access to this type of information was limited and at best the data are included in the application dossier that is submitted to the regulatory authorities, which file is also not accessible for the general public. Today, the pharmaceutical company (i.e. the Marketing Authorisation Holder) that seeks approval of a new product is required to also submit a ‘pharmacovigilance specification’ indicating potential risks. This enables the regulators to specify additional conditions for the drug’s surveillance, which generally entails targeted epidemiological research. Drug-safety monitoring methods such as the spontaneous reporting system employed in pharmacovigilance may also devote extra attention to these potential risks. It is recommended to involve (post-marketing) pharmacovigilance experts in the pre-marketing risk assessments. This pro-active surveillance is part of a new approach in pharmacovigilance also referred to as ‘Risk Management Strategy’. The drug development process must incorporate early thinking and planning for risk management, integrating risk management into the early stages of the product lifecycle, beginning well before launch.

Both in the USA and in Europe steps have been taken to formulate a concrete risk management policy. The International Commission on Harmonisation (ICH) has also announced plans for the development of a guideline on ‘prospective planning of pharmacovigilance’. Europe seems to lead the pack in realising the proposed plans. Here, risk management is defined as ‘the identification and implementation of strategies to reduce risk to individuals and populations’. The basic idea is that for each product, starting with new products for which marketing approval has been applied, a product risk management plan is to be drawn up and submitted. Table 1 lists the elements such a plan needs to cover.

We do need to prevent regulations like these from causing bureaucratic red tape: their aim should be the identification of potential risks and any subsequent measures and not meeting regulations, as is now sometime the case, for instance with the obligation to sent in serious reports within 15 days.

Implementation of new knowledge

In the Introduction a circle was used to represent what pharmacovigilance is all about. In the past the emphasis was mainly on deriving knowledge from the
experiences made in the clinical practice. However, implementing this new information, i.e. applying the acquired knowledge in practical situations allowing the individual patient to benefit from these new developments, is equally important. In Chapter 4.4 on Labelling it is concluded that we fall short in this respect. Practical measures are mostly restricted to scientific publications whose impact on the daily practice or regulation is often not immediate, and frequently merely leads to a moderation of the content of the Summary of Product Characteristics (SPC) or the distribution of a ‘Dear Doctor letter’. In the more serious cases the marketing authorisation for the drug involved will be withdrawn. This latter measure was taken relatively frequently in the past decade, which has prompted a debate on whether the decisions were always justified.(22) Medication that may constitute a risk for a particular population might be the appropriate treatment for other groups. There have been cases where drugs were taken off the market because warnings were not issued or precautionary measures were not taken.(23,24) Because the regulatory authorities cannot afford to take risks, in a number of such cases it was decided to withdraw the marketing authorisation.

To change these practices will require much effort. The development of new activities like prospective pharmacovigilance and risk management as mentioned in the previous section are the first expressions of such a change. However, it is essential to not only assess a drug in terms of its risks but also in terms of its merits. In other words: one should balance the drug’s intrinsic value per case against its likely harmful effects, preferably also at an individual level. This will lead to a more thorough assessment of the risks involved than when evaluations are merely based on numbers and averages.(25) The criticism that has been levelled at drug approval agencies like the FDA in the USA and the MCA in the UK in recent years shows that this is no easy matter. Chapter 4.4 (‘Labelling’) also provided a number of possible solutions to help change the perception of adverse drug reactions. The aim is to enhance the knowledge doctors, pharmacists and consumers, as well as those representing the consumer at a political level, have of drugs, both with respect to medical-pharmaceutical aspects and risk perception. The training programmes for medical students and pharmacists should devote more space to pharmacovigilance. And, as indicated above, existing knowledge should be enhanced and made more easily accessible for all parties concerned. Only then will we be able to translate what we know into practical applications and will drugs be prescribed at a more individual basis than is common today. It is the task of pharmacovigilance to supply the building blocks, making use of both established and new scientific areas, possibly with pharmacogenetics in a prominent role.
Chapter 5.2

Independent pharmacovigilance

This thesis has been written within the setting of the Netherlands Pharmacovigilance Centre Lareb, which is no coincidence because Lareb offers both the practical and scientific environment within which applied pharmacovigilance research can flourish.

The precondition that such an environment should be impartial is fulfilled since Lareb is an independently operating foundation. Its activities, though commissioned and funded by the national government and does its task on behalf of the Dutch Medicines Evaluation Board, are controlled by a board whose members all belong to medical organisations and pharmacists' and patients' associations. It is therefore not surprising that the theme of the 2001 conference celebrating Lareb’s 10th anniversary was ‘independent pharmacovigilance’.

