ISDB EU:
Berlin Declaration on Pharmacovigilance

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Content

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SUMMARY

Pharmacovigilance, the process for evaluating and improving the safety of medicine, must be strengthened.

Adverse drug reactions (ADRs) significantly diminish quality of life, increase hospitalisations, prolong hospital stay and increase mortality. Furthermore, the financial cost of ADRs to health care systems is enormous. There are several recent trends in the regulation of medicines that are likely to expose more people to ADRs: for example, new drugs are being approved for marketing more quickly and without adequate long-term safety studies, supranational marketing is making drugs available to many more people at an early stage, and removal of restrictions on availability is leading to some medicines being used more widely by patients for self-medication.

The problems

- Systems for pharmacovigilance are not well organized and funded to serve patients and the public optimally. So, for example, the European Medicines Agency (EMEA) is attached to the Enterprise Directorate General (DG) in charge of industry and not to the DG Health and Consumer Protection, an obvious conflict of interest; there is little sharing of information on ADRs between regulatory authorities and health professionals. EMEA and national agencies are funded to a great extent by industry, and so far no law requires that pharmacovigilance be funded by the public part of an agency's budget.
- Information about ADRs is often poor and secret**.** There is insufficient research on ADRs, so that the exact incidence (either population- or prescription-based) of specific ADRs is unknown. Information about ADRs from the pharmaceutical industry and regulatory authorities is usually not accessible by the public.
- Health professionals' motivation for pharmacovigilance is low, there is little encouragement for them to be involved in the process and ADRs are generally under-reported.
- Patients receive inadequate and poorly understandable information about ADRs. Reports directly from patients, the only ones to actually experience the ADRs, are often not accepted by professionals in established monitoring centres and by regulatory authorities.

ISDB* Europe convened a regional working group to discuss how to achieve more effective phamacovigilance and so achieve the safer use of drugs. The group met in Berlin on 31 October and 1 November 2003. The declaration culminates with several proposals to all parties involved in pharmacovigilance. The main themes of the proposals are:

Towards greater openness – Transparency, based on freedom-of-information legislation, should be the norm. From the day a medicine is marketed, regulators and the pharmaceutical industry must allow access to all relevant data from clinical and pre-clinical trials, including animal studies. These data need to be publicly available to enable health professionals and drug bulletins to assess the benefit/harm ratio of treatments more thoroughly than can be done from the Summary of Product Characteristics (SPCs) and material industry is willing to provide. Health care providers need to be informed promptly about new findings on ADRs. There must be policies for disclosing potential conflicts of interest wherever they exist.

Summary

Sharing pharmacovigilance data – There must be more cooperation and integration among national and international bodies in the form of a network for pharmacovigilance. Standardized methods of investigating drug accidents must be established leading to avoidance strategies.

Better reporting and information gathering – Reporting of ADRs after marketing should be actively encouraged and should involve all those concerned (e.g. doctors, pharmacists, nurses, midwives, healers and patients). To facilitate this, learning about pharmacovigilance should start early in the professional training of healthcare students. In the case of specific drug safety concerns, governmental or non-governmental institutions (such as insurance companies) should initiate appropriate studies.

Better information for, and collection of feedback from, patients – At the start of any treatment, patients must be given full, unbiased information about the potential benefits and harms of the therapy. Independent drug information for patients should be made available to patients wherever they are treated (including in hospital). The wording and presentation of such information should have been tested for clarity.

*** The International Society of Drug Bulletins (ISDB)**

ISDB is a worldwide network of bulletins on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry. Members of the International Society of Drug Bulletins (ISDB) publish evidence based, comparative and independent information about drugs and therapeutics to help health professionals optimise their therapeutic activity in the best interests of patients. ISDB was founded in 1986. Its overall aim is to assist the development of independent drug bulletins and to facilitate cooperation among them.

