Hazards of Drug Therapy

On the Management of Adverse Drug Reactions: From Signal Detection and Evaluation to Risk Minimization

KARIN HEDENMALM
Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Ingång 50, Uppsala, Friday, September 16, 2005 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Spontaneous reporting systems (SRSs) for adverse drug reactions (ADRs) have been developed as a result of the thalidomide disaster, whereby thousands of children world-wide were born with birth defects. The Swedish Adverse Drug Reactions Advisory Committee was established in 1965. Since 1975, reporting has been compulsory for all suspected serious or new ADRs. International collaboration started in 1968 with countries contributing their ADR reports to an international database set up by the World Health Organization.

ADRs represent the negative side of the benefit-to-risk balance that in theory needs to be counteracted by perceived or established positive drug effects. All drugs are subject to preclinical and clinical testing prior to marketing authorization. However, these studies are insufficient to detect rare ADRs, ADRs that occur after long-term administration or with latency. ADRs that occur in special patient groups such as children, the elderly, patients with renal or hepatic insufficiency or patients on concomitant drug treatment, and ADRs that represent a modest increase in the risk of diseases (including mortality) that are prevalent in the study population. Postmarketing surveillance of drugs is therefore essential, and regulatory action may be needed on the basis of new ADR information.

SRSs are important sources of ADR information as exemplified here by the evaluation of peripheral sensory disturbances with fluoroquinolones, hypotension with antidepressants, blood dyscrasias with dipyrone, glucose intolerance with atypical antipsychotics, pulmonary embolism with combined oral contraceptives and extrapyramidal symptoms with selective serotonin reuptake inhibitors. SRSs can be used to study clinical manifestations of ADRs (that can give insights into potential ADR mechanisms), risk factors for the ADR or for specific outcomes of the ADR, and ADR reporting incidences when combined with sales data. Signals from SRSs may need to be studied further e.g., by use of large-scale epidemiologic studies based on record linkage between drug prescription databases and health databases. Owing to the rapid availability of information, however, SRSs are likely to remain of major importance for the post-marketing surveillance of drugs.

Keywords: adverse drug reactions, spontaneous reporting systems, drug regulation, pharmacovigilance, incidence

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urn:nbn:se:uu:diva-5866 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-5866)
To my parents. To
Marko, Victoria, Astrid
and Eric
List of Papers


VI. Hedenmalm K, Yue QY, Dahl M-L, Spigset O. Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme and serotonin and dopamine transporter and receptor mutations. Manuscript in preparation.
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<tr>
<td>ACE</td>
<td>Angiotensin Converting Enzyme</td>
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<tr>
<td>ADH</td>
<td>Anti-Diuretic Hormone</td>
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<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ALAT</td>
<td>Alanine-Aminotransferase</td>
</tr>
<tr>
<td>APC</td>
<td>Antigen Presenting Cell</td>
</tr>
<tr>
<td>ASAT</td>
<td>Aspartate-Aminotransferase</td>
</tr>
<tr>
<td>BCPNN</td>
<td>Bayesian Confidence Propagation Neural Network</td>
</tr>
<tr>
<td>CD</td>
<td>Cluster of Differentiation molecules on the cell surface</td>
</tr>
<tr>
<td>CD4+</td>
<td>Cells expressing CD4 on the cell surface (T helper cells)</td>
</tr>
<tr>
<td>CD8+</td>
<td>Cells expressing CD8 on the cell surface (cytotoxic T cells)</td>
</tr>
<tr>
<td>CI</td>
<td>Cumulative Incidence</td>
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<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>COC</td>
<td>Combined Oral Contraceptive</td>
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<tr>
<td>COX</td>
<td>Cyclo-Oxygenase</td>
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<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medicinal Products</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P-450</td>
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<tr>
<td>DAT1</td>
<td>Dopamine Transporter gene</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>DES</td>
<td>Diethylstilbestrol</td>
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<tr>
<td>DNA</td>
<td>Dioxiribonucleic Acid</td>
</tr>
<tr>
<td>DRD2</td>
<td>Dopamine D2-receptor gene</td>
</tr>
<tr>
<td>DRD3</td>
<td>Dopamine D3-receptor gene</td>
</tr>
<tr>
<td>EF</td>
<td>Etiologic Fraction</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries Association</td>
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<tr>
<td>EFTA</td>
<td>European Free Trade Area</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<td>EPS</td>
<td>Extra-Pyramidal Symptoms</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>G6PD</td>
<td>Glucose-6-Phosphate Dehydrogenase</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>3-Hydroxy-3-Methylglutaryl Coenzyme A</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostasis Model Assessment for Insulin Resistance</td>
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<tr>
<td>5HTTLPR</td>
<td>5-Hydroxytryptamine Transporter gene Linked</td>
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</tbody>
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Polymorphic Region
IAAA International Agranulocytosis and Aplastic Anemia study
IC Information Component
ICH International Conference of Harmonization
IFPMA International Federation of Pharmaceutical Manufacturers Association
Ig Immunoglobulin
INR International Normalized Ratio
INTDIS International Drug Information System
IR Incidence Rate
JPMA Japan Pharmaceutical Manufacturers Association
MAH Marketing Authorization Holder
MHC Major Histocompatibility Complex
MHW Ministry of Health and Welfare
Msc1 Micrococcus species restriction enzyme
Na+ Natrium (sodium) ion
NADPH Nicotinamide Adenine Dinucleotide Phosphate
NSAID Non-Steroidal Anti-Inflammatory Agent
PAHA Procaine-Amide Hydroxyl-Amine
PhRMA Pharmaceutical Research and Manufacturers of America
PSD Peripheral Sensory Disturbance
PSUR Periodic Safety Update Report
RFLP Restriction Fragment Length Polymorphism
RR Relative Risk
RYR1 Ryanodine Receptor gene
SG Glucose Sensitivity = insulin-independent glucose uptake
SADRAC Swedish Adverse Drug Reactions Advisory Committee
SI Insulin Sensitivity
SIADH Syndrome of Inappropriate ADH secretion
SSRI Selective Serotonin Reuptake Inhibitor
SWEDIS Swedish Drug Information System
Taq1A Thermus aquaticus restriction enzyme
Th1 T helper cell type 1
Th2 T helper cell type 2
VNTR Variable Number of Tandem Repeat polymorphism
VTE Venous Thrombo-Embolism
WHO World Health Organization
UNESCO United Nations Educational Scientific and Cultural Organization
Introduction

One of the oldest principles in practicing medicine is the one of not introducing harm to the patient, *Primum Non Nocere Est*. However, in pharmacotherapy this is not a realistic goal as no pharmaceutical agent is completely free from harmful effects. Therefore, the goal must be to minimize risk.

The aims of this thesis are:

- to give an overview of the development of regulatory systems for the management of adverse drug reactions (ADRs)
- to discuss examples of ADRs and their mechanisms
- to discuss how to evaluate and quantify ADRs
- to discuss management and the concept of risk minimization of ADRs from a regulatory perspective

All publications included in the thesis are studies of different ADRs in spontaneous reporting systems that mainly address questions of how to evaluate and quantify ADRs. One of the publications in the thesis also concerns the withdrawal of a pharmaceutical agent in Sweden.
Short historical background of three drug disasters of major importance

Two major drug disasters, thalidomide and diethylstilbestrol, have played a key role for the awareness of ADRs as a real threat and the resulting development of drug regulation safety requirements. A third more recent example of a major drug disaster is exemplified here by the lipid-lowering drug cerivastatin.

Thalidomide
Thalidomide was first approved as a non-barbiturate hypnotic agent in 1956 in Germany, advocated to ensure a good nights sleep and to prevent morning sickness in pregnancy. It was thought to be a comparatively safe drug.

Subsequently, thalidomide was approved in several additional countries. A publication appeared in 1961, where a physician from New Zealand noted among his patients that 20% of women who had ingested thalidomide during pregnancy gave birth to babies with skeletal malformations such as polydactyly, syndactly and abnormally short long bones (1). An editorial comment published along with the paper declared that a previous issue of the journal had included a statement from the manufacturer referring to reports from two overseas sources possibly relating thalidomide to harmful effects on the fetus in early pregnancy.

The association between thalidomide and phocomelia, a very rare form of limb reduction, was later established by epidemiological studies. Worldwide, it has been estimated that thousands of children have been affected (2). First trimester exposure was found to carry a risk of around 10-50% (2).

Because of this high risk, thalidomide was withdrawn from the market in 1962-1963. Animal reproductive studies have shown that single doses are sufficient to induce teratogenic effects (3;4). Interestingly, different animal species show varying sensitivity to the teratogenic effects of thalidomide; rats are relatively insensitive to its effects. This has led to a regulatory demand that teratogenic effects should be tested not only in rodents but also in non-rodents.

Diethylstilbestrol
The first publication of an association between diethylstilbestrol (DES), a synthetic estrogen, and the emergence of clear cell carcinoma, an adenocarcinoma, of the vagina in young women exposed to the agent in utero, appeared in 1971 (5). DES had been used in early pregnancy to prevent spontaneous abortion in 7 out of 8 cases with clear cell carcinoma compared with none out of 32 matched controls (p<0.0001). This is the first
time that developmental exposure to estrogens has been associated with an increase in a human cancer.

Vaginal adenosis was seen in about 90% of vaginal and 30% of the cervical adenocarcinomas associated with DES exposure (6). The reported occurrence of adenosis in DES exposed offspring varied from 30 to 90% (6). Gross cervicovaginal abnormalities also appeared in about 20% of the exposed patients (6).

As with thalidomide, the identification of an increased risk of clear cell carcinoma with DES relied upon epidemiological studies. In this case, a large increase in relative risk made it possible to detect a relatively small increase in absolute risk. It was estimated that only about one case of clear cell carcinoma occurred in every 1000 exposed women (7).

The affected women were 7 to 34 years of age with most cases between 14 and 22 years of age (7). Possible risk factors included maternal history of prior miscarriage, early gestational exposure, a fall season of birth, and prematurity. The sensitive period of exposure appeared to be before pregnancy week 18 (6).

The long delay between the use of DES and the occurrence of clear cell carcinoma illustrates the need for constant post-marketing surveillance of drugs.

In Sweden, DES was not marketed for use in pregnant women, and there was no indication that such use had taken place. DES-containing products were not withdrawn from the Swedish market until 1980.

Cerivastatin

Cerivastatin, a potent HMG-CoA-reductase inhibitor, was first authorized in 1997 for the treatment of hypercholesterolemia. HMG-CoA-reductase inhibitors, also known as statins, reduce the production of cholesterol. The first statins were approved in the late 1980s.

All statins have been associated with serious muscle toxicity including rhabdomyolysis in rare cases (8). The occurrence of muscle toxicity is known to be dose dependent. Its cause is unknown, but there have been numerous speculations including e.g. reduced production of isoprenoids such as ubiquinone or regulatory proteins (8-10), and increased release of intracellular calcium in muscle cells (11).

In August 2001, the Marketing Authorization Holder (MAH) of cerivastatin withdrew the drug from the market world-wide due to reports of rhabdomyolysis including over 100 deaths (12). These fatalities and the cases of severe ADRs have caused about 10 000 litigations, many of which have not yet been settled.

Subsequent analyses have shown that reporting of rhabdomyolysis including fatal cases was comparatively higher with cerivastatin than with the other statins available during the same period of time (8;13;14) despite
the fact that cerivastatin did not provide additional efficacy (15). Furthermore, gemfibrozil was shown to interact with cerivastatin to a greater extent than with the other statins resulting in markedly elevated cerivastatin concentrations during combination therapy (8).

The reasons for the apparently increased myotoxicity with cerivastatin monotherapy in seemingly equipotent doses in comparison with other statins are unknown.

It is generally unknown if myotoxic effects of statins are due to inhibition of HMG-CoA-reductase or due to some other effect of the drug molecule. The different metabolic pathways of statins have also not been fully characterized, and it is not well understood how these drugs enter and exit muscle cells, i.e. through passive diffusion or active transport mechanisms, and whether or not they bind to specific muscle proteins. A better understanding of these different factors is needed to more accurately predict the risk of rhabdomyolysis with both older and newer statins.

The rapid world-wide withdrawal of cerivastatin prompted a review of its safety profile compared with other statins marketed in the European Union (CPMP/811/02). The review concluded that:

The efficacy of cerivastatin is comparable to that of other statins.

There is a safety concern regarding the risk of rhabdomyolysis.

The risk of rhabdomyolysis is substantially increased during concomitant treatment with gemfibrozil or clopidogrel; these interactions could not be foreseen on the basis of the known metabolic profiles of the drugs.

The difficulty to predict and consequently to warn against other drugs which may interact with cerivastatin poses a continuous risk.

The risk benefit balance is negative.

I consider these disasters to be of major importance, notwithstanding that other accidents have also contributed to the development of pharmacovigilance world-wide.
Drug regulation: Requirement of efficacy and acceptable safety

The development of drug regulation over time differs between countries and regions. The industrial revolution, which brought about large-scale production of drugs, made it necessary to introduce laws to regulate their use. One important landmark in this area is the requirement for all medicinal products to be registered, thereby making the control of impurities and appropriate labeling possible. Another is the requirement for pre-licensing toxicological and human studies.

International efforts that have been undertaken for harmonization include the Council for International Organizations of Medical Sciences (CIOMS) initiative in the early 1980s, and establishment of the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) in 1990. These efforts have led to increased harmonization and transparency in the drug approval process and handling of drug safety/pharmacovigilance issues worldwide.

CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. The CIOMS working groups on drug development and use consist of representatives from both regulatory authorities and drug manufacturers. The recommendations from six CIOMS working groups dealing with assessment and monitoring of ADRs have been published, see Table 1.

The ICH was established as a joint initiative between regulatory agencies and the research-based pharmaceutical industry in Japan, the European Union and the United States of America. The main purpose of ICH has been to eliminate duplication of work and procedures caused by different regulatory requirements. The regulatory party is the European Commission for Europe, the Food and Drug Administration (FDA) for the USA, and the Ministry of Health and Welfare (MHW) for Japan. The corresponding industry parties in each of the three regions are represented by the European Federation of Pharmaceutical Industries Associations (EFPIA), the Pharmaceutical Research and Manufacturers of America (PhRMA) and Japan Pharmaceutical Manufacturers Association (JPMA). The International Federation of Pharmaceutical Manufacturers Association (IFPMA) ensures contact with the research-based industry outside the ICH regions. The WHO, the European Free Trade Area (EFTA) and Canada are observers.

ICH documents include e.g. the following: 1) ICH E1A Population exposure: The extent of population exposure to assess clinical safety, which for the evaluation of drugs intended for long-term treatment of non-life-threatening diseases suggests that at least 1500 individuals should be treated with the drug for a few months, and at least 100 individuals for a minimum of one year, 2) ICH E2A Clinical safety data management: Definitions and standards for expedited reporting, 3) ICH E2B Clinical safety data

The ICH guidelines are not in themselves regulatory requirements. They have to be adopted and incorporated into local legislation to have such status.