In her thesis Lindquist remarks that pharmacovigilance is especially effective in countries where its centres have been in existence longer. The second key factor to success proved to be their independence. It is striking that particularly in countries where the pharmacovigilance systems are essentially autonomous the centres make the most significant contributions. Besides Lareb, this is illustrated by the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and other independent institutes like the WHO’s Uppsala Monitoring Centre and the Drug Safety Research Unit (DSRU) in Southampton, England.

A pharmacovigilance centre has dealings with various bodies and organisations.

Next, we will take a closer look at some of the main parties.

- The national government
It was the legislation which the various national governments adopted in the second half of the previous century that provided the framework for the development of pharmacovigilance. Within the context of public health care the authorities are responsible for the surveillance of the efficacy, safety and quality of drugs. Since the 1960s the national and international rules have been further refined and criteria and procedures have been carefully formulated. For the main part the guidelines for regulatory pharmacovigilance were drawn up by the CIOMS and ICH in which the major industrialised countries and governments participate.

However, there is the risk of over-regulation: compliance with such a multitude of rules and regulations may require so much time and effort that one may lose sight of the original aims and objectives. For instance, pharmaceutical companies are
required to report serious adverse events that have come to their attention within a 15-day limit. This is so short that much of their efforts are spent on achieving these statutory perimeters, which sometimes goes at the cost of the report's actual content. Also this matter clearly needs to be looked into.

With respect to the, ideally, independent position of pharmacovigilance another aspect concerning the role of the authorities needs mentioning. The government has many tasks, and these include policies on medicinal drugs. Among other issues, drug approval, reimbursement of medication-related costs and economic aspects fall under their responsibilities. Seen against this background it is crucial for pharmacovigilance to have a fair degree of autonomy to ensure that the collection and analysis of ADR reports and the dissemination of the knowledge attained does not suffer too much from government interference. Of course it is the responsibility of the national authorities, i.e. the Health Inspectorate, to oversee the quality of the pharmacovigilance activities.

- The pharmaceutical industry

Medicinal drugs, pharmacovigilance's object of study, are the products of the efforts of the pharmaceutical industry. As indicated earlier, basically, for the larger part of their 'life cycle' drugs are an economic product and pharmaceutical companies are quite influential when it comes to the therapeutic chain.(29) Also in relation to the monitoring of product safety, the companies have their own responsibilities, both with regard to the health and ethical aspects of their activities as well as the commercial and legal implications. The sector has increased its efforts and expanded their pharmacovigilance activities. This is partly in response to new and more stringent rules and the increased supervision on their implementation, and partly due to the fact that the number of new chemical entities that the sector releases has become smaller, offering the industry more scope to monitor their marketed products more closely.

The methods employed to gather reports on ADRs differ per country. In a number of countries, among which the USA, Germany and Sweden, the majority of the reports the national pharmacovigilance centres receives stem from the pharmaceutical industry. In most other countries this is less common and here most reports are sent in by doctors and pharmacists. Generally, this is the favoured system, provided that there is an adequate exchange of information between the centres and the industry. There are no grounds why doctors, pharmacists or patients should report their observations to the pharmaceutical companies and have them pass on the reports to the national centres. Direct reporting is faster and affords the national pharmacovigilance centre the opportunity to contact the sender to obtain any additional information it may need. Moreover, the reports the industry submits tend to be of inferior quality compared to those of doctors and
pharmacists. (30) Having several routes may also be confusing for potential contributors.

- Universities
  The field of pharmacovigilance is associated with several academic disciplines, more specifically clinical pharmacology, clinical pharmacy and pharmacoepidemiology as part of the medical and pharmacy faculties. Pharmacovigilance may be seen as an independent science with its own paradigm, methodology, rationale and history. As yet there are no separate chairs for pharmacovigilance where an integrated approach to the questions surrounding drug safety can be developed on the basis of this paradigm. (31) In some countries, for instance France and Italy, academic centres do, however, fulfil the role of regional reporting systems.

- Professional groups and patients
  The safety of drugs and more specifically their adverse effects are of equal concern to physicians, pharmacists and nurses - in their professional capacity - and patients. The doctor decides on the type of drug to be used, involving the pharmacist and nursing staff each in their own capacity. (32,33) The patient is the one who uses the drug. Thus, all parties have a direct involvement in the care provided and are not concerned with the commercial aspects of the medication. Their professional and personal interest in the care aspect of drugs and their direct involvement in their use make health professionals and patients the most likely people to exercise responsibility for the practical implementation of drug safety surveillance.
  In between all these parties pharmacovigilance needs its own independent place.
Chapter 5.3
The role of the pharmacist

It was the role the pharmacist plays or should play in pharmacovigilance that sparked the present thesis. In several chapters the various aspects of this role were discussed in detail. As was concluded in Chapter 3.1, pharmacists indeed have a prominent role to play with respect to knowledge as well as attitude and commitment, and their contribution is already substantial in many countries.