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I PURPOSE AND CONTEXT

1. The key objectives

During the development of medicines and before marketing, the pharmaceutical industry works to assess the efficacy and the unwanted effects of their drugs. The information gathered is, however, of limited value as pre-marketing observations are made on relatively few people (early clinical trials rarely involve more than 3000 people), data collection is secretive and selective, and the information collected does not relate to the use of medicines in clinical practice (aspects concerning the safety of new drugs are addressed in the "ISDB Declaration on therapeutic advance in the use of medicines"[1], Paris, 15-16 November 2001). To remedy this, it is important to have in place arrangements for detecting, identifying, and responding to adverse events (AE; see annex) and adverse drug reactions (ADRs; see annex), remembering that an AE has to be regarded as ADR when the causal relationship between event and the drug cannot be excluded or further investigation as to the event's circumstances and pathophysiology make it plausible that the reaction was indeed a response to the drug in question. Key objectives of such pharmacovigilance which can be briefly defined as the process of evaluating and improving the safety of medicines (see annex),[2] are to consolidate what is already known, quickly detect ADRs that were previously unknown or incompletely documented, and to inform about ADRs in order to reduce ADRs and medication errors in future.[3] Through robust pharmacovigilance, the frequency of ADRs can be estimated, balances made between benefit and harm, comparisons made between the ADRs of alternative treatments, and advice given to health professionals and patients on treatment choices. At least a quarter of ADRs and a half to a third of drug induced deaths could be avoided.[4-6] It follows that better and earlier detection and collation of ADRs will improve the chances of medicines being used safely.

In recent years, efforts have been made worldwide to strengthen pharmacovigilance. One way to help achieve this would be by making information about ADRs held by industry and the regulatory authorities widely available. In 1997 the Erice Declaration[7] set out basic principles for communicating drug safety. However, the work of the European Medicines Agency (EMEA) and most national regulatory authorities of the European Union has not become noticeably more transparent, and little progress has been made in communicating information on drug safety to patients and health professionals. As a consequence, the burden of ADRs on patients and the public health has remained essentially unchanged.

2. Learning from failures

Not only are the arrangements for discovering ADRs weak, but when problems do arise thorough investigation of the underlying cause is not the rule. Aviation accidents are studied exhaustively, and the lessons learned are disseminated widely, with important and expensive interventions made obligatory by regulatory authorities. In contrast, even after hundreds of deaths have led to a drug's withdrawal from the market, the regulatory authorities do not systematically investigate thoroughly the cause and what mistakes might have led to the events. Learning from failures has generally been fragmentary with methods of investigation and intervention under-developed.

3. Pharmacovigilance is essential

A properly working pharmacovigilance system is essential if medicines are to be used safely, effectively and with confidence. Moreover, such a system benefits all parties and so not only the individual patient and the public, but also health professionals, health insurance systems, health policy makers and regulatory authorities. In addition, it also helps the pharmaceutical industry to avoid lawsuits which would be costly in terms of money and image, although companies have traditionally shown little enthusiasm, believing that information about ADRs can hamper drug promotion and diminish sales and so the profit of shareholders.

Further aims of the declaration are:

- to strengthen the awareness among the public about pharmacovigilance as an issue of public health,
- to encourage regional strategies of pharmacovigilance,
- to accelerate the transmission of European directives into national legislation,
- to support the conversion of national legislation into effective organisational structures,[8]
- to consider carefully the process of EU legislation (Directive 2004/27/EC and Regulation [EC] No 726/2004)[9-11] and the international cooperation in pharmacovigilance.

II THE NEED TO IMPROVE PHARMACOVIGILANCE IS BECOMING MORE URGENT

1. The starting point

When a product is first marketed, there is little experience on its safety and efficacy in clinical practice, with the information available coming from clinical trials that have focused mainly on the demonstration of efficacy, have lasted a relatively short time, and are done in hospital or in closely-monitored settings. Pharmacovigilance should help improve understanding about safety, but in practice many factors conspire to frustrate such arrangements and make a review of pharmacovigilance procedures particularly relevant now.