Table 1. Council for International Organizations of Medical Sciences (CIOMS) Working Groups

<table>
<thead>
<tr>
<th>CIOMS Working Group, year</th>
<th>Topic</th>
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<tr>
<td>CIOMS I, 1990</td>
<td>&quot;International Reporting of Adverse Drug Reactions&quot;, which introduced the CIOMS1 international reporting form</td>
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<tr>
<td>CIOMS II, 1992</td>
<td>&quot;International Reporting of Periodic Drug-Safety Update Summaries&quot;, which proposed a standard for periodic safety update reports that served as a basis for the development of the official ICH guideline for such reports</td>
</tr>
<tr>
<td>CIOMS III, 1999</td>
<td>&quot;Guidelines for Preparing Core Clinical-Safety Information on Drugs - Including New Proposals for Investigator's Brochures (second edition)&quot;</td>
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<tr>
<td>CIOMS V, 2001</td>
<td>&quot;Current Challenges in Pharmacovigilance: Pragmatic Approaches&quot;</td>
</tr>
<tr>
<td>CIOMS VI, 2005</td>
<td>“Management of Safety Information from Clinical Trials”</td>
</tr>
<tr>
<td>CIOMS VII</td>
<td>“Developmental Safety Update Report (DSUR)”</td>
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Development of spontaneous reporting systems, WHO initiative, Eudravigilance

The thalidomide disaster gave birth to worldwide initiatives to monitor ADRs. At a World Health Organization (WHO) meeting in May 1962 it was requested that this issue should be investigated. Following recommendations by the WHO Scientific Group in 1964 and requests by the World Health Assembly in the following years, a pilot research project for international monitoring of ADRs was set up in 1968. Ten countries from Australasia, Europe and North America agreed to participate and send their ADR reports to the WHO centre in Alexandria, USA. The centre was moved to WHO headquarters in Geneva in 1970. Since 1978, it is situated in Uppsala, Sweden. As of October 2004, a total of 75 countries contribute to the WHO Program for international drug monitoring, and the database now contains over 3.1 million ADR reports. The way in which the WHO analyzes and communicates this information towards the safer use of drugs has recently been presented in a thesis from the Uppsala Monitoring Centre (16).

National initiatives had led to the setting up of spontaneous reporting systems during the 1960’s and 1970’s in most industrialized countries. Most often the national centre is part of the drug regulatory authority, and reporting by health care professionals is voluntary. In a few countries, however, reporting of suspected serious ADRs is mandatory for certain health care professionals such as physicians and dentists. Some countries also accept reports directly from consumers. Apart from reporting by health care professionals or consumers, the MAHs are obliged to submit ADR reports to regulatory authorities in most countries (cnf ICH E2A and ICH E2D).

The differing nature of spontaneous reporting systems needs to be taken into account when evaluating ADR reports from different sources or from different countries. Differences concern both the quantity (e.g. number of reports per million inhabitants per year), and the quality (e.g. amount of information available in each report) of the reports. The minimum required information in an ADR report is: a) an identifiable patient (e.g. initials, age, sex) b) an identifiable reporter, c) at least one suspected ADR, and d) at least one suspected drug.

Eudravigilance, a common data processing network and database management system for the direct electronic exchange, processing and evaluation of ADR reports related to medicinal products authorized in the European Economic Area, has recently been implemented and will allow for rapid exchange of ADR information within the European Union.
The ‘spontaneous’ reporting system in Sweden

The spontaneous reporting system for ADRs in Sweden was established in 1965. Since 1975, reporting to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) has been compulsory for all suspected new or serious ADRs. SADRAC receives ADR reports from physicians, dentists and nurses. A special reporting form is available, but SADRAC also accepts other forms of documentation. The following information is requested on the reporting form: 1) name, age and sex of the patient, 2) names, dosage forms, treatment dates, doses, and routes of administration of suspected and concomitant drugs, 3) relevant medical history or other background information, 4) a description of the occurrence, seriousness, and outcome of suspected ADRs, and 5) results of possible drug discontinuation/re-introduction. ADR reports are submitted to SADRAC’s regional centers at the Swedish clinical pharmacology departments of the six university hospitals.

Since the start of SADRAC, the annual number of reports has increased to around 2500-3500 in the last 20 years. This is equivalent to 280-390 reports per million inhabitants per year. The annual number of reports is shown in Figure 1. Over 4000 reports were received in 2004. The entire database now contains around 90 000 ADR reports.

Swedish ADR reports are considered to be of high quality. The majority of reports are supported by information from medical records including, when relevant, results from laboratory or other investigations. Care is also taken to obtain and record drug use accurately. All of this information can be critical for a thorough assessment of the ADR and its causal relation to drug treatment. Efforts by regional centers to obtain this information are crucial to the maintenance of high quality reports. Patient identification via unique person-numbers also makes it possible for SADRAC to request follow-up/supplementary information from the reporting physicians as necessary.
Figure 1. Annual number of reports of adverse drug reactions in Sweden between 1965 and 2004
Pharmacovigilance responsibilities of marketing authorization holders

All potential problems with marketed use of drugs cannot be foreseen from the pre-marketing clinical trial experience.

The sample size needed to obtain at least one case of an ADR with 95% probability when the true frequency is 1/N is ≈ 3N (17). Needless to say, this approach is only meaningful for ADRs that can easily be identified as drug-induced. The coefficient 3 arises because the probability of at least one event (as opposed to no event) in the next k*N patients can be approximated by:

\[ P = 1 - e^{-\frac{(1/N)N^k}{k}} \]

which for k = 3 gives 1 - e^3 ≈ 0.95.

A similar rule, the rule of three, states that the upper 95% confidence limit of the frequency of an adverse event that is not observed in a cohort of size N is 3/N or 3/(N+1) (18;19). The first of these formulas is based on binomial or Poisson distributions, whereas the second is based on the Bayesian beta distribution (assuming a beta prior of 1). The coefficient 3 is derived from the natural logarithm of 0.05 (≈3).

For short-term pre-marketing clinical trials including at least 1500 patients on active treatment, these formulas indicate that at least one case of an ADR that has a true frequency of 1/500 during the 3-month period of the study is likely to be included, which is equivalent to 1/500 (or 1/501) being the upper 95% confidence limit for the observation. Likewise, for long-term pre-marketing clinical trials including at least 100 patients on active treatment for a year, at least one case of an ADR that has a true frequency of 1/33 during the one-year period is likely to be included. It should, however, be acknowledged that a single case of an ADR may for various reasons fail to be recognized.

It follows from the above reasoning that only relatively common ADRs that tend to appear first after more than 3 months of treatment can be detected in pre-marketing clinical trials. The possibility of detecting such reactions is, however, restricted to the first year of treatment (since this is the required length of long-term premarketing clinical trials), and importantly does not include ADRs resulting from even longer-term treatment. Any ADR that is rare (i.e. less than 1/1000), even if it occurs within the first 3 months after start of treatment, is also unlikely to be detected in pre-marketing clinical trials.

Because in pre-marketing studies the number of patients on long-term active treatment with the drug usually refers to open-label extension studies without placebo controls, the possibility that prolonged use of the drug
increases the risk of adverse health outcomes not recognized to constitute ADRs, e.g. increased general morbidity or mortality, cannot be ruled out.

In addition to the above, pre-marketing clinical trials are unlikely to include a sufficient number of patients in potential risk groups such as children, the elderly (who are often on multiple concomitant drug treatments), patients with decreased hepatic or renal function, and pregnant or lactating women. Therefore, continued and active surveillance is essential after marketing of a new drug.

The MAH is responsible for maintaining active and continuous surveillance of all relevant safety information associated with its products, and for taking appropriate action upon safety issues without unnecessary delay. This means e.g. that the MAH must be able to receive ADR reports and other relevant information from any source, and to actively search for such information in the published literature. For products authorized in the European Union, the MAH must have a designated qualified pharmacovigilance person within the Union.

Further responsibilities include e.g. the expedited reporting of serious ADRs or of serious and unexpected ADRs to regulatory authorities within 8 or 15 calendar days, as well as the preparation of periodic safety update reports (PSURs) to regulatory authorities; 6-monthly in the first two years, yearly until the 5-year renewal application, and thereafter every three years. The PSURs should include assessments of individual ADRs, relevant information from clinical studies, and any information related to drug interactions, overdose, abuse/misuse, long-term use, and use in special patient groups such as children, elderly, and pregnant or lactating women during the period covered by the PSUR.
Mechanisms of adverse drug reactions, pharmacogenomics

It is a great challenge to categorize ADRs. One of the most established categorizations so far divide ADRs into those that are common and therefore typically arise from the known pharmacology of the drug - type A (‘accentuated’) reactions, and those that are rare, and often unpredictable – type B (‘bizarre’) reactions (20;21). This categorization has been extended to include type C (‘chronic’) reactions to describe long-term drug effects including adaptive changes and withdrawal effects, and type D (‘delayed’) reactions involving carcinogenesis and effects associated with reproduction (22). Because the distinction between type A and type B reactions among other things is based on the frequency of the ADR (the system takes a descriptive rather than a mechanistic approach), this system for categorization does not divide ADRs according to their underlying mechanisms. Since that is the intention here, type A and type B reactions will not be further discussed. The special merit of the type A type B classification, however, follows from the realization that in contrast to common type A ADRs, uncommon type B ADRs are characterized by an unusual sensitivity of the individual, be it genetic, acquired or both. However, the commonly stated concept that type A reactions are dose dependent while type B are not, seems to be unfounded and improper.

ADRs are as complex as any pharmacological response. There are always both genetic and environmental components involved. It needs to be underscored that often, particularly in case of rare ADRs, the exact underlying mechanisms are poorly understood, and available information may be insufficient for an evaluation in individual cases.

Here, ADRs will only be broadly categorized into those that are a consequence of direct effects of the drug molecule, i.e. pharmacological, and those that arise from activation of a specific immune response toward a foreign molecule or molecule/protein complex (antigen), i.e. hypersensitivity reactions. Only selected examples will be presented. It deserves to be mentioned that the emergence of ADRs often leads to increased knowledge of mechanisms of drug action, sometimes resulting in the development of new indications.

Pharmacological effects are understood to include all established aspects of drug action, e.g. physical and chemical properties, physiological actions, absorption, metabolism, and excretion.
ADRs due to direct effects of the drug molecule

These ADRs can be further subdivided into those which are due to the pharmacological effects of a single drug only, and those which arise through interaction with other drugs. All have in common that they are typically dose- and/or concentration dependent. However, different effects (e.g. ADRs) may have different dose or concentration vs. effect curves, which is for example described in the term therapeutic index. Importantly, these curves may also show inter-individual variation. A part of this inter-individual variation is due to genetic factors, such as polymorphisms in drug metabolizing enzymes or receptor targets. Another part is due to acquired (e.g. age-related) changes such as reduced or induced drug metabolism or increased organ sensitivity.

It is important in this context to differentiate between competitive and non-competitive binding of the drug since in case of non-competitive binding the degradation process of the target protein also needs to be taken into account.

Inability to identify a dose and/or concentration dependency of an effect may be due to differences in organ sensitivity (e.g. low doses may be sufficient to exert a maximal effect) or differences in the handling of the drug in the body.

Pharmacokinetic drug interactions

A good example is the anticoagulant warfarin, which needs to be meticulously monitored in order to avoid exaggerated or insufficient effects resulting in an increased bleeding tendency or thrombosis.

Warfarin has a narrow therapeutic index, and is prone to interactions with other drugs. It is a racemate, the S-form being 3-5 times more potent than the R-form (23;24). The S-form is mainly metabolized by the polymorphic cytochrome P-450 enzyme CYP2C9, and drugs that inhibit this enzyme regularly cause exaggerated warfarin effects. Studies have also suggested that individuals with defective alleles associated with reduced CYP2C9 enzyme activity have impaired metabolism of S-warfarin (25) and an increased risk of bleeding complications during treatment with warfarin (26-29). In contrast, drugs that affect the metabolism of R-warfarin lead to exaggerated warfarin effects only under certain circumstances, e.g. individuals who experienced an INR increase after the addition of tramadol tended to have a reduced CYP2D6 activity either genetically or acquired (30). Both tramadol and R-warfarin are metabolized by CYP3A4, and tramadol is also metabolized by the polymorphic enzyme CYP2D6. Warfarin remains the number one cause of ADR fatalities.
**ADRs related to the primary drug target**

All changes in the drug concentration resulting e.g. from pharmacokinetic drug interaction (including interaction with food products), change in the administered dose, or altered function in organs responsible for drug metabolism or excretion, can induce ADRs related to the primary drug target.

Another example is the development of tolerance after continuous stimulation of certain receptors, which has been shown for e.g. caffeine, benzodiazepines and opioids, and leading to the need to increase the dose in order to obtain the same effect.

Tolerance may be greater for some of the effects of a drug than for others. If administration is stopped, various symptoms may occur that are often opposite to those induced by the drug. Withdrawal symptoms may also occur with drugs that do not induce tolerance (i.e. a need to increase the dose), e.g. SSRIs (31-37), beta-blockers (38-40), and anticholinergics (41;42).

**Other pharmacological ADRs**

*Effects on cardiac repolarization*

Several non-cardiac drugs, e.g. phenothiazines, cisapride, and terfenadine, inhibit the repolarization of the heart, which can be measured as QT prolongation on the ECG. This is the mechanism of action of certain cardiac drugs (class III anti-arrhythmic agents).

QT prolongation is a potentially dangerous condition due to an increased risk of life-threatening ventricular arrhythmias such as torsades de pointes.

Hereditary forms of QT prolongation have been identified, including changes in genes coding for potassium channel subunits or sodium channels (43) that result in either excess late inward sodium current (gain of function) or reduced outward potassium current (impaired function) (44).

Drug-induced QT prolongation appears to often be caused by a blockade of rapid delayed rectifying potassium channels, $I_{Kr}$ (45). An evaluation of the risks associated with QT prolongation is complex; it is difficult to accurately measure QT prolongation due to its variation with heart rate, there is no clear relation between the degree of QT prolongation and the risk of cardiac arrhythmia, and there is no clear relation between blockade of rapid delayed rectifying potassium channels and the risk of cardiac arrhythmia (45).

Risk factors for arrhythmic events in patients with QT prolongation include e.g. the presence of heart disease, bradycardia and electrolyte disturbances (hypokalemia, hypomagnesaemia).

Recently, a hereditary condition has been identified with exceptionally short QT intervals resulting from mutations in potassium channel subunits that lead to a gain of function of rapid delayed rectifying potassium channels (46). This condition is also associated with an increased risk of sudden
cardiac death, which further illustrates the complexities involved in evaluating arrhythmogenic potential (46).

Studies in rodents suggest that drugs that block $I_{Kr}$ can cause fetal malformations because of an increased sensitivity of the fetal embryonic heart to $I_{Kr}$ blockage resulting in cardiac arrhythmias, hypoxia and subsequent ischemia (47). The sensitive period ranges from start of the early embryonic heart beats until the embryonic heart is innervated (47). The importance of these findings to humans has not yet been determined. However, a known teratogenic drug, phenytoin, has been shown to block $I_{Kr}$ (47).

**Tumor promoting effects**

An example is the increased tumor growth associated with erythropoietin administration in patients with breast or head/neck cancer.

Erythropoietin stimulates the production of red blood cells. Its receptor is normally expressed on hematopoietic stem cells in the bone marrow. However, it has also been identified e.g. in tumor tissue. The stimulation of the erythropoietin receptor in tumor tissue is hypothesized to lead to increased tumor resistance with antineoplastic agents and/or to increased neo-vascularization.