It is recommended to increase their participation especially in those countries where they are not authorised to report or where their contribution is limited. In several countries, specifically in the Scandinavian countries, this means that pharmacists need to be acknowledged as independent reporters of ADRs. In other countries the formal acknowledgment needs to be followed up by measures to enhance their actual participation. Modifications of the pharmacy curriculum are required as well as changes in the interpretation of the pharmacist's scope of duties. The attitude doctor's take towards the profession is also in need of change. As Wade wrote in 1970: 'Doctors should learn to make use of the pharmacist's knowledge and skills'.

The rationale for founding Lareb was the idea that the pharmacist might fulfil a coordinating role in the detection of ADRs and that the collaboration between doctors and pharmacists would significantly enhance pharmacotherapy. General practitioners and community pharmacists have already made considerable headway towards intensifying their collaboration.

In Chapter 3.3 we showed that the pharmacists' share in the total number of reports Lareb received during a period of five years was substantial, as was their qualitative contribution. The pharmacist reports, in the Netherlands chiefly originating from community pharmacists, have their own specific characteristics, which makes them a valuable addition to the reports received from physicians. When we look at the way the pharmacists perceive their role in ADR reporting, as was done in Chapter 3.2 we find that they are not only highly motivated but also consider it an integral part of their professional duties. In Chapter 3.1, an overview covering a large number of countries participating in the WHO International Drug Monitoring Programmes demonstrated that the quantitative contribution pharmacists make to the national systems is small. Clearly, on a global scale major improvements can be made and the extent of ADR underreporting can be considerably reduced by actively involving pharmacists in the surveillance of drug safety within the context of the pharmaceutical care they provide. That their contribution can indeed be crucial was illustrated in Chapter 3.4 by an article on Yasmin®. Here a well-
documented report that a community pharmacist had submitted led to an important message for prescribers and others parties concerned.

- Hospital pharmacists in the Netherlands lagging behind
In the Netherlands, and possibly in many other countries as well, a great deal remains to be done at the hospital level. The volume of reports from Dutch hospitals is relatively low.(35) Hospital pharmacists, who often take a keen interest in the scientific aspects of their profession, could exert their influence when it comes to raising awareness of ADRs within the context of patient care. Particularly in complicated circumstances their expertise is insufficiently put to use. Exploitation of their know-how and experience could prevent much harm. They could also contribute to ADR reporting in a coordinating capacity, as is the case in the US and Canada.(36,37) However, the status of the hospital pharmacist as an expert and co-consultant in pharmacotherapy needs to be acknowledged first. It is recommended to incorporate this task description in the regulations, e.g. the policies regarding quality control, that oblige hospitals to provide good quality ADR reporting procedures. The medical insurance providers in the US and the association of hospital pharmacists in Canada have made this a precondition. In the Netherlands the first steps have been taken to draw up such a task description for the hospital pharmacist but it will still take quite some time before a structured or even mandatory plan will become effective.(38)

- The contribution of pharmaceutical sciences to pharmacovigilance
The contribution of the pharmacist, or rather pharmacy, to pharmacovigilance should not be limited to the above-mentioned aspects. The various pharmaceutical disciplines could also greatly enhance our understanding of the nature of adverse drug reactions. For the detection and assessment of possible ADRs pharmacokinetics, pharmacodynamics, and knowledge of chemical relations are often indispensable. However, within these fields adverse reactions to drugs have not received systematic attention and their contribution to pharmacovigilance is consequently still rather limited. Here, again, there is room for improvement both with respect to the proactive and passive surveillance of ADRs. If those involved in pharmacy can rise to this challenge, they will significantly help deepen our insights and widen the scope of pharmacovigilance.
Chapter 5.4

Pharmacovigilance as a scientific discipline

In the Introduction part of this thesis an attempt was made to define pharmacovigilance as a scientific domain in its own right with its own specific methodology. As its core tasks we have mentioned deriving knowledge from the clinical practice and the subsequent development of techniques to implement this new information. In the last few years much has been achieved as far as the first task is concerned. Chapters 2.1 and 2.2 were dedicated to the history of pharmacovigilance. In Chapter 4.4 we have listed the many items that are still on the agenda with regard how to implement the second task.

In this section we will elaborate this latter issue as well as the contributions Lareb has made in further delineating the science of pharmacovigilance. Starting from two concepts, i.e. the importance of case studies and a positive view on the risk aspect of drugs, we will catalogue several facets that need to be attended in order to advance pharmacovigilance as a scientific discipline.