2. Shorter approval times

The reliability of pre-marketing drug safety evaluation suffers from the increasing pressure from the pharmaceutical industry (and sometimes from patient groups, often supported directly or indirectly by industry) on politics and regulatory authorities to shorten the approval time for new medicines. Apart from issues surrounding the collection of data, it must be recognised that robust scientific analysis of the information that is available takes time. Accordingly, as the approval period is shortened, the risk of discovering unexpected ADRs after market release may increase.

3. Globalisation creates large (supranational) markets

The greater the number of users of a newly launched drug, the greater will be the potential number of victims of ADR. In an era where the launch of a new product can be supranational (so for example, simultaneously launched across the EU and often at the same time in other regions) and is accompanied by aggressive marketing, there is the added risk that ADRs that were not recognized in clinical trials can affect thousands of patients before efficient steps can be taken to minimise harm. The globalisation of marketing has not been paralleled with a global ADR monitoring system.

4. New drugs undermine the advantages of familiarity

The growing number of me-too products without therapeutic advantage over previously existing options reduce the use of well-known standard drugs with which prescribers (and patients) are familiar (the 'familiarity dividend'). The willingness of clinicians to prescribe, and patients to take, new drugs inevitably (and unnecessarily) exposes millions of people to insufficiently studied and

unfamiliar drugs without any obvious benefit. Furthermore actions of new drug classes (e.g. anti-tumor necrosis factor antibodies like infliximab) are becoming more complex and powerful, and often ADRs too.

5. Widening the self medication market

There is an increasing move to make medicines traditionally available only on prescription (Prescription-Only Medicines; POMs) available for purchase by the public over the counter (OTC). This switch weakens traditional pharmacovigilance arrangements, as clinicians are no longer involved and ADR reporting by the prescriber is bypassed, with no systematic approaches for the public to report and in many countries without involvement of pharmacists.

6. Direct to consumer advertising (DTCA)

In countries where direct to consumer advertising (DTCA) is permitted (USA and New Zealand) clinicians are put under increasing pressure to prescribe new prescription drugs by requests from patients influenced by DTCA. By its very nature, DTCA potentiates the problems of explosive marketing. 'Direct to consumer information' is now the new term coined for DTCA.

7. Disease mongering

Using marketing devices, opinion-formers and the lay media, drug companies create new indications that can result in drugs (particularly newly marketed ones) being prescribed when there is no definable clinical need,[12] e.g. drugs for male pattern baldness. Rapidly widening markets can have the same effects as explosive marketing.

8. The internet and the unsupervised provision of medicines

The internet is widely used for DTCA (which is forbidden for prescription drugs in the European Union with the exception of special vaccination campaigns), but in addition and through the internet, medicines (often POMs) have become available to the public across national borders, and without real control by national or international drug laws, regulatory agencies or health professionals. Medicines obtained in this way are like OTC medicines outside the scrutiny of traditional pharmacovigilance arrangements.

9. "Lifestyle medications"

Medicinal products are being used increasingly in the hope of improving lifestyle quality rather than for clinical issues, and so preventing, diagnosing or alleviating illness. This development, which will inevitably trivialise use of medicines and may well affect the reporting of ADRs, exposes a growing number of healthy people to drugs and their hazardous effects.

10. Complementary and alternative medicines

Complementary medicines largely escape official systems of approval and quality control, and certainly those for pharmacovigilance. Traditional medicines are often used outside the normal controls on packaging and labelling and so it may be difficult to identify what caused an ADR if the active component of the product is not clear from the packaging. Moreover, users may not see an event as a product's side effect (and so not worth telling a health professional), if they believe the treatment to be natural and without risk.

11. Trends leading to greater patient autonomy

Patients are taking more responsibility for therapy with the shift from hospital-based medically supervised treatment to community- or home-based therapy. Accordingly, drugs with a high inherent risk (e.g. cytotoxic agents or heparins) which were previously used only in hospital settings

are now self-administered by the patient at home. One effect of this change is that the ADRs observed might differ in quality and quantity and perceived severity. In addition, as already noted, reporting arrangements, and so phamacovigilance, are not designed to respond to patient generated observations.