**Tumor causing effects**

Alkylating agents such as cyclophosphamide, chlorambucil, melphalan, busulfan and ifofamide increase the risk of tumors by causing DNA breaks that increase the risk of aberrant cells that ultimately can become tumorous. Immuno-suppressive agents such as cyclosporine increase the risk of tumors by weakening the immune response to infective agents that can cause tumors.

**Toxic effects**

The word toxic does not imply a specific mechanism, but rather the absence of an immunologic mechanism. It is typically used for dose-related organ damage, mainly affecting the liver and/or kidneys, which are the principal organs for drug metabolism and excretion.

An example is paracetamol, which gives rise to potentially fatal dose-related liver toxicity. Paracetamol is bioactivated by cytochrome P-450 enzymes to a reactive metabolite, which becomes inactivated by binding to nucleophilic scavengers such as glutathione. Toxicity occurs when the amount of reactive metabolite formed exceeds the available glutathione supply. Toxicity is enhanced when the formation of reactive metabolite is increased by enzyme inducers or when the glutathione supply is decreased as with long-term paracetamol treatment or malnutrition.

Another example is renal tubular necrosis, which is a rare complication of non-steroidal anti-inflammatory agents (NSAIDs) in susceptible patients.
Under certain conditions, e.g. decreased renal or hepatic function or heart failure, renal blood flow is dependent on the production of prostaglandins, which is inhibited by NSAIDs.

The ability of angiotensin converting enzyme (ACE) inhibitors to induce acute renal failure is considered diagnostic of renal artery stenosis. The maintenance of adequate glomerular filtration in patients with renal artery stenosis is dependent on angiotensin II, which constricts the efferent arteriole. ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II.

The phototoxic effects of certain drugs including diuretics, antibacterial drugs and NSAIDs, can also be mentioned here. Phototoxic drugs absorb ultraviolet and/or visible radiation, which results in non-enzymatic degradation of the drug molecule and formation of free radicals or reactive oxygen species (48).

_Pseudo-allergic reactions_

Some drugs, e.g. opioids and radiocontrast media or neuromuscular blocking agents, can cause direct mast cell degranulation in sensitive individuals (49-51). The reaction resembles IgE-mediated hypersensitivity. In contrast to true IgE-mediated reactions, minuscule amounts of the drug are unlikely to cause life-threatening reactions (51), and the drug can usually be readministered after pre-treatment and appropriate dosing (51).

Aspirin and other NSAIDs can also cause IgE-like reactions in susceptible individuals. This sensitivity is thought to be mediated by blocking of the cyclooxygenase I (COX 1) enzyme, leading to an increased production of bronchoconstrictive leukotrienes (51).

Angioedema associated with ACE inhibitor treatment resembles hereditary angioedema (52). Inhibition of the metabolism of inflammatory mediators such as bradykinin (52;53), and substance P (54), is thought to be involved in the pathogenesis. ACE inhibition may enhance the reaction from a snake bite or bee sting (55).

_Unusual effects_

Genetic defects are the cause of unusual and serious reactions to certain drugs.

This includes glucose-6-phosphate dehydrogenase (G6PD) deficiency rendering individuals susceptible to oxidizing agents causing hemolysis, which may be life-threatening and lead to acute renal block.

G6PD catalyses an initial step in the degradation of glucose in erythrocytes whereby reduced nicotinamide adenine dinucleotide phosphate (NADPH) is formed, which is required for the maintenance of reduced glutathione (56). Reduced glutathione keeps enzymes on the red blood cell surface in a reduced and active state that is essential for normal cell permeability.
Genetically, G6PD deficiency is an x-chromosomal disorder that is relatively common (up to 27%) in endemic malaria regions (56). It is thought to confer resistance to infection with falciparum malaria. The genetic defects typically lead to decreased enzyme production or to production of a less active enzyme.

Known polymorphic genetic variants of G6PD deficiency include e.g. the G6PD Mediterranean variant, the G6PD African variant (G6PD A-), and oriental variants (56). Drugs known to cause hemolysis in such patients include e.g. certain sulfonamides, certain antimalarials, nitrofurantoin and nalidixic acid. Fava beans or large doses of ascorbic acid may also induce hemolysis.

Another example is acute porphyria. Acute porphyria constitutes a variety of disorders including acute intermittent porphyria, variegate porphyria, hereditary coproporphyria and plumboporphyria, that are characterized by an acute onset of severe abdominal pain, autonomic instability, electrolyte disturbances and neuropsychiatric manifestations; attacks may range from mild disturbance to fulminating attacks with a fatal outcome (57).

Most of these conditions are autosomal dominant with variable expression (57) and are caused by deficiencies in enzymes involved in the biosynthesis of heme. In its biologically active form, heme is bound to various proteins to form hemoproteins, which include hemoglobin, myoglobin, and all of the cytochromes together with numerous other compounds involved in oxidation and hydroxylation reactions (57).

Among acute porphyrias, acute intermittent porphyria is the most common with a prevalence ranging from 1-2 per 100 000 in most developed countries to as high as 1:1000 in northern Sweden (58).

Acute exacerbations of porphyria are precipitated by events that lead to increased demand of heme production (e.g. through induction of cytochrome P-450 enzymes) or failure of heme inhibitory feedback mechanisms (57), resulting in activation of heme biosynthesis and overproduction of intermediates before the block (57). Enzyme-inducing drugs are considered to be the most important triggering factors (57).

Malignant hyperthermia is a life-threatening complication of anesthesia in susceptible patients (59-62), which is characterized by an increase in myoplasmic calcium leading to muscle rigidity, hypermetabolism, hyperthermia, hypoxia and acidosis following exposure to inhalation anesthetics or depolarizing skeletal muscle relaxants such as succinylcholine.

It was first described in 1960 (59), and used to be associated with a high frequency of fatalities (ca 70%) prior to use of the effective antidote dantrolene, which inhibits calcium release in the skeletal muscle.

Subsequent studies have shown that muscle tissue from patients who have suffered from malignant hyperthermia exhibits increased sensitivity to contracture from exposure to caffeine and halothane, which forms the basis of the standard in vitro muscle contracture test.
Malignant hyperthermia appears to be associated with certain myopathies, with otherwise unexplained exercise- or heat-induced rhabdomyolysis (59-61), and even with the neuroleptic malignant syndrome and sudden infant death syndrome (59).

Susceptibility to malignant hyperthermia is mainly inherited in an autosomal dominant way (63). The genetic background is heterogeneous (61;63), but a significant proportion of affected individuals appear to carry mutations in the ryanodine receptor gene (RYR1) encoding the skeletal muscle sarcoplasmic reticulum calcium release channel (59-61) that lead to increased calcium release in response to triggering agents. Some mutations are not rare with estimated incidences up to 10% of the investigated population (63).

It is important to note that a history of previous uneventful anesthesia with halothane and/or succinylcholine does not exclude the diagnosis of malignant hyperthermia on a subsequent occasion (59). Interestingly, two patients who developed muscle symptoms and increased leakage of muscle enzyme associated with statin treatment were both shown to have positive in vitro muscle contraction tests indicating susceptibility to malignant hyperthermia (64).

ADRs resulting from hypersensitivity (immunological) reactions
The characteristic of hypersensitivity reactions is the initial ability to tolerate doses much higher than those tolerated once the individual has been sensitized.

Hypersensitivity reactions in the true sense are the result of a specific immune response.

Types of hypersensitivity reactions
All types of hypersensitivity reactions can be induced by drugs: type I: IgE-mediated immediate hypersensitivity, type II: antibody-mediated cytotoxic hypersensitivity, type III: antigen-antibody complex mediated hypersensitivity, and type IV: cell mediated delayed-type hypersensitivity.

All hypersensitivity reactions, however, do not easily fit into these descriptions. The exact mechanisms of hypersensitivity reactions are only partly understood and are difficult to study. Identified antibodies may for example not necessarily be pathogenic. Proposed mechanisms below are therefore best regarded as a possible theoretical framework and not as definitive truth.

Hapten theory
Drugs or their metabolic products are small molecules that typically can not act as antigens on their own. Instead they act as haptons and combine covalently with endogenous products to form an antigenic complex.
A few drugs are capable of binding themselves covalently to endogenous proteins (50). Most drugs, however, first need to be bioactivated by cytochrome enzymes, peroxidases or prostaglandin synthetases to form reactive metabolites that react with endogenous proteins in their immediate vicinity (65;66).

The formation of reactive metabolites can take place not only in liver cells but also in e.g. keratinocytes, leukocytes or alveolar cells (50;67;68). Drugs associated with lupus like reactions, e.g. phenytoin, carbamazepine or hydralazine, have all been shown to undergo oxidative metabolism by activated neutrophils (66).

**Activation of the immune system**

Activation of the immune system starts with the presentation of antigen to T lymphocytes; antigen-presenting cells (APC; e.g. dendritic cells, macrophages, B-lymphocytes) process the hapten-modified protein complexed with major histocompatibility complex molecules (or the drug/metabolite binds directly to MHC molecules covalently or reversibly) displayed on the cell surface.

Intracellular hapten-modified proteins enter the MHC class I (endogenous), and extracellular hapten-modified proteins enter the MHC class II (exogenous) pathway (50).

**Type of immune response**

The neoantigen may induce synthesis of specific antibodies or of autoantibodies (Th2 – B cell response), and/or activated T-cells exert cytotoxic effects (Th1 – T cell response), usually after a latent period of at least 1 or 2 weeks. T cells are now believed to be involved in various drug allergic reactions (69).

What triggers a specific type of immune response, and why only a subset of patients develop the reaction, is not well understood.

T cells presumingly interact with B cells in eliciting antibodies of the IgE or other classes that then mediate allergic type I, II, or III reactions (66;70).

Experiments have shown that drug-specific T cell clones are often MHC restricted (69;71). Drug-specific CD4+ and CD8+ T cells secrete cytokines (69). CD8+ and CD4+ T cell clones are capable of exerting cytotoxic activity mediated by perforin (69).

**Examples of immune responses**

_IgE-mediated hypersensitivity_

IgE-mediated hypersensitivity reactions have been described with e.g. penicillin and other beta-lactam antibiotics. They range from urticaria to angioedema or anaphylaxis (50).
**Drug-induced lupus**

Symptoms of drug-induced lupus include rashes, fever and serositis, but rarely nephritis or cerebritis (72).

Antinuclear antibodies are common, whereas antibodies against double-stranded DNA are typically absent (65;73). Only a minority of the patients who become antinuclear antibody positive develop clinical illness (72). Once the drug is withdrawn the illness remits (72;73), but antinuclear antibody remains positive for many months (72).

Drugs that can cause lupus include e.g. procainamide, hydralazine (72-74), isoniazid, penicillamine, practolol (73), and minocycline (75). Procainamide- or hydralazine-induced lupus is more common in slow acetylators (74).

**Drug hypersensitivity syndrome**

The drug hypersensitivity syndrome has been described with e.g. antiepileptic drugs. It is characterized by skin rash, fever, eosinophilia, lymphadenopathy and internal organ involvement (65;76).

**Immune-mediated hepatic injury**

Different types of immune-mediated hepatic injury have been described. Some drug reactions have a striking allergic component, e.g. sulfa drugs, phenytoin or halothane (77). The pattern of injury may be hepatocellular, e.g. diclofenac, isoniazid or nefazodone, cholestatic, e.g. chlorpromazine, or mixed, e.g. carbamazepine (77). Each drug has its own pattern of injury (77). The most frequent hepatotoxic drug reactions are moderate to severe hepatocyte injury characterized by malaise, jaundice and increased aminotransferase levels (77). Signs of allergic reaction are absent in most patients (77). Acute liver failure may develop, particularly if the patient has continued the drug after onset of symptoms (77).

**Drug-induced auto-immune reactions**

Various autoimmune reactions can be induced by drugs, e.g. autoimmune hepatitis, autoimmune hemolytic anemia or autoimmune lupus-like disease (66). These are characterized by binding of antibodies to endogenous proteins even in the absence of drug, reactive drug metabolite or haptenated form of the drug (66), and therefore may take a long time to resolve or become persistent.

**Sensitivity to the development of immune-mediated ADRs**

Since all individuals are capable of producing reactive metabolites, it has been suggested that patients who develop drug hypersensitivity reactions have deficiencies in normal phase 2 detoxication processes such as the glutathione-generating system (50). However, as yet studies have failed to
show specific deficiencies in phase 2 enzymes in patients who have
developed drug hypersensitivity reactions (50;65).

In contrast, certain MHC alleles have been implicated in drug
hypersensitivity reactions associated with e.g. abacavir, carbamazepine and
chlorpromazine (76;78-80).

Other situations that have been associated with an increased tendency to
develop drug hypersensitivities include HIV, Epstein Barr virus and human
herpes virus 6 infections (50). For example, the frequency of maculopapular
exanthema during treatment with aminopenicillins is several times increased
if the patient has infectious mononucleosis (51).

The risk of a drug hypersensitivity reaction may also be increased by
other types of cell injury (65), and it is possible that variations in genes that
encode for or control the expression of inflammatory factors such as
cytokines etc. are also involved in the risk (81).
Signal detection

A signal has been defined by the WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

The first signal of a new ADR or of a new, mostly more severe manifestation of a previously known ADR to a marketed product usually originates from individual case reports or case series that have been published in medical journals, submitted to spontaneous reporting systems or reported directly to the MAH. Occasionally, experimental findings such as drug interaction studies or toxicological studies form the basis for a signal of a new ADR.

A signal of a change in the frequency of a previously known ADR requires some comparative data, and thus is often based on published or unpublished studies including clinical trials or epidemiological studies.

Ways to systematically review data from spontaneous reporting systems or reporting to the MAH for signal identification include giving particular attention to reports with a fatal outcome, reports with critical ADRs or reports with ADRs that have not previously been reported (New In System).

Other complementary ways include the use of automated signal detection tools that look for statistical associations (dependencies) between drugs and ADRs within a database. Automated signal detection tools are considered particularly useful for large databases.