- The contribution of the Netherlands Pharmacovigilance Centre Lareb

The Netherlands Pharmacovigilance Centre Lareb, formerly known as the Netherlands Pharmacovigilance Foundation Lareb, has made significant contributions to the development of pharmacovigilance. To illustrate this we would like to specifically mention four dissertations. In 1994 G.H.P. de Koning received his PhD for his thesis on the development of a regional reporting system founded on the collaboration of pharmacists and general practitioners and aimed at supporting pharmacotherapeutic interventions. In 1997 A.C.G. Egberts published his combined studies on the sources, detection and interpretations of signals, based on his findings on antidepressants. Also R.H.B. Meyboom, who describes the Dutch contributions to pharmacovigilance, has had significant impact especially on the theoretical underpinnings of pharmacovigilance. He writes: ‘This thesis aims at increasing our understanding of the scientific basis of pharmacovigilance’. His work has indeed fostered the development of the models for signal detection, causality assessment and Good Pharmacovigilance Practice. In his thesis published in 2001, E.P. van Puijenbroek describes various methods for the detection of quantitative signals in extensive ADR databanks that can be applied for the detection of adverse drug reactions as well as drug-drug interactions and syndromes, i.e. an aggregate of associated symptoms resulting from the use of drugs.
Pharmacovigilance's distinguishing features

The characteristics that distinguish pharmacovigilance from other fields deserve special mentioning. In Chapter 2.4 it was demonstrated how a specific pharmacovigilance-based approach can prevent ambiguity, as was illustrated by the various interpretations given to the term underreporting.

Two aspects of drug safety that warrant a special pharmacovigilance-based approach in the near future are research on the basis of cases and the risks associated with drugs.

- The individual case as the foundation for pharmacovigilance

The first aspect concerns the significance of the individual case. The fact that a tragedy of enormous proportions lay at the root of the advent of pharmacovigilance and that surveillance of drug safety was primarily seen as a matter of public health may have caused the epidemiological side of pharmacovigilance to be given priority. Also the fact that regulatory authorities prefer to base their decisions on numbers like incidence rates, and their decisions always affect large patient groups or even the entire population, may have played a role here. And more recently, the potential impact of automated data processing and the systematic analysis of large datasets on drug safety monitoring has raised the expectations for this aspect even further. Nevertheless, ultimately it will always be the individual, the single case that lies at the heart of pharmacovigilance. It was Claude Bernard who stated that there was no such thing as the average patient.(42) Whether the aim is tracing new adverse effects or finding practical applications for the newly acquired knowledge, it is the individual patient that should be the subject of attention. In ADR detection averages and anonymous data covering larger samples could never be the foundation on which conclusions are based. Rather, on the basis of individual cases it needs to be assessed whether the data on which conclusions are drawn are correct.(43)

The same principle applies to the implementation of new insights: although decisions may be right for the average population, they may be less favourable for the individual patient or smaller categories of patients. When drugs that may be of therapeutic value for particular patient groups are taken off the market too quickly this may cause unnecessary harm. Methods need to be developed to prevent this. Paradoxically, the drug that best illustrates this need is thalidomide, the very drug that shook the foundations of the pharmaceutical world, as was described in Chapter 2.1, has nowadays find a new place in pharmaceutical therapy.(44,45,46)

Innovations should not only include such areas as education, communication and legislation, but possibly also the field of pharmacogenetics and pharmacotherapy ethics.
- The risk aspect of drugs

It is an old axiom that says that basically each drug is a poison and that it is the dose that predominantly determines its therapeutic effect. Despite the many benefits the pharmacotherapeutic innovations have brought in the previous century, the fundamental attitude towards drugs has been one of scepticism, which seems to have become more pronounced in the last few years. In their ‘future model of pharmacovigilance’ Waller and Evans have proposed that, rather than trying to identify risks, pharmacovigilance’s central theme should be about demonstrating safety. (31) Although it seems as if they were merely toying with two sides of the same coin, there is more to it than that. The authors stress that, based on a prospective approach we first need to gain insight into the level of safety that has already been demonstrated, before we investigate any possible concerns. Thus, their model provides a better idea of a drug’s safety on which its application in the clinical practice can be based. This model does imply that doctors need to be cautious when prescribing new drugs. (47) The benchmark should be the drugs proven safety rather than it’s proven risks! It is strange that we give a new drug the benefit of the doubt based on relatively few hard facts and start experimenting with it in the real world. The reverse approach, i.e. to balance the expected health benefits of a drug we wish to prescribe against the available data on its safety, seems far more rational. If little is known about the safety of a newly marketed drug, the risk will often be considered too high (and will thus become too much of a gamble), which will tip the balance in favour of a more established treatment for which more evidence is available and whose safety records are wellocumented. It needs to be noted that this model is already applied for the unborn child in the risk assessments of drugs used by the mother.

In the coming years it will be pharmacovigilance’s main challenge to further define and refine its mission, its paradigm, its methodology and the implementation of knowledge in both the clinical and pharmaceutical practice.
References