12. Substandard drugs

Counterfeit or contaminated medicines are increasingly penetrating the drug market (even in industrialised countries) and these could bring a new spectrum of ADRs.

13. Economic aspects

ADRs significantly diminish quality of life, increase hospitalisations, prolong hospital stay and increase mortality. The financial burden of ADRs in hospital is enormous, with estimates suggesting a cost of between 7 million and 18 million Euro per 1 million inhabitants.[13]

III OBSTACLES TO PHARMACOVIGILANCE

1. Basic obstacles

1.1. Incomplete knowledge

At the time a drug is approved knowledge about its risk is incomplete. Tests in animals are necessary and useful to discover toxic effects, but do not allow sufficient conclusions about human safety. Clinical studies focus on demonstrating efficacy statistically instead of comparing benefits and ADRs with those of existing drugs. The small number of patients involved in, and unsatisfactory length of, clinical studies limit the value of their findings. Thus, pre-approval clinical data include only information about the most common ADRs. In addition, specific doses are used and patients who may be at greater risk from ADRs are usually not studied during the development of a drug, e.g. young children, elderly people, pregnant or lactating women, patients concomitantly using other drugs or other therapies, patients with complicated disease conditions, sub-populations carrying known and relevant genetic polymorphism and patients of different racial and/or ethnic origins.[14] Thus, clinical studies give very limited information about risk and efficacy in real life conditions. Reporting of harms-related data from clinical studies needs improvement.[15]

The design of randomised clinical studies (and later of meta-analyses) - typically made by clinicians and not by experts in pharmacovigilance - usually concentrates on efficacy. Generally, statistical power of a study is calculated for efficacy, not for ADRs. Furthermore adverse events are inadequately and inconsistently reported in most clinical trials, and if the investigators decide that an event is unrelated to treatment it is usually not mentioned at all.

Drug regulatory agencies worldwide routinely rely on selective data presented by companies.[16] The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention.[17] The worst possible situation occurs when incomplete data lead to the promotion of an ineffective and harmful intervention, for instance by the suppression of negative trials of serotonin-selective reuptake inhibitors (SSRI) in children.[18]

1.2. Shortcomings of spontaneous reporting: under-reporting

Spontaneous reporting is the backbone of pharmacovigilance. It is available immediately after a new drug is marketed, continues indefinitely and, potentially, covers all patients receiving the drug. It helps to generate safety signals by accumulating data on similar ADRs. The great weakness of spontaneous reporting is health professionals' limited ability to recognise unknown and unexpected adverse events and then their failure to report what they do observe. Throughout Europe, the level of spontaneous reporting of ADRs is low (so-called under-reporting).[19]

Prejudices can also lead to under-reporting. Examples are the belief that complementary medicines are "natural" and therefore without the potential to cause ADRs, and the misinterpretation of ADRs such as fever as typical "initial deterioration" indicating that the medicine is effective.

Limited data exist on the incidence of ADRs. It is generally acknowledged that most ADRs - even fatal ones - are not reported. Under-reporting delays the recognition of new ADRs and leads to the perception that injuries from ADRs are less common than they really are. Little research has been performed in this area compared with other major causes of death such as heart disease or cancer. Reporting rates in clinical trials and in spontaneous reporting systems suggest that only between 2% and 5% of all ADRs are reported in many spontaneous systems. Dedicated pharmacovigilance centres achieve reporting rates between 10% and 20%.