For example, the WHO has developed an automated signal detection tool, the Bayesian Confidence Propagation Neural Network (BCPNN) method (82;83), which has been shown to be effective in highlighting new drug-ADR combinations (82;84-86). BCPNN measures quantitatively how much more or less often a specific ADR occurs with a specific drug relative to their background occurrences in the database. The statistical measure of disproportionality, which is called the IC (Information Component), is defined as:

\[
\text{IC} = \log_2 \frac{p(x,y)}{p(x)p(y)}
\]

Where:

- \( p(x) \) = probability of a specific drug ’x’ being listed on a case report
- \( p(y) \) = probability of a specific ADR ’y’ being listed on a case report
- \( p(x,y) \) = probability that a specific drug-ADR combination ’x and y’ is listed on a case report
See Figure 2 for an illustration. When \( p(x) \) and \( p(y) \) are independent (null hypothesis of no association between the drug and the ADR), \( p(x,y) = p(x) \times p(y) \), and the IC is zero. The IC is a probability distribution rather than a point estimate. The expected value of the IC and the variance of the IC are calculated under the assumption that the IC is normally distributed. The expected values for \( p(x) \), \( p(y) \), and \( p(x,y) \) are all assumed to be beta distributed, see formulas below (87). Priors are set so that the IC will be robust to fluctuation and tend to zero at low numerical values, so avoiding highlighting drug-ADR combinations at very low numerical values, e.g. when there is only one report of a drug-ADR combination. The number of reports for drug ‘x’, the number of reports for ADR ‘y’, and the total number of reports in the database affect the prior distribution of the IC. A drug-ADR combination is considered to constitute a signal when the IC value and its lower 95% confidence level are above zero.

\[
\begin{align*}
\mathbb{E}\{p(x)\} &= \frac{c_x + \alpha_1}{C+\alpha_1} \\
\mathbb{E}\{p(y)\} &= \frac{c_y + \beta_1}{C+\beta_1} \\
\mathbb{E}\{IC\} &= \log_2 \left( \frac{(c_y + \gamma_1)(C+\alpha)(C+\beta)}{(C+\gamma)(c_x + \alpha_1)(c_y + \beta_1)} \right)
\end{align*}
\]

Where:

\( E \) = expected value for the parameter
\( p(x) \) = probability of a specific drug ‘x’ being listed on a case report
\( p(y) \) = probability of a specific ADR ‘y’ being listed on a case report
\( p(x,y) \) = probability that a specific drug-ADR combination ‘x and y’ is listed on a case report
\( c_x \) = number of reports with specific drug ‘x’
\( c_y \) = number of reports with specific ADR ‘y’
\( c_{xy} \) = number of reports with specific drug-ADR combination ‘x and y’
\( C \) = total number of reports
\( \alpha_1 = 1, \, \alpha = 2, \, \beta_1 = 1, \, \beta = 2, \, \gamma_1 = 1, \) and

\[
\gamma = \frac{\gamma_{11}}{\mathbb{E}(p_x)\mathbb{E}(p_y)} = \gamma_{11} \left( \frac{(C+\alpha)(C+\beta)}{(C_x + \alpha_1)(c_y + \beta_1)} \right)
\]
Figure 2. Illustration of the principle of signal detection by use of BCPNN (Bayes Confidence Propagation Neural Network)

All reports in the database

All reports with specific drug 'x'

All reports with specific adverse drug reaction 'y'

All reports with both drug 'x' and specific adverse drug reaction 'y'
Signal evaluation

Causality evaluation

When evaluating individual ADR reports for causality, the possibility that the ADR was caused by another drug or by a concurrent disease always needs to be considered. ADRs that mimic spontaneously occurring disease are for this reason difficult to attribute to drug treatment.

Causality is supported when the ADR disappears after discontinuation of the offending drug. A close temporal relation between administration of the drug and occurrence of the ADR also supports causality, e.g. in acute hypersensitivity reactions. A reappearance of the ADR following reintroduction of the drug is considered a strong indication of causality.

Other criteria for causality include e.g. biologic plausibility, absence of other more likely causes, quantitative strength of the association (this refers to the magnitude of the difference), and evidence of a dose-response relationship, see also (88). When the BCPNN method is applied to spontaneous ADR reports in the WHO database, consistent positive IC and IC-2SD values in combination with a narrowing of the confidence intervals for the IC value over time, may also serve as an indication of causality, although potential pitfalls need to be considered (see Results and discussion section, study 4).

As the clinical implication of an ADR is a composite of the frequency of the ADR and its clinical manifestations, exact determination of the frequency of an ADR is particularly relevant for common ADRs and for ADRs that have potential serious clinical consequences.

Frequency estimation

When determining the frequency of an ADR, it is important to differentiate between true drug-induced events and events that to a significant degree also occur spontaneously without drug treatment, since in the latter instance the natural occurrence rate of the disease (preferably in patients who have the same diagnosis as those treated with the drug) needs to be subtracted from the occurrence rate of the disease during drug treatment.

This may be a complex task. For example, in epidemiological studies various biases may exist that make firm conclusions difficult to draw. The strongest evidence therefore comes from double blind placebo controlled randomized clinical trials. However, such studies may not be feasible. Rarely, biochemical tests may exist that attribute the event with certainty to a specific drug.

Some remarks about the estimation of the frequency or risk of an ADR need to be made. Risk is generally perceived as the probability that the ADR will occur in an individual (89). On a population level this translates into the
proportion of treated individuals who experience the ADR. Time is also an essential component of risk. The following formula provides a crude risk estimate (89):

\[ CI = \frac{X}{N} \]

Where:

CI = cumulative incidence
X = number of individuals with ADR
N = total number of individuals exposed to the drug

In order to estimate the cumulative incidence, we need to follow a number of people treated with the drug for some duration of time. The cumulative incidence is the proportion of individuals who suffer an ADR during that period of time in relation to all individuals who were initially being followed.

A proportion can take any value between 0 and 1. A drawback of this formula is that individuals who are lost to follow up still contribute to the denominator, which can dilute the risk estimate. One way to address this problem is to estimate a different measure of ADR occurrence, the incidence rate, which is calculated in the following way (89):

\[ IR = \frac{X}{T} \]

Where:

IR = incidence rate
X = number of individuals with ADR
T = total time of exposure to the drug for the subjects followed

The incidence rate is the number of events that occur during a specified person-time exposure to a drug that is equal to the sum of times at risk for all individuals. Each individual contributes with person-time information only as long as he/she is followed up. The ADR can occur either once or repeatedly depending on the type of ADR studied.

An incidence rate can take any value between 0 and approaching \( \infty \). For ADRs, the incidence rate may vary over the treatment duration. In that situation, separate incidence rates need to be calculated for sufficiently short intervals so that the incidence rate applied to it can be considered approximately constant.

The method of calculating risks over a time period with changing incidence rates is known as survival function. The survival function calculates the proportion of individuals that do not develop the ADR within
a specific time interval conditional on ‘having survived’, i.e. not developed the ADR, up to the start of the time interval.

The survival function is related to the hazard, which is the instantaneous risk at a specific time given that the event has not occurred up to that time. The hazard function therefore describes the relation between the incidence rate (risk) of the ADR and the treatment duration (specific time).

When assessing the risk of ADRs, a non-constant hazard function often needs to be assumed (90). The relation between the hazard function and the survival function is shown below (91):

\[ S(t) = e^{-\int_{0}^{t} \lambda(t) \, dt} \]

Where:

\[ S(t) = \text{survival function} \]

\[ \lambda(t) = \text{hazard function} \]

The cumulative incidence is obtained by taking \( 1 - S(t) \). When presenting ADR risks, the shape of the hazard function needs to be revisited.

If the incidence rate is nearly constant, the cumulative incidence will eventually approach one, and therefore be non-informative. In that situation, therefore, it is more appropriate to present the incidence rate itself. The cumulative incidence will also approach one in situations where the incidence rate increases over time. However, here the different incidence rates should be presented separately for different time periods.

In situations where an initial incidence rate decreases to zero with increasing treatment duration, the cumulative incidence may be an appropriate measure of risk. Preferably, the different incidence rates for different time periods should be presented in addition.

Hypersensitivity reactions are examples of ADRs, where the risk typically increases steeply in the first weeks to months after the first exposure, and then decreases towards no risk with continued exposure. When calculating the risk of a hypersensitivity reaction, therefore, it is of particular importance to let \( t_0 \) be equal to the first exposure to the drug.

Because hypersensitivity reactions are usually rare and constitute a reason for discontinuation of the drug, it is also of particular importance to have complete follow-up information from all patients.

For ADRs that are related to the direct effects of the drug molecule (see section above on mechanisms of ADRs and pharmacogenomics), \( t_0 \) can usually be any point in time from which the patients are followed. The hazard function for delayed effects tends to increase with increasing treatment duration.
If the risk is related to the cumulative dose, then instead of time the hazard function can be made to describe the risk in relation to the cumulative dose with $d_0$ as the lowest cumulative dose level. The hazard function in this case will tend to increase with increasing cumulative doses, e.g. neurotoxicity with metronidazole.

Delayed effects need to be distinguished from latency, meaning the period since last intake of the drug until occurrence of the ADR. The latency period can be different for different types of ADRs, depending on e.g. the pharmacokinetics of the drug and the pharmacodynamics of the reaction (signs and symptoms). It needs to be underscored that abnormal biochemical parameters often predate the onset of symptoms of the reaction.

**Further characterization of risk**

Knowledge of what determines risk is an essential part of risk communication and minimization.

Apart from the influence of the treatment duration itself, the presence of patient-related risk factors, the drug dose/concentration, and concomitant drug treatments need to be considered.

An overview of how different sources can be used to study risk factors as well as ADR frequencies and hazard functions is presented in Table 2. Depending on the potential clinical implications, further studies to characterize the frequency and/or risk factors for an ADR may be needed.
Table 2. Use of different sources to study risk factors, adverse drug reaction (ADR) frequencies and hazard functions

<table>
<thead>
<tr>
<th>Source</th>
<th>Comparisons for identification of potential risk factors</th>
<th>Frequency estimation</th>
<th>Hazard function estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports/ADR database</td>
<td>Comparisons can be made within subgroups of cases, e.g. fatal cases vs. non-fatal cases. Cases with the ADR can be compared with cases with unrelated ADRs treated with the same drug.</td>
<td>If sales data are available, the reporting rate can be estimated.</td>
<td>Distribution of treatment durations can give an indication of the hazard function.</td>
</tr>
<tr>
<td>Case control study</td>
<td>Cases with disease/ADR are compared with controls that have not had the disease/ADR.</td>
<td>The risk ratio/relative risk, or odds ratio, can be estimated.</td>
<td>Hazard function may be estimated if drug treatment is common. Lifetime exposure information should be collected.</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Cases with the ADR can be compared with individuals treated with the same drug without the ADR.</td>
<td>The incidence rate and the cumulative risk can be estimated.</td>
<td>Estimation of hazard function possible. Treatment-naive patients should be studied.</td>
</tr>
<tr>
<td>Randomized clinical trial</td>
<td>Same as above (but number of patients and treatment duration may be more restricted compared with cohort study, leading to fewer ADR cases).</td>
<td>The absolute risk can be estimated.</td>
<td>Same as above (but number of patients and treatment duration may be more restricted compared with cohort study, leading to fewer ADR cases).</td>
</tr>
</tbody>
</table>

1 Patients are included according to disease/ADR and not according to drug treatment. Drug treatment is considered a risk factor. Depending on the size of the study only drug treatment that is relatively common can be studied.

2 The measures indicate how much higher or lower the risk of having the ADR is (on the relative scale) in exposed individuals compared with unexposed individuals.

3 In the case of hypersensitivity reactions.

4 Depending on the size of the study only relatively common ADRs can be studied.

5 The absolute risk is the incidence rate (or cumulative incidence) in exposed individuals minus the incidence rate (or cumulative incidence) in unexposed individuals. This measure can also be estimated from a cohort study provided that both exposed and unexposed individuals are included in the study.
Aims

The overall aim of this thesis was to study the occurrence and characteristics of ADRs as identified in spontaneous reporting systems, and to discuss how this information can be used. Specific aims of the respective studies were:

**Study 1**
To review symptoms and possible risk factors for peripheral sensory disturbances related to fluoroquinolones, and to provide an estimate of the reporting frequency.

**Study 2**
To identify risk factors associated with the development of hyponatremia during treatment with antidepressant drugs.

**Study 3**
To describe the pattern of blood dyscrasias, identify possible risk factors, and calculate the incidence of agranulocytosis associated with dipyrone.

**Study 4**
To examine the association between glucose intolerance and the use of the atypical antipsychotics clozapine, olanzapine or risperidone, and to identify possible risk factors for the development of glucose intolerance during treatment with these drugs.

**Study 5**
To study risk factors for a fatal outcome from pulmonary embolism associated with combined oral contraceptive (COC) treatment, and to calculate the reporting rates of fatal and non-fatal pulmonary embolism associated with COC treatment.

**Study 6**
To review symptoms and possible risk factors of extrapyramidal symptoms related to selective serotonin reuptake inhibitors, and to investigate the importance of polymorphisms in drug metabolizing enzymes (CYP2D6, CYP2C9 and CYP2C19) and of serotonin and dopamine transporters and receptors for the development of extrapyramidal symptoms during treatment with these drugs.
Materials and methods

All studies in this thesis are based on spontaneously reported ADRs. Study 6, which included blood sampling and analyses of genetic information, was approved by the ethics committee at Uppsala University Hospital.

Study subjects

Studies 1, 3, 5 and 6 are based on ADR reports that had been submitted to SADRAC. Cases were identified through a search in the database SWEDIS (Swedish Drug Information System) using specific ADR terms. The original ADR documentation was reviewed in each of the studies. In studies 3 and 5, further documentation was requested from the reporting physicians as necessary. In study 6, a form with specific questions was posted to the reporting physicians. Study 6 also included blood sampling for analyses of polymorphisms in drug metabolizing enzymes (CYP2D6, CYP2C9 and CYP2C19) and of serotonin and dopamine transporters and receptors. Other ADR reports than the ones studied for the study drugs were used in some of the comparisons in study 6.

Studies 2 and 4 are based on international ADR reports in the WHO database INTDIS (International Drug Information System). Again, cases were identified through a search in the database using specific ADR terms. Other ADR reports than the ones studied for the study drugs were used for comparison. All information was extracted from the database.

Methods

Signal detection

The studies were based on ADR cases, where in general a causal relationship to treatment with the suspected drugs was considered plausible. Results of treatment discontinuation and/or treatment reintroduction were taken into account. Study 4 also used the BCPNN method to analyze the association between the study drugs and the ADR.
Characterization of the clinical picture
In all studies, reports were classified according to different clinical manifestations of the ADR. This information was analyzed descriptively.

Identification of risk factors
Two different approaches were taken in order to identify risk factors for the ADR:

In studies 1 and 3, possible risk factors were identified among reported cases and analyzed descriptively.

In studies 2, 4, and 6, the presence of possible risk factors for the ADR was compared between cases with the ADR and cases without the ADR. Cases without the ADR were selected from other ADR reports of the study drugs. Similarly, in studies 3, 5, and 6, possible risk factors were compared between subgroups of cases, e.g. a fatal outcome vs. a non-fatal outcome.

Risk quantification
In studies 1, 3, and 5, sales volumes of the study drugs were obtained from the National Corporation of Swedish Pharmacies (Apoteket AB), which is responsible for the collection of routine sales statistics in Sweden including volumes distributed to pharmacies and hospitals and volumes dispensed in pharmacies. Total sales of drugs from pharmacies have been computerized since 1972. Sales volumes can be expressed as e.g. the number of defined daily doses (DDDs) or the number of packages sold. The DDD is the average daily dose of a drug for its main indication. Since 1 January 1996, the total number of prescriptions dispensed in pharmacies can also be obtained, as they are registered through bar codes. One prescription may cover a maximum period of 3 months.

Study 1 used the total number of packages sold, assuming that one package of an antibiotic equals one treatment. Study 3 used the total number of prescriptions dispensed in pharmacies (i.e. the total number of iterations), which equals the maximum number of patients that could have received the drug if there were no reiterations. Study 5 used the total number of DDDs sold. This figure was converted into treatment-years.

Statistical methods
The Fisher’s exact test, $\chi^2$-test, Student’s $t$-test, Wilcoxon rank sum test, and Mann-Whitney U-test were used for comparisons. The Poisson distribution was used for the calculation of confidence intervals around reporting incidences in studies 3 and 5.
Results and discussion

Only the most important results are summarized here. For a more complete account the respective papers are referred to (see Appendix).

Study 1. Peripheral sensory disturbances (PSD) related to treatment with fluoroquinolones

A total of 37 reports of PSD were identified in the SWEDIS database until 1993 (31 norfloxacin, 5 ciprofloxacin, 1 temafloxacin).

Possible predisposing factors for neuropathy were reported in 11 cases (29.7%): concomitant treatment with another drug known to cause neuropathy (5 cases), inflammatory processes (3 cases), impaired renal function (2 cases), diabetes mellitus (2 cases), lymphatic malignancy (2 cases), and previous anorexia nervosa (1 case).

When cases with a CNS effect or allergy were excluded (n=13), there was some evidence of dose dependency with shorter mean times to onset with increasing daily doses (11 days at 200 mg/day, 6 days at 300 mg/day, 3.5 days at 400 mg/day and 3.4 days at 800 mg/day).

Evidence in favor of a possible dose dependency suggests a pharmacological mechanism of PSD with fluoroquinolones, at least in some cases. The exact mechanisms are, however, unknown. One of the patients in our study underwent EMG and testing of nerve conduction that revealed normal findings despite continuing symptoms. In contrast, in a more recent publication a patient who experienced sudden muscle weakness 36 hours after initiating trovafloxacin treatment was found to have abnormal nerve conduction consistent with demyelinating polyneuropathy (92).

Reporting was highest in the first few years after market introduction of fluoroquinolones. When relating cases reported with norfloxacin during 1988 and 1989 (norfloxacin was introduced in the autumn of 1986) to the total number of packages sold in the same years, and assuming that only 5-10% of cases are reported, a risk of one case for every 1250-2500 treatments could be expected.

This study has several limitations. We reviewed all cases with PSD as a single group, although it is possible that each constellation of symptoms has a different pathogenesis, and that therefore the different constellations of
symptoms should preferably have been analyzed separately. The same could be stated for the different fluoroquinolones, which may potentially cause PSD by different mechanisms. Our study was, however, too small to analyze subgroups. It is important to note that the majority of cases were associated with norfloxacin.

It could furthermore be argued that not all cases with suspected PSD due to treatment with fluoroquinolones were caused by the treatment. However, a fairly rapid improvement in symptoms following treatment discontinuation suggests a possible causal relation in most cases.

Depending on the degree to which cases may have been reported that were not causally related to treatment and the degree of underreporting, the incidence of PSD may have been over- or underestimated. The calculated incidence is only relevant for norfloxacin, since it was based on cases reported with norfloxacin in relation to sales of norfloxacin during the first years after market introduction.

The degree to which reported cases are in agreement with all cases of PSD associated with fluoroquinolones treatment cannot be estimated. In general, however, reporting is influenced by the seriousness or severity of the reaction, and evidence in favor of a causal relation to drug treatment. Reported cases may therefore occur earlier after treatment initiation when a causal relation is easier to suspect. Also, other potential causes of the reaction including other drugs may be less prominent and symptoms more severe in reported cases. See also under General discussion.

A summary of 45 cases of peripheral neuropathy associated with fluoroquinolones that had been retrieved from Internet Web sites has been published during the last years (93). Whereas most of our cases reported mild symptoms, the cases obtained from Internet Web sites reported severe symptoms in 80% of cases, and symptoms lasting more than one year in 58% of cases. In the majority of cases with severe symptoms, the patients had continued or restarted the fluoroquinolone treatment after the adverse event had occurred. The physician had missed or dismissed the patients’ symptoms in 40% of cases. This is an important difference compared with our study, where the suspected fluoroquinolone was discontinued due to the suspected ADR. It may be more difficult to assume a causal relationship to a drug if the ADR does not resolve after treatment discontinuation. It is not surprising that patients who take the time and energy to engage in Internet Web Sites are those with severe and/or long-lasting ADRs. The example indicates that consumer reports may be of particular importance for characterizing severe (interfering with every-day life) and/or persisting ADRs.

PSD is included as an ADR in the Swedish summary of product characteristics of norfloxacin.

A total of 668 reports of hyponatremia with antidepressants were identified in the database until the end of 1993.

Compared with all other ADR reports to antidepressants, cases with hyponatremia were older (mean 66.6 years vs. 48.6 years) (p<0.0001) and more often female (77.7% vs. 69.0%) (p<0.0005). A greater proportion of hyponatremia cases occurred during the summer season (31.0% vs. 25.0%) (p<0.02).

No obvious dose dependency was seen when cases with hyponatremia were compared with cases with non-dose dependent type I immune reactions.

Hyponatremia associated with antidepressants may be related to increased levels of serotonin at the synapse, and is therefore likely to constitute a pharmacological ADR. There is evidence that serotonin has a stimulatory effect on antidiuretic hormone (ADH) secretion (94), which may lead to water retention and hyponatremia.

This study has the following strength: Since the control group was chosen from among other ADR reports to the same drugs, the same general potential biases are likely to apply to both cases and controls. Any risk factor that is associated with ADRs in general or with the tendency to report an ADR would on the other hand be more difficult to identify with this design compared with a design where controls are chosen from a non-selected group of treated patients. Negative findings (i.e. no associations identified) are therefore less conclusive than positive findings (i.e. identified associations). The positive findings in this study have been supported by others: One study found that old age (95) constitutes a risk factor for antidepressant-induced hyponatremia. A review article concluded that there are gender-related differences in the mechanisms of Na+ transport (96) that may explain why female gender constitutes a risk factor for drug-induced hyponatremia. Another study found that hyponatremia was more common in the summer season among children hospitalized for emergency care (97).

Hyponatremia and/or syndrome of inappropriate ADH secretion (SIADH) are included as ADR in the Swedish summary of product characteristics of most antidepressants.
Study 3. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole)

A total of 66 cases were identified in the database until the end of 1999 of which 52 (78.8%) concerned agranulocytosis, 9 (13.6%) concerned bi- or tricytopenia, and 5 (7.6%) concerned neutropenia.

The median number of cumulative treatment days until onset of blood dyscrasia was 14 days; 33 out of 36 cases (91.7%) occurred within a cumulative treatment period of 2 months.

There was no evidence of dose dependency in that the median number of cumulative treatment days until onset stayed the same during the years 1966-1994 compared with 1995-1999 despite a much lower mean daily dosage during the first period (1.2 g vs. 2.8 g).

Before 1995, 15 out of 52 cases (28.8%) were fatal. In contrast, none of the 14 cases between 1995 and 1999 died.

Compared with non-fatal cases, a significantly higher proportion of fatal cases had bi- or tricytopenia, and a borderline significantly higher proportion had all three hematopoieses affected according to a bone marrow sample.

Potential risk factors for blood dyscrasia were identified in 24 cases (36.4%) including the possible contribution of another drug in 10 cases, a personal or family history of drug allergy in 8 cases, and a personal history of another allergic condition in 7 cases.

When relating all cases of agranulocytosis associated with prescription use of the drug between 1995 and 1999 to the total number of prescriptions dispensed during the same period of time, a risk of one case per 1362 prescriptions (95% confidence interval 1:692, 1:3157) could be estimated.

This study had no control group of patients treated with the same drug who did not develop agranulocytosis. The group of patients that experienced other ADRs that were judged to have at least a possible causal relation to dipyrone was too small for a comparison (n=14 total for the two time periods). Exact estimates on how the risk varies with the treatment duration or with the dose of the drug could therefore not be obtained. Also, the importance of potential risk factors for blood dyscrasia could not be assessed.

However, it is clearly an impressive finding that over 90% of cases with information available occurred within a cumulative treatment period of 2 months. The finding is consistent with the generally expected occurrence of a hypersensitivity reaction during the initial months of exposure following a sensitization period of 3-7 days. In fact, a recent publication from Spain supports that the risk of agranulocytosis with dipyrone varies with the treatment duration (98). Three positive re-exposures (i.e. patients that re-experienced the ADR following a re-exposure to the drug) including one patient who received only a half tablet are also consistent with a hypersensitivity reaction. Indirect evidence in favor of a hypersensitivity
reaction is further provided by the lack of evidence of dose dependence, although this finding is non-conclusive due to absence of a control group. A recent publication found that cases with dipyrone-induced agranulocytosis in Spain had on average lower daily doses of dipyrone compared with our cases (98). However, there was no indication that the Spanish cases had higher average daily doses than their own controls, a more relevant comparison, so it cannot be concluded that dose is a risk factor for dipyrone-induced agranulocytosis.

In the majority of patients where information was available and it would not be expected from their underlying disease, slight increases in liver enzymes and/or bilirubin were found, which could be consistent with cell lysis/hemolysis and/or a transient liver affection.

The finding that bi- or tricytopenia were significantly (and an affection of all three hematopoieses borderline significantly) associated with a fatal outcome is biologically plausible. Furthermore, it is likely that similar reporting biases apply to cases with and cases without a fatal outcome. Comparisons concern, however, only specific risk factors for a fatal outcome conditional of having the blood dyscrasia and are restricted to risk factors available in the reported material. Due to low study power resulting from the small number of cases compared, negative results (i.e. no associations identified) are less conclusive than positive results (i.e. identified associations).

The risk of agranulocytosis with dipyrone has been the subject of much scientific debate (90;99-101). The debate has at least in part been triggered by confusion about the use of terminology, and has resulted in apples being compared with pears, see e.g. (98).

In the Spanish publication (98), the incidence of agranulocytosis leading to hospitalization in a given population (3.46 per million person-years) was estimated from the number of cases admitted to hospital due to agranulocytosis (n=273), and the size of the population multiplied by the study duration (78.7 million person-years). Cases occurring during hospitalization (n=123), cases not leading to hospitalization, and cases not fulfilling the strict inclusion criteria for agranulocytosis in the same population (e.g. 14 cases with bicytopenia, 13 cases with sepsis/septicemia) were not considered. From interviewing the cases and matched controls a relative risk of 25.8 could be estimated for exposure to dipyrone sometime during one week before onset of symptoms of agranulocytosis. Since 30 out of 177 interviewed cases (16.9%) were exposed to dipyrone during one week before onset of symptoms of agranulocytosis, the etiologic fraction (fraction of exposed cases that were due to exposure with dipyrone) was found to be 16.3% calculated from the formula below (102):

$$EF = [(RR - 1) / RR] * P_e$$
Where:

EF = etiologic fraction
RR = relative risk
Pe = proportion of exposed cases

The excess incidence (i.e. the incidence that is caused by exposure to the drug) can be calculated from the following formulas (102):

\[
IR_1 = RR(\text{IR})(1-EF)
\]

\[
IR_0 = \text{IR} (1-EF)
\]

Where:

\[
IR_1 = \text{incidence rate among exposed individuals}
\]

\[
IR_0 = \text{incidence rate among unexposed individuals}
\]

\[
\text{IR} = \text{incidence rate in the entire population}
\]

\[
RR = \text{relative risk}
\]

\[
EF = \text{etiologic fraction}
\]

The excess incidence is obtained by taking \( IR_1 - IR_0 \).

The excess incidence in the study can be calculated as follows:

\[
IR_1 \approx 25.8 \times \frac{3.46}{1000000} \times 0.837 \approx 74.7/1000000 \text{ person-years}
\]

\[
IR_0 \approx 3.46/1000000 \times 0.837 \approx 2.9/1000000 \text{ person-years}
\]

\[
IR_1 - IR_0 \approx 71.8/1000000 \approx 1:13900 \text{ person-years}.
\]

This estimate is difficult to interpret in that person-time here does not refer to person-years of exposure, since the measure of relative risk does not refer to a specified exposure (it refers to the chance of “any exposure during a one-week-period”). Therefore, the interpretation of the denominator is something like “person-years of any use within a week”. Most importantly, the number of users cannot be extracted from this information.

A previous study, the International Agranulocytosis and Aplastic Anemia (IAAA) study (see Risk management under General discussion), had the same problem in that the excess risk referred to the number of cases per million “person-weeks of any use within a week” (103).

Both studies had few controls exposed to dipyrone (9 and 12 exposed controls respectively), which makes it difficult to obtain estimates from subdivided categories of exposure. Otherwise, it should be possible to calculate relative (and excess) risks for the separate categories of 1, 2, 3, 4, 5, 6, and 7 days of exposure during the 7-day exposure window in relation to no exposure during the 7-day exposure window. Hypothetically, the excess
incidence associated with exposure for one day during the 7-day exposure window could be 20/1000000 person-years for a one-day exposure in a 7-day period, which can also be expressed as 140/1000000 exposed person-years. In order to obtain the total excess risk associated with exposure during the 7-day period, the excess risks associated with the different exposure subcategories ought to be added to each other.

Another factor of importance when determining the risk of agranulocytosis with dipyrone includes the difficulty to separate the treatment indication from an ADR in cases where dipyrone is used for fever.

In the last publication concerning the risk of agranulocytosis with dipyrone (98), the authors have not calculated the excess incidence. Instead, they have calculated the fraction of the population incidence of agranulocytosis leading to hospitalization that was due to exposure with dipyrone by multiplying the etiologic fraction of 0.163 with the population incidence of 3.47 per million person-years, which yields 0.56 cases per million person-years. The population incidence can be seen as the number of individuals with the ADR in relation to person-years of follow-up for both exposed and unexposed individuals. Here, the authors have taken the number of cases of agranulocytosis that were due to dipyrone and divided them with the number of person-years of follow-up for both exposed and unexposed individuals. Thus, the estimate is diluted by the number of person-years of unexposed individuals, and it is therefore not an adequate measure of risk in relation to exposure. Instead it presents how many cases in a given population would not have been recorded if there had been no exposure to dipyrone.

For example, for a drug that is associated with a relative risk approaching \( \infty \) (indicating an extremely high risk), the fraction of the population incidence that is due to the exposure is approximately equal to the population incidence multiplied by the proportion of exposed cases. The smaller the usage of the drug in the population, the smaller the proportion of exposed cases, and consequently the number of cases in the population during the study period that would not have been recorded had that (rare) exposure ceased to exist (all the way down to only one or a few exposed cases; those being the only ones exposed).

It is fascinating to see how much effort goes into spreading misleading information about the risk of agranulocytosis with dipyrone. However, it may be that there is a difference in attitudes to risk in that individual risk is considered to be of less importance than population risk. It needs to also be underscored that it seems to be the case that the majority of individuals who are susceptible to dipyrone develop agranulocytosis during the first months of treatment. This complicates comparisons of the benefit to risk balance in relation to drugs that are associated with a constantly increased incidence of a serious ADR throughout treatment (or worse with an increased incidence that further increases during treatment). The proportion of affected
individuals (i.e. the cumulative incidence) will be the same after some (unknown) treatment duration for agranulocytosis with dipyrone and for the serious ADR with the drug that constantly increases the incidence. Thereafter, the proportion of affected individuals will continue to increase with the drug that constantly increases the incidence, whereas it is likely to change very little or not at all for dipyrone.

Some words about the limitations of our risk estimate need to be included. Since the baseline risk of agranulocytosis without the involvement of drugs is negligible, a baseline incidence need not be subtracted from the estimate.

Two of the cases included in the incidence calculation received concomitant drug treatments that could potentially cause or contribute to agranulocytosis. If these cases are omitted from the incidence calculation, the risk is reduced to 1:1820 prescriptions.

The risk estimate is influenced by the degree of reporting (see General discussion). If it is assumed that 50% of cases are reported, the risk increases to 1:681 prescriptions.