Deaths due to ADRs are common.[20-22] For example, fatal ADRs rank from the fourth to the sixth leading cause of death in the United States of America. ADRs are estimated to cause 3-7% of all hospital admissions.[23,24] More than half of these ADRs are not recognised by the attending physician on admission. ADRs may be responsible for the death of 15 of 1000 patients admitted.[25]

1.3. Shortcomings of other strategies

There are other pharmacovigilance strategies. Chart review in hospitals can detect ADRs more systematically than voluntary reporting, but is costly and so not suitable for routine use. Cohort studies may allow measurements to be made of the incidence of a common ADR but are considered poor at detecting new safety issues mainly because of difficulties in obtaining high-quality data on medication use and of limitation in size.[24] Postmarketing clinical trials can be valuable in addressing particular safety issues, but if they are sufficiently large and well conducted they may become prohibitively expensive.[26]

Computer-assisted tools for identifying ADRs, such as natural language processing or automated signal generation (data mining) are now being developed.[27] They are of limited value because they are non-clinical and most flagged signals represent known associations or confounding by indication.[28] All signals have to be further evaluated. Thus, these tools must aid human review and not replace it.[29,30]

1.4. Imprecise evaluation

ADR data from spontaneous reporting are usually based on suspicion, and may be preliminary, ambiguous, doubtful or wrong. The poor quality of data often affects the interpretation. Thus, spontaneous reporting cannot provide definitive answers. Attempts to standardise causality assessments by using checklists and algorithms have not produced consistent and helpful evaluations of ADRs. The uncertainties remain.

In many causality assessment systems, the fact that a reaction is not known substantially decreases the causality score, making such a system less appropriate for the purpose of signal detection.[31] Computer-assisted algorithms and calculations may result in quasi-accurate probabilities.

Limiting an evaluation of ADRs to events that are rated as 'definite/certain' and 'probable/likely' underestimates the true incidence of ADRs. While including 'possible' events may overestimate the incidence. 'Unlikely' reports are sometimes rated as worthless. But these cases may be of special interest from the point of hypothesis generation, especially in connection with other adverse event (AE) or ADR information and/or preclinical data such as animal toxicology trials, and may put a different complexion on an AE when new findings emerge.

1.5. Lack of transparency

Studies performed or sponsored by drug companies for the evaluation of drug safety are now held centrally, and little or no detail is available to health professionals and the public.

Even when the number of reported ADRs is available, prescribing data, which are essential for estimating their incidence and which are demanded by EU legislation, are mostly not in the public domain. In most countries, drug companies and their market research firms keep sales data secret, as do some large health insurance organisations. Some national healthcare systems publish data on drugs prescribed in the community (e.g. annual Arzneiverordnungs-Report, Germany). But no data are publicly available on drugs used in hospitals or OTC products.

Because most media and scientific journals derive huge incomes from drug advertising, information on ADRs for the public and health professionals is heavily biased. Industry-sponsored journalists may assist industry's marketing in masking and playing down drug harms, e.g. in connection with hormone replacement therapy.[32]

1.6. Lack of effective organisation

In some countries there is no supporting organisation, and often no one has official responsibility for investigating ADRs that occur in hospital or private practice. So while hygiene and nosocomial infections are considered important issues, ADRs occurring in hospitals are often ignored.

2. Policy makers and drug regulators

2.1. Lack of transparency

Information on ADRs is still inadequate despite repeated calls for more transparency from independent drug bulletins, Health Action International (HAI) and other groups and networks. ISDB editors and patient organisations have told the EMEA about persistent deficiencies and failures in its structure and work in this regard.[19,33]

Like most national health authorities, the EMEA, as it adheres closely to the letter of the European law, continues to protect what is called the intellectual property rights of drug companies, rather than support the rights of patients and professionals to have access to complete information about the reported risks of drugs. The wording of the new Regulation 726/2004/EC that information on "serious adverse reactions and other pharmacovigilance data ... shall be made publicly accessible, if relevant, after evaluation" (article 26)[10] is an insufficient signal of transparency. Secrecy surrounding, and difficulties in access to information on ADRs are major barriers to safe drug use because harm and benefit cannot be properly understood and evaluated. Secrecy undermines the patient's and health-care provider's confidence in medicines, the pharmaceutical industry and the health authorities. This can potentially lead to crisis, panic and the inevitable unwarranted abrupt treatment interruptions when a drug is withdrawn or its use restricted. The argument that secrecy is necessary because drug companies do not trust each other to refrain from exploiting each other's scientific