Two of the cases included in the incidence calculation had treatment durations in excess of 3 months, and one prescription can cover a maximum treatment period of 3 months. Thus, the number of prescriptions must be higher than the number of treated patients. If we, based on a dipyrone utilization study in northern Sweden (104), assume that 28% of patients treated with dipyrone (31/112) iterated their prescription once (some of them may have iterated the prescription more than once, and some may have received more than one prescription for dipyrone, but this was not investigated in the study), then the 10892 prescriptions would refer to 8531 patients treated with dipyrone, and the risk in relation to the number of treated individuals would change to 1:1066.

In the case of a hypersensitivity reaction the risk may be approximated by the cumulative incidence (see Frequency estimation under signal evaluation in the Introduction section). The cumulative incidence can be approximated by the sum of the individual incidences:

\[
CI = \sum_{t=0}^{\infty} \frac{X_t}{N_t}
\]

Where:

CI = cumulative incidence  
\(X_t\) = number of individuals with ADR during time period \(t\)  
\(N_t\) = number of individuals exposed to the drug at the beginning of time period \(t\)

If the total number of individuals exposed to a drug stays the same at all time points, the cumulative incidence will be the same as the uncorrected
estimate obtained by dividing the total number of individuals with the ADR with the total number of individuals exposed to the drug. Let’s for sake of simplicity assume that the 10892 prescriptions dispensed in Sweden refer to the same number of individuals that all received dipyrone for a total treatment duration of exactly 3 months (each prescription in Sweden can cover a maximum treatment duration of 3 months), even though we know that some patients must have reiterated their prescriptions since two of the cases included in the incidence calculation had treatment durations in excess of 3 months. Let’s divide the cases into the following treatment duration categories: ≤ 14 days (3 cases), 15-30 days (0 cases), 31-60 days (3 cases) and >60 days (2 cases). The cumulative incidence would be calculated as follows: 3/10892 + 0/10892 + 3/10892 + 2/10892 = 8/10892 ≈ 1/1362.

As the number of individuals exposed to a drug usually decreases with increasing treatment duration, the cumulative incidence will typically be higher than the uncorrected estimate. Let’s therefore assume that between each category, the number of treated individuals’ decreases by one third. Then the cumulative incidence would be calculated as follows: 3/10892 + 0/7261 + 3/4841 + 2/3227 ≈ 1/660.

In fact, since all the different factors that lead to an underestimation of the risk have to be considered simultaneously, it cannot be excluded that the risk (in terms of cumulative incidence) is in the order of magnitude previously reported for amidopyrine (105;106), 1:120 treated patients.

Study 4. Glucose intolerance with atypical antipsychotics

A total of 868 reports of glucose intolerance with clozapine, olanzapine and risperidone were identified in the database until December 2000. When using the BCPNN method, all three atypical antipsychotic agents studied were significantly associated with glucose intolerance. In contrast, the two conventional antipsychotic agents chlorpromazine and haloperidol were not associated with glucose intolerance (see Figures; reprinted with permission from Drug Safety). The apparently higher IC values with clozapine and olanzapine compared with risperidone are consistent with results from studies demonstrating more profound effects with clozapine and olanzapine, e.g. (107;108).

Compared with all other ADRs for the atypical antipsychotic agents, an underlying diabetic condition (odds ratio 10.22), an increase in weight (odds ratio 2.36), male gender (odds ratio 1.27), and concomitant use of valproic acid (odds ratio 1.97), selective serotonin reuptake inhibitors (odds ratio 1.63), or buspirone (odds ratio 2.24) were more common among reports of glucose intolerance. The prescribed doses in cases of glucose intolerance did
not differ significantly from those in all other adverse reactions, and concomitant treatment with enzyme inhibitors was not overrepresented among cases with glucose intolerance. In support of our findings, the concomitant use of lithium or valproate in another study was associated with greater increases in weight and glucose levels compared with olanzapine treatment alone (107). Similar trends towards greater increases in weight and triglycerides were noted among patients treated concomitantly with lithium or valproate compared with patients treated with risperidone alone in the same study.

The mechanisms by which atypical antipsychotics promote weight gain and glucose intolerance have not been fully elucidated, but involve insulin resistance, hyperleptinemia, and increases in serum lipids (107-113), and are likely to constitute pharmacological effects.

The atypical antipsychotics clozapine and olanzapine were associated with more weight gain than the conventional antipsychotics haloperidol and chlorpromazine after 10 weeks of treatment in a meta-analysis, whereas risperidone was associated with a similar increase in weight as chlorpromazine (114). Overweight is a well recognized risk factor for the development of glucose intolerance and type II diabetes mellitus. However, it may not be the only factor involved in the development of glucose intolerance associated with atypical antipsychotics. After one year of treatment, olanzapine was associated with significantly greater increases in triglycerides, cholesterol and glucose compared with risperidone among patients under 60 years of age (107). A significant increase in weight was noted for both drugs, but weight changes did not correlate significantly with changes in triglycerides, cholesterol or glucose (107). Glucose and lipid changes have furthermore been demonstrated in non-obese patients treated with clozapine and olanzapine (108).

A positive correlation between insulin levels and serum concentrations of clozapine has been identified in two studies (115;116), but not in another (108). Two studies found an inverse correlation between the serum concentration of a metabolite to olanzapine, desmethyl-olanzapine, and blood glucose, triglycerides and cholesterol (109;115), which suggests that desmethyl-olanzapine may counteract the effects of olanzapine itself. A positive correlation between olanzapine serum concentrations and insulin resistance calculated by HOMA-IR was seen in another study (108). In the latter study, concentrations of 9-hydroxy-risperidone, a metabolite to risperidone, were found to correlate with the insulin-independent glucose uptake, SG (108).

One of the suggested mechanisms behind the development of glucose intolerance associated with atypical antipsychotic agents is an inhibitory effect on insulin-sensitive glucose transporters (108;117;118).

Patients treated with clozapine or olanzapine exhibited increased insulin resistance (i.e. decreased insulin sensitivity = SI) and reduced insulin-
independent glucose uptake, SG, compared with patients treated with risperidone (108). Five out of 24 subjects in the clozapine and olanzapine groups exhibited markedly reduced acute insulin responses to glucose in addition to reduced SI and SG.

In a placebo-controlled study of 4-6 weeks treatment with olanzapine and risperidone in dogs, effects on body fat disposition and glucose and lipid metabolism were studied (119). Olanzapine- and risperidone-treated dogs experienced an initial decrease in body weight, which was followed by an upward trend resulting in an increased body weight for olanzapine at the end of the study of 1.7 kg and a return to baseline levels for risperidone. Placebo-treated dogs experienced a steady increase in body weight that reached 1.5 kg at the end of the study. Olanzapine treatment was associated with greater total fat deposition compared with risperidone or placebo treatment. Insulin sensitivity, SI, tended to decline after both olanzapine and risperidone. Peripheral sensitivity was, however, not significantly altered by treatment in any group, whereas liver sensitivity to insulin was impaired by olanzapine resulting in a failure to suppress hepatic glucose output during hyperinsulinemia. In individuals with reduced insulin sensitivity there should normally be an upregulated response in insulin secretion to glucose. However, dogs treated with olanzapine failed to upregulate the insulin response to glucose, and 8 out of 10 dogs actually demonstrated a paradoxical decline in insulin response.

The BCPNN method does not eliminate potential errors associated with spontaneous reporting (see also General discussion). A general assumption is that the total number of ADRs reported with a drug is a fair approximation of the total number of patients treated with the drug. A significant positive association is seen when the ADR is more commonly reported with a specific drug compared with how often it would be expected to occur based on available information in the database (see Signal detection under Introduction). Such a significant positive association can reflect a true drug-ADR association (i.e. the ADR occurs at a higher rate with the drug), it can reflect an increased tendency to report the ADR in patients treated with the drug thereby causing a disproportionately higher reporting rate with the drug (e.g. because of media attention), or it can reflect a lower occurrence or reporting rate of other ADRs in patients treated with the drug so that the study ADR takes up a larger proportion of the reported ADRs with the drug. A false positive association can occur by chance or be the result of systematic errors (biases).

While it is easier to assume that a significant positive association indicates a causal relation between the drug and the ADR, it is more debatable if a drug-ADR combination that does not show a significant association or that shows a significant negative association should be taken to indicate a non-causal relation between the drug and the ADR. The latter interpretation may appear reasonable in a database, where all events
regardless of causality are included (e.g. a database including all adverse events from clinical trials). The interpretation in a database that includes only spontaneously reported ADRs is more complex, and among other things needs to take into account the occurrence of the ADR in a drug-free patient population (since the interpretation is different for ADRs that are typically drug-induced and for ADRs that occur regardless of drug treatment), and the patient population treated with the drug (since the occurrence of the ADR may be different for different patient populations and therefore depends on the treatment indication). A negative association may be due to less frequent occurrence or reporting of the ADR or alternatively, due to more frequent occurrence or reporting of other ADRs so that the study ADR takes up a smaller proportion of the reported ADRs with the drug.

In this case, we used the BCPNN method not only to estimate the associations between the three atypical antipsychotic agents and glucose intolerance. We also estimated for comparison the associations between two conventional antipsychotic agents and glucose intolerance. These patient groups should be broadly similar, since they share the same indications. However, it cannot be excluded that atypical antipsychotics are preferentially prescribed to patients at greater risk of glucose intolerance. It is also possible that media attention has contributed to the differences. Media attention may not only lead to increased reporting per se but also to increased testing for glucose abnormalities (i.e. diagnostic biases).

Hyperglycemia is included as ADR in the Swedish summary of product characteristics of clozapine, olanzapine and risperidone.
Figure 3. The strengths of the associations over time between glucose intolerance and clozapine, olanzapine and risperidone. An information component (IC) value increasing with time, with an IC –2SD value above zero, demonstrates a significant positive quantitative association between the drug and the adverse reaction.
Figure 4. The strengths of the associations over time between glucose intolerance and chlorpromazine and haloperidol. In contrast to the atypical agents, no associations were found.
Study 5. Pulmonary embolism associated with combined oral contraceptives: reporting incidences and potential risk factors for a fatal outcome

A total of 248 cases of suspected pulmonary embolisms were identified in the database (207 non-fatal, 41 fatal) of which a venous thromboembolism (VTE) diagnosis was supported by a positive verifying investigation such as phlebography, ultrasonography, computer tomography, magnetic resonance tomography, scintigraphy, angiography, or autopsy in 213 cases (172 non-fatal, 41 fatal).

Compared with non-fatal cases, fatal cases were more likely to:
- be > 35 years of age
- have a deep vein thrombosis above the knee level
- have vein or lymph vessel malformation
- receive treatment with other drugs known to increase the risk of VTE such as antipsychotics or drugs with estrogenic or antiandrogenic effects
- present with nausea or abdominal pain
- have no recorded previous use of combined oral contraceptives

and less likely to:
- present with chest pain
- be diagnosed with VTE within 14 days after start of VTE symptoms

The reporting incidence of pulmonary embolism with a verified VTE was 1.72 cases per 100 000 treatment years, and of fatal pulmonary embolism 0.25 cases per 100 000 treatment years.

The mechanisms behind an increased risk of VTE with combined oral contraceptives are likely to include changes in procoagulatory, anticoagulatory and fibrinolytic activity, and these constitute pharmacological effects. The clinical relevance associated with a certain change in a specific activity is unknown.

Several acquired (e.g. trauma, immobilization), and genetic risk factors for VTE (e.g. the Factor V Leiden mutation, the prothrombin G20210A mutation, and deficiencies in protein C, protein S or antithrombin), have been identified (120) that increase the risk of VTE in COC users.

This study is similar to study 3 in that cases with a fatal outcome were compared with cases with a non-fatal outcome. The study period during which fatal and non-fatal cases were compared was, however, longer. The possibility of period effects has to be considered, especially since information about specific risk factors among fatal and non-fatal cases may vary in a time-dependent manner.
On the other hand, fatal VTE among COC users is rare. Studies comparing fatal and non-fatal VTE cases, therefore, either have to include large patient groups or long follow-up periods.

Spontaneously reported cases may be biased in relation to all cases. However, similar biases are likely to apply to cases with and cases without a fatal outcome.

For some of the potential risk factors, information was only available from a subset of cases. This included information on body weight, smoking, family history of VTE, and previous use of COCs. It cannot be excluded that cases where information on such factors was provided were biased in relation to all cases. Findings relating to these factors are therefore uncertain.

Analysis of the time from onset of symptoms of VTE until diagnosis or death, whichever came first, was based on a subset of fatal cases (n=27) where the woman had visited the healthcare system due to symptoms of VTE. The result of this analysis supports the possibility that diagnostic delay may be implicated in the risk of a fatal outcome. The remaining fatal cases had either no recorded previous symptoms of VTE (n=5) or had not visited the healthcare system despite symptoms of VTE (n=9).

Analysis of the distribution of a deep vein thrombosis was based on cases diagnosed with a deep vein thrombosis (39 non-fatal cases, 22 fatal cases). The result of this analysis supports that a deep vein thrombosis above the knee level may be implicated in the risk of a fatal outcome. However, the finding is uncertain, since proximal veins are more likely than distal veins to be dissected at autopsy.

The findings that nausea and abdominal pain, which are unspecific symptoms of VTE, were more common among fatal cases and that chest pain, a more specific symptom of VTE, was more common among non-fatal cases may indicate either that specific VTE symptoms are important for a prompt diagnosis and/or that chest pain is a more benign symptom than nausea or abdominal pain.

The reporting incidence of pulmonary embolism in our study can be compared with estimated incidences of idiopathic VTE among COC users in cohort studies varying from 22 to 41 cases per 100000 treatment years (121-125). Since pulmonary embolism represents only a fraction of all cases with VTE, however, the proportion of reported cases of pulmonary embolism cannot be estimated. In a separate study where cases of reported fatal VTE were compared with all cases of fatal VTE among COC users 15-44 years of age during the years 1990-1999, the identified proportion of reported cases was 36% (126). This estimate is similar to a previously published estimate from New Zealand (127).
Study 6. Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors (SSRIs)

A total of 64 cases with extrapyramidal symptoms (EPS) were identified in the database (25 citalopram, 23 paroxetine, 7 sertraline, 5 fluoxetine, 5 fluvoxamine). Twenty-eight forms (46%) were returned, and 20 blood samples were obtained.

Compared with all other ADR reports with SSRIs, a significantly larger proportion of cases was 65 years of age or above (42.9% vs. 26.1%) (p=0.0054). Among EPS cases, patients reported to have parkinsonism (median age 69 years, 25th – 75th percentile 59-78 years) were older than patients reported to have acute dystonia (median age 44 years, 25th – 75th percentile 28-53 years) (p=0.0019), akathisia (median age 44 years, 25th – 75th percentile 36-56 years) (p=0.0091) or dyskinesia (median age 53 years, 25th – 75th percentile 44-66 years) (p=0.0424).

The A1 allele of the dopamine D2 receptor gene (DRD2) Taq1A restriction fragment length polymorphism (RFLP) was more commonly identified among EPS cases compared with pooled European literature controls (128-130) (32% vs. 15%; p=0.017) (relative risk 2.4; 95% confidence interval 1.2 – 4.5). No relationship was apparent for gender, drug dose or other polymorphisms investigated in genes coding for CYP isoenzymes (CYP2D6, CYP2C9 and CYP2C19), the dopamine D3 receptor (DRD3 Msc1), the dopamine transporter (DAT1 VNTR), and the serotonin transporter (5HTTLPR). At least one additional potential risk factor for EPS such as history of a CNS disorder, alcohol or substance abuse, epilepsy, Parkinson’s disease, previous or current exposure to antipsychotic drugs, concomitant treatment with other antidopaminergic or serotonergic agents, or a history of EPS was found in 93% of cases. Reporting was highest in the first years after market introduction.

EPS are known pharmacological ADRs of antidopaminergic agents. Dopamine receptor blockade has generally been accepted as the most likely mechanism involved (131). Although the mechanisms involved in SSRI-induced EPS are not fully understood, SSRI-induced EPS are also likely to constitute pharmacological ADRs. It has been proposed that serotonin may have an inhibitory influence on dopamine neurotransmission (131).

The identified association with the A1 allele of DRD2 Taq1A is biologically plausible. The A1 allele of DRD2 Taq1A has been associated with movement disorders independent of drug treatment (132), e.g. Parkinson’s disease (128;130). However, no consistent associations between the A1 allele of DRD2 Taq1A and antipsychotic-induced EPS have been found (133;134).
The finding that patients who were reported to have EPS were older than patients who were reported to have other ADRs to SSRIs is consistent with results from a previous review (135).

The finding that patients who were reported to have parkinsonism were older than patients who were reported to have acute dystonia, akathisia or dyskinesia is also consistent with another review that found that patients who experienced parkinsonism were older than patients who experienced akathisia (136), as well as data related to EPS with antipsychotic drug treatment (137).

The possibility of a pharmacokinetic interaction resulting in increased antipsychotic drug concentration needs to be taken into account for patients treated concomitantly with such agents (21% of cases with detailed drug history).

The study has several weaknesses related to spontaneous reporting. Not all EPS cases are reported, and reported cases of EPS may not be representative of all cases of EPS. Furthermore, cases for whom the form was filled and a blood sample obtained may not be fully representative of all cases reported, although they did not differ significantly with respect to age, gender or reported EPS reactions. It is also possible that different types of EPS have different etiologies, and that the results therefore are dependent on the relative proportions of the different types of EPS included in the study.

Moreover, the sample was small, which also limits the conclusions that can be drawn from the study. This concern relates particularly to polymorphisms in CYP isoenzymes, since only between 2-8 blood samples were obtained for each of the SSRIs.

On the other hand, apart from a tendency for spontaneous reports to be influenced by the type of ADR, its severity and its causal relation to the suspected drug (as well as media attention etc.) there are no obvious specific biases by which genetic subtypes would be selected, especially since no genetic information was available when the cases were reported.

Extrapyramidal symptoms are included as ADRs in the Swedish summary of product characteristics of most SSRIs.
General discussion

Pros and cons with spontaneous reporting

Strengths and merits

There is no doubt that spontaneous reporting systems provide an efficient and cost-effective way of gathering information about ADRs. Information can be entered into a database as soon as it is received. This means that it is possible to retrieve and act upon ADR information without time delay. Follow-up information, as well as changes due to case validation can be entered subsequently. Thus, ADR reports in databases for spontaneous reporting should be regarded as dynamic images that undergo changes in relation to further information and assessment.

It is important to point out that the strengths and merits of spontaneous reporting systems rely on adequate and prompt reporting of high quality medical information. This means that it is not only important that the degree of reporting (the proportion of all ADR cases that are reported) is high. High quality information is also important as it is a prerequisite for a thorough case assessment, where the different aspects that influence causality can be taken into account, e.g. a virus infection that may represent a differential diagnosis may be excluded after serological testing. In Sweden, the availability of a unique person identifier makes it possible to request follow-up information. Furthermore, specific tests can be suggested that can be used in the analysis and causal evaluation of cases.

Spontaneous reporting systems are of particular value for the collection of rare ADRs that can readily be attributed to drug treatment for obvious reasons. An ADR that is suspected to be due to the drug is more likely to be reported than an adverse event that is not suspected to be due to the drug. Other available systems for monitoring rare ADRs, such as record-linkage based surveillance, also have limitations that may include e.g. the ability to only monitor ADRs leading to hospitalization or ADRs related to prescription drugs, a restriction to limited populations or to population subgroups only (e.g. Medicaid, Medicare), a relative paucity of information concerning life-style factors, the need to obtain informed consent or ethics committee approval in order to receive individual clinical information, and a time lag for updating the register.
Apart from publications included in this thesis, the Swedish spontaneous reporting system has e.g. provided signals about drug interactions with St John’s wort (138;139), the interaction between warfarin and tramadol (30), Steven Johnson’s syndrome with lamotrigine (140), drug-related blood dyscrasias (141-145), the Guillain-Barré syndrome associated with zimelidine (146), myocarditis and venous thromboembolism associated with clozapine (147;148), lactic acidosis with biguanides (149;150), dyspnea, asthma and bronchospasm related to treatment with ACE inhibitors (151), tardive dyskinesia related to metoclopramide (152), and orlistat-associated hypertension (153).

It is becoming increasingly recognized that automated signal detection methods can improve the identification of signals in spontaneous reporting systems. The statistical measure of association provided for by automated signal detection methods is useful for selecting ADRs for further evaluation.

Underreporting, selective reporting, causality

Spontaneous reporting systems rely on the recognition of adverse (untoward) events, suspicion that such events may be drug-induced, and reporting to the MAH or to national reporting centers in those latter instances.

For obvious reasons, 100% reporting can never be achieved. The patient may not recognize or report symptoms to the health care system. The health care system in turn may fail to recognize that symptoms reported by the patient constitute adverse events or suspect that reported adverse events from the patient are drug-induced, i.e. represent ADRs. Finally, the health care system may fail to report suspected ADRs to the MAH or to national reporting centers.

On the other hand, not all adverse events (or ADRs) are recognized and reported even in double-blind randomized clinical trials, and the methods for collecting adverse event information influence the degree of completeness (154). Furthermore, there is a risk that true drug-induced events are not identified in randomized clinical trials because of a relative reliance on statistical differences in occurrence rates between the placebo group and the actively treated group. For rare ADRs, with perhaps only one or two cases in a study, it is important instead to emphasize the role of causality evaluation in individual cases. However, this requires that clinical information is available based on which non-drug causes may be verified or excluded, and including, where applicable, follow-up information after treatment discontinuation.

The most common reasons for physicians not to report suspected ADRs that have been proposed, the ‘seven deadly sins’ (155), include: 1) complacency, the mistaken belief that only safe drugs are allowed on the market, 2) fear of involvement in litigation, 3) guilt because harm to the patient has been caused by the treatment the doctor has prescribed, 4)
ambition to collect and publish a personal series of cases, 5) ignorance of the requirements for reporting, 6) hesitance about reporting mere suspicions which might lead to ridicule, and 7) lethargy – procrastination, lack of interest or time, an inability to find a report form, etc.

In an attitude survey of ADR reporting by health care professionals across the European Union (156), ignorance of how and where to report as well as lack of time to report were the most common reasons for not reporting ADRs, whereas concerns about confidentiality, fear of legal liability, fear of appearing foolish, or ambition to publish were only viewed as deterrents to reporting by a small proportion of respondents in each country. In six out of nine countries in the survey, less than 10% of respondents believed that all marketed drugs are safe. Seriousness of the reaction was considered to be the most important factor in deciding whether to report an ADR (81.3% to 94.9% of respondents in different countries), followed by unusualness of the reaction (63.3% to 88.9% of respondents in different countries), involvement of a new product (63.7% to 90.8% of respondents in different countries), and confidence in the diagnosis of the ADR (28.7% to 75.5% of respondents in different countries). Similar results have been obtained in separate attitude surveys in Sweden (157;158).

These attitude surveys show that spontaneous reporting systems are not only subject to underreporting but also subject to selective reporting. Among other things, ADRs are more likely to be reported if they are serious, if a non-drug etiology has been considered unlikely, if the drug is new, and in the case of media interest.

Another issue that needs to be addressed is the possibility that there is no true association between the drug and the ADR, i.e. that the reports reflect a mere coincidental occurrence of an ADR during drug treatment or that the ADR is due to another concomitant drug. The number of expected coincidental occurrences of an ADR during drug treatment resulting from the background incidence of the event (ADR) can be calculated as follows:

\[ E = IR \times N \times T \]

Where:

IR = the incidence rate of the event (ADR) in the population
N = number of individuals treated with the drug
T = the duration of treatment with the drug

The number of reported expected coincidental occurrences is less than the number of expected coincidental occurrences since not all ADR cases are reported. It has been calculated that for rare ADRs, the number of reported expected coincidental occurrences is usually so small that it does not constitute an important limitation of spontaneous reporting systems (159).
Reporting rates as estimated from spontaneous reporting of ADRs are likely to be underestimates of the true occurrence rates of an ADR because of underreporting.

Because of the potential for selective reporting of ADRs in spontaneous reporting systems, it cannot be assumed that reported cases are representative of all cases. Based on results from attitude surveys it could be anticipated that there is more evidence in favor of a drug-induced disorder among cases that have been reported compared with not reported cases. It could also be anticipated that reported cases have more serious manifestations of an ADR compared with not reported cases. These biases are not considered to invalidate the identification of risk factors for the ADR, but have to be taken into account whenever attempts are made to extrapolate findings from reported cases to all cases.

Other methodological considerations

All studies included in the thesis are hypothesis generating rather than hypothesis testing. When multiple comparisons are done, some spurious associations must be anticipated (on average one out of 20 comparisons with a p value of 0.05). In general, results therefore need to be supported by findings from independent investigations. Comparisons were also performed for each factor individually rather than including all factors in a multiple regression analysis. It is possible, therefore, that associations may have occurred that are due to covariation with another, measured or unmeasured, causally related factor.

When no control group is included in the analysis of risk factors, the importance of identified risk factors cannot be quantified.

When the control group is selected from among other ADR reports to the study drugs, it may be difficult to identify risk factors because the same factor may be a general risk factor for ADRs with the study drugs. This effect would work in favor of any identified differences being more likely to be true.
Risk management

From the regulatory perspective, the following main possibilities for risk management exist: 1) to suspend or withdraw the drug, 2) to amend the product information (i.e. vary the summary of product characteristics), e.g. 2a) limit the indications for the drug, 2b) contraindicate or warn against the use of the drug in certain situations or for certain patient populations, 2c) include information about the ADR, and 3) to inform prescribers and the community through other means of communication.

Often, a combination of measures is necessary. When communicating risks, all components of risk characterization need to be considered, and the information needs to be tailored for the receiver of the information.

It is important to establish whether or not a risk can be managed by information and changes to the product information or if it is necessary to withdraw the drug from the market. If the first alternative is chosen, an evaluation of the impact of those measures on the subsequent risk should be made.

Before deciding what measures to take the ADR needs to be put into perspective, i.e. the overall balance between benefits and risks needs to be evaluated in comparison with other drugs that are available on the market for the same indications. Although this may sound simple in theory, it is often impossible to perform complete benefit risk comparisons due among other things to a relative lack of comparative information, meaning that important drug risk information usually derives from spontaneous reporting and not from controlled randomized clinical trials, which is why decisions have to be made on the basis of information that indicates rather than verifies a negative benefit risk balance.

Furthermore, the documentation of efficacy may be old and relative comparisons to modern drugs may be missing. Any analysis is also complicated by the fact that risk scenarios may be different in different patient groups.

It also needs to be evaluated whether or not the drug is essential for certain patient groups and therefore cannot be replaced by other drugs. In the latter respect important differences exist between different countries as in some countries the regulatory authority can approve the use of a non-licensed drug in an individual patient on a compassionate use basis. This provides an opportunity for better control of the use of the drug, but is dependent on the continued availability of the drug such as when the drug is still marketed in other countries.

An alternative approach to withdrawing the marketing authorization of a drug with particular ADR risks is to restrict the use of the drug to patients who consent to be included in a follow-up safety study. However, as in the case of cisapride in the European Union, if the legal basis for such a decision
is inadequate, adherence to the protocol may be low and its usefulness therefore questionable.

It could be argued that if a drug poses a serious risk to patients that cannot be managed by information and changes to the product information (regardless of whether or not this is because other risk groups exist that are not covered by changes in the product information or because prescribers do not adhere to the product information) the drug should not be available on the market. On the other hand, there will always be patients who will benefit from or tolerate better a specific drug that is generally less safe for patients.

Prescribers who have personal (positive) experience with a drug may be reluctant to change their prescribing habits in light of new safety information, particularly if the indications for use of the drug have been severely restricted, e.g. when a drug used historically for long-term treatment of a chronic condition is restricted to acute use for that condition.

Cognitive biases active in the perception of benefit and harm are discussed in a publication by Greenhalgh et al (160). Preference for status quo, i.e. the reluctance to change current behaviors, such as taking or prescribing a particular drug, even when the objective evidence of benefit changes, may be due to persistence of prior beliefs and expectations (160;161)

Another challenging situation arises when the ADR mainly occurs with use of the drug outside of the conditions specified in the product information, e.g. unauthorized indications or patient populations for which the risk-benefit balance is negative or has not yet been established (e.g. children), higher than recommended doses or concomitant use of prohibited medications (or alcohol)

These situations all need to be taken into account, including the possibility to minimize risk through information and changes to the product information, when assessing the overall benefit risk balance of a drug.

Table 3 gives examples of drugs that have been withdrawn from the market and/or not approved for marketing in Sweden, where safety issues have played a significant role in the decision process.

It needs to be underscored that the regulatory authority does not always take the decision. Indeed, the MAH may come to the conclusion that the continued marketing of a drug is not warranted, although its decision may have been preceded by discussions with regulatory agencies about the safety profile and the possible need for restrictions to the use of the drug. Below the withdrawals of dipyrone and nefazodone in Sweden will be presented in more detail.
Table 3. Examples of drugs withdrawn from the market and/or not approved for marketing\(^1\) in Sweden, where safety issues have played a significant role in the decision

<table>
<thead>
<tr>
<th>Substance or group of substances</th>
<th>Therapeutic class/indication</th>
<th>Principal adverse drug reaction/s leading to marketing withdrawal and/or non-approval of application for marketing authorization</th>
<th>Year not approved/year withdrawn in Sweden (^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Hypnotic</td>
<td>Teratogenicity</td>
<td>1962</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Psycho-stimulant</td>
<td>Psychosis, drug dependence</td>
<td>1968</td>
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<tr>
<td>Amidopyrine</td>
<td>NSAID</td>
<td>Agranulocytosis and other blood dyscrasias including aplastic anemia</td>
<td>1973</td>
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<tr>
<td>Clozapine (^3)</td>
<td>Antipsychotic</td>
<td>Agranulocytosis</td>
<td>1974</td>
</tr>
<tr>
<td>Dipyrone (metamizole) (^4)</td>
<td>NSAID</td>
<td>Agranulocytosis and other blood dyscrasias including aplastic anemia</td>
<td>1974</td>
</tr>
<tr>
<td>Hydroxyquinolines (^5)</td>
<td>Anti-infective</td>
<td>Subacute Myelo-Optic Neuropathy</td>
<td>2000</td>
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<tr>
<td>Practolol (^6)</td>
<td>Beta-blocker</td>
<td>Oculomucocutaneous syndrome, psoriasiform skin eruption</td>
<td>1975</td>
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<tr>
<td>Methaqualone</td>
<td>Hypnotic</td>
<td>Drug dependence</td>
<td>1979</td>
</tr>
<tr>
<td>Diethyl-stilbestrol</td>
<td>Estrogen</td>
<td>Tumor development in female offspring</td>
<td>1980 (^7)</td>
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<tr>
<td>Phentermine</td>
<td>Anorectic</td>
<td>Psychosis, drug dependence, pulmonary hypertension</td>
<td>1981</td>
</tr>
<tr>
<td>Amfepramone</td>
<td>Anorectic</td>
<td>Psychosis, drug dependence, pulmonary hypertension</td>
<td>1981</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>NSAID</td>
<td>Renal damage, renal tumor development</td>
<td>1982</td>
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<td>Zimelidine</td>
<td>Antidepressant</td>
<td>Polyradiculitis (Guillain-Barré)</td>
<td>1983</td>
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<tr>
<td>Barbiturates (^8)</td>
<td>Hypnotic</td>
<td>Drug dependence</td>
<td>1984</td>
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<td>Fenfluramine (^9)</td>
<td>Anorectic</td>
<td>Psychosis, drug dependence, pulmonary hypertension</td>
<td>1988</td>
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<td>Terodiline</td>
<td>Urinary spasmolytic</td>
<td>Proarrhythmia</td>
<td>1992</td>
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<td>Temafloxacin</td>
<td>Antibiotic</td>
<td>Hemolysis, hepato-renal syndrome</td>
<td>1992</td>
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<tr>
<td>Encaidine</td>
<td>Anti-arrhythmic</td>
<td>Proarrhythmia</td>
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<td>Phenyl-butazone</td>
<td>NSAID</td>
<td>Agranulocytosis and other blood dyscrasias including aplastic anemia</td>
<td>1994</td>
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<td>Sparfloxacin</td>
<td>Antibiotic</td>
<td>Serious hepatic injury</td>
<td>1995</td>
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<tr>
<td>Troglitazone</td>
<td>Antidiabetic</td>
<td>Drug interactions resulting from non-competitive inhibition of e.g. CYP3A4</td>
<td>1997</td>
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<td>Mibebradil</td>
<td>Calcium channel blocker</td>
<td>Churg Strauss syndrome</td>
<td>1999</td>
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<td>Zafirlukast</td>
<td>Leukotriene receptor antagonist</td>
<td>Churg Strauss syndrome</td>
<td>2001</td>
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<td>Trovafloxacin</td>
<td>Antibiotic</td>
<td>Serious hepatic injury</td>
<td>2001</td>
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<td>Pimozide</td>
<td>Antipsychotic</td>
<td>Proarrhythmia</td>
<td>2001</td>
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<tr>
<td>Nefazodone</td>
<td>Anti-depressant</td>
<td>Serious hepatic injury</td>
<td>2002</td>
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<td>Cerivastatin</td>
<td>Lipid-lowering drug</td>
<td>Rhabdomyolysis</td>
<td>2002</td>
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<td>Levoacetymethadol</td>
<td>Heroin addiction</td>
<td>Proarrhythmia</td>
<td>2002</td>
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<tr>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>Proarrhythmia</td>
<td>2002</td>
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<tr>
<td>Grepaflloxacin</td>
<td>Antibiotic</td>
<td>Proarrhythmia</td>
<td>2003</td>
</tr>
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</table>
Dipyrone (metamizole)

Dipyrone was first approved in Sweden in 1934. It had, however, been available on the Swedish market prior to this date. In 1934 a new law was passed requiring all medicinal products to be approved. After the establishment of SADRAC in 1965, reports of agranulocytosis with dipyrone and other butazolone derivatives became a major concern.

The risk of agranulocytosis with dipyrone was estimated at one case in 3000 treated patients, based on one reported case per 10 000 patients and a known reporting rate of 30 percent of cases (162). This level of risk was considered unacceptable, and all dipyrone-containing medicinal products were withdrawn from the Swedish market in 1974.

Dipyrone was re-introduced to the Swedish market in 1995, following results from an international case control study of agranulocytosis, the International Agranulocytosis and Aplastic Anemia (IAAA) study, suggesting a much lower risk of agranulocytosis, only ca one case per 900 000 users per week (103).

Soon thereafter, the first new cases of agranulocytosis with dipyrone were reported to SADRAC. The updated (minimum) risk of agranulocytosis with dipyrone was estimated at one case per 1361 prescriptions (8 cases per 10892 prescriptions) (study 3). Due to this high risk, dipyrone was suspended from the market in April 1999, and withdrawn in 2000.

It was considered that no obvious risk groups could be identified. A restriction to short-term use did not appear meaningful because there was no evidence that repeated short-term exposure would constitute a lower risk compared with continued exposure. Furthermore, a review of all cases of
blood dyscrasias with dipyrone that had been submitted to SADRAC (study 3) indicated that in 11 percent of cases, all hematopoieses were affected.

Nefazodone

Nefazodone, a combined serotonin reuptake inhibitor and 5-HT2 blocker, was approved in Sweden for the treatment of depression in 1995.

In 1997, the MAH was requested to update the product information following reports of increased liver enzymes in PSURs. In 1998, a more thorough review of the hepatic safety of nefazodone was prompted by one case report of acute liver failure with a fatal outcome associated with the use of nefazodone in a young otherwise healthy Swedish woman.

The MAH was requested to submit all available information on hepatic ADRs, including experience from clinical trials.

Already in premarketing clinical trials, elevated liver enzymes were reported in over one percent of nefazodone-treated patients, and were significantly more common compared with placebo.

When including information from postmarketing clinical trials, the frequency of more severely increased liver enzymes, defined as more than 5 times the upper limit of normal of alanin-aminotransferase (ALAT) or aspartate-aminotransferase (ASAT), was 49 out of 7324 patients (0.67%). The difference between nefazodone and SSRIs (0.17%) was statistically significant. A total of 7 patients (0.1%), all in the nefazodone group, experienced increases in transaminases above 20 times the upper limit of normal. None of the patients in the clinical trials developed acute liver failure, but one patient developed mild jaundice 3 days after stopping nefazodone. Since all patients who had at least one follow-up laboratory test were included in the incidence calculations regardless of the treatment duration, the true incidences taking into account the decreases in the denominator with time are higher than those estimated.

In Sweden, a cumulated total of 6847100 DDDs (400 mg) of nefazodone had been sold up through December 2000, equivalent to 18760 patient-years. Until 31 December 2000, there had been a total of 18 reports of liver injury with nefazodone with at least a possible causal relation. The outcome in one of these cases was fatal following two unsuccessful liver transplants. In 5 additional cases, transient liver failure was documented with > 50% increase in prothrombin time (INR > 1.3). The incidence of liver transplantation/death due to liver failure in Sweden was estimated at 53 cases per million patient years. The incidence of liver failure in Sweden was estimated at 320 cases per million patient-years, and the incidence of adverse liver reactions leading to hospitalization at 480 cases per million patient-years. The frequency of reported serious adverse hepatic reactions with nefazodone was higher than for any other antidepressant in Sweden.
Worldwide, estimated sales data corresponded to 1.6 million patient-years. The MAH had received a total of 15 reports of liver transplantation/death due to liver failure until the end of year 2000, corresponding to an incidence of liver transplantation/death due to liver failure of 9.6 cases per million patient-years. The worldwide incidence of liver failure could not be estimated due to insufficient information to determine the presence of liver failure in the reported cases.

SADRAC considered that the comparatively high risk of serious hepatic injury made nefazodone unsuitable for first-line treatment of depression.

Documentation from clinical trials suggesting that nefazodone may have less prominent sexual ADRs compared with SSRIs could support a second-line indication for patients who had experienced intolerable sexual ADRs with SSRIs. However, this indication could only be approvable in the presence of an appropriate liver monitoring program.

The MAH agreed that nefazodone was associated with rare but serious liver injury, however questioned if the risk could be reduced by liver monitoring. Instead, the MAH chose to withdraw the marketing authorization.
Risk minimization strategies

With increasing knowledge of general ADR mechanisms, improved preclinical toxicological models to predict safety issues are likely to be developed that could eventually lead to safer drugs being put on the market.

Today, most drugs undergo preclinical (in vitro studies, animal studies) pharmacological-toxicological, reproductive, and cancer studies (see for example 163-175).

During the 1980’s and 1990’s, the link between QT prolongation and life-threatening ventricular arrhythmias as well as the link between certain drugs and QT prolongation, were established. Animal models to predict the risk of QT prolongation have since been developed, and are used in the evaluation of possible QT prolongation for a new drug (176).

New drugs also undergo more extensive characterization of drug metabolism prior to marketing authorization, see for example (177-183), which allows for a better evaluation of the potential for drug interactions, and also provides information as to whether the new drug is subject to polymorphic metabolism.

A new ICH guideline, the ICH E2E on Pharmacovigilance planning has recently been implemented. It has identified the following situations that should be addressed in a Pharmacovigilance Specification before a marketing authorization is granted:

1. Non-clinical safety concerns that have not been resolved by clinical data.
2. Possible clinical concerns related to in- and exclusion criteria in clinical trials and implications of such limitations for predicting the post-marketing safety of the drug taking into account the populations likely to be exposed in medical practice, and the extent of the world-wide exposure.
3. Specific populations not studied in the pre-approval phase, e.g. children, elderly, pregnant or lactating women, patients with hepatic or renal disorders, subpopulations with genetic polymorphisms, and patients of different ethnic origins.
4. Identified or potential safety issues that require further evaluation.
5. Identified or potential interactions and their possible mechanisms.
6. Morbidity and mortality in the target population (i.e. related to the indication), including possible differences in the distribution of risk factors in different geographical regions.
7. Possible class effects (i.e. pharmacological ADRs that can be predicted from the same mechanism of action).
Ideally, pharmacovigilance activities should start at the beginning of drug development, and continue throughout the whole life cycle of the drug. This means that pharmacovigilance expertise needs to be involved in the decision processes as early as possible, both at the level of the pharmaceutical company/MAH, and at the regulatory agency level. Identification of insufficient resources at pharmaceutical companies/MAHs to carry out pharmacovigilance obligations is also part of this evaluation, and if necessary, pharmacovigilance inspections can be performed.

The ICH E2E guideline under development states that issues discussed in the Pharmacovigilance Specification document should form the basis of a Pharmacovigilance Plan. The two documents should be developed in conjunction.

It is important that any potential safety issues as indicated above are adequately evaluated, and an action plan proposed and discussed. Such an action plan could e.g. include a more active follow-up of treated patients (e.g. in the form of registries or follow-up safety surveillance studies) as well as proposals for specific studies. Feasibility, acceptable timelines for finalization, and ability to solve the specific scientific question are also important points to be covered in the document. Specific studies and/or follow-up of treated patients can be a requirement for the granting of a marketing authorization.

Apart from the design of prospective studies, retrospective studies can also be conducted, and make use of available databases that contain drug prescription and disease information such as the General Practitioners Research Database in Great Britain (184-186). Cohorts of patients who have been prescribed a certain drug can be identified and followed over time, and disease/ADR incidences can be estimated. However, use of over-the-counter drugs that can be purchased without a prescription may not be included in these databases.

Safety issues of particular importance are rapidly communicated to other countries within the European Union through a special ‘rapid alert system’, which ensures that the information reaches and is taken care of by the other regulatory authorities within one working day. Important safety issues are also discussed at regular meetings between regulatory authorities in the European Union, and between the European Union and the FDA at regular telephone conferences. Furthermore, regulatory authorities worldwide participate in communicating drug safety issues through the WHO.

When different regulatory agencies communicate to health professionals or the general public about the same safety issues, the information may need to be synchronized.
Activities of identifying, evaluating and quantifying ADRs are carried out throughout the lifecycle of medicinal products. Spontaneous reporting systems, a response to the thalidomide disaster, remain a major source of ADR information.

Exceptionally, as exemplified here by dipyrone, risk estimates from spontaneous reporting systems can be more accurate than those from epidemiological studies. Spontaneous reporting systems can also be of value for studies of risk factors for ADRs. However, they cannot replace specific studies when such studies are needed.

Assessment of risk may be a complex task. Therefore, pharmacovigilance expertise should preferably be available as early as possible during the drug development process, and work in collaboration with other expertise involved in preclinical and clinical studies.

One important question is how much emphasis should be put on investigating the safety of drugs prior to marketing. For example, a randomized double-blind placebo controlled study showed a doubling in the risk of myocardial infarction and stroke after more than 18 months of treatment with rofecoxib. The study was performed several years after marketing when millions of patients had already been exposed to the drug. The study results prompted the MAH to withdraw rofecoxib from the market world-wide. A previous large randomized double-blind long-term study that had used the active control naproxen had also shown an increased occurrence of cardiovascular thromboembolic events that was assumed to be due to absence of a preventive effect of rofecoxib (naproxen is known to inhibit the production of thromboxane in thrombocytes).

At the other end of the spectrum, many patients may not gain access to an effective new drug if large placebo-controlled long-term studies would be needed prior to marketing, although compassionate-use programs could be a way to address the issue. Also, the cost of developing a new drug would increase, which would make the drug more expensive for patients and the healthcare system. But perhaps most importantly, it would be difficult beforehand to determine the level of safety that could be considered acceptable, i.e. how large an increase in risk the study would have to exclude for how long a treatment duration.

Therefore, regardless of pre-marketing demands, investigation of the safety of a new drug will predominantly remain a post-marketing issue. The
question is how to go about this. One way may be to put particular emphasis on the known pharmacological properties of the drug (e.g. mechanism of action, pharmacokinetic properties including potential for drug interaction, effect on cardiac repolarization) and the general knowledge of the safety profile of drugs with similar pharmacological properties. This should provide a good basis for the need to address potential issues in well-designed studies. Issues that cannot be addressed in specific mechanistic studies have to be investigated in epidemiological studies or controlled randomized clinical trials. The long-term effects of hormones or other drugs acting on nuclear receptors on cancer risk are examples of such issues.

In contrast to pharmacological ADRs, hypersensitivity ADRs can usually readily be detected and evaluated in spontaneous reporting systems, although more reliable estimates of the frequency of such ADRs may need to be obtained from randomized clinical trials, long-term follow-up studies or epidemiological studies.

In Sweden, the ability to monitor the safety of drugs post-marketing would be further improved by the introduction of a nationwide drug-prescription database, which could be linked with other registries such as the registry of hospital admissions, the cause of death registry, the cancer registry, and the pregnancy registry. Strategies to increase spontaneous reporting are also important, since it can take more than a year to obtain validated registry information.

Needless to say, drugs with hitherto unknown pharmacological properties need particularly stringent post-marketing surveillance.

The availability of accurate and continuously updated information on possible risks with medicinal products is essential for a timely and appropriate regulatory action to be taken.

Risk needs to be communicated taking into account the general perception and acceptance of risk in the target group/general population. When the information is attempting to change behavior in a group of people, measures to evaluate the effect of the intervention are important. Studies to evaluate the general impact of risk information to prescribers and patients should also be encouraged in order to better understand how a specific communication strategy is perceived and what its results are so that future communication strategies can be continuously improved.

Pharmacovigilance is an area of increasing interest and importance. More emphasis will be put on pharmacovigilance as new therapeutic principles are introduced, and the number of medicinal products on the market steadily increases. As a result of this, there is also likely to be further increased need for transparency and sharing of evaluations between regulatory agencies in the future.
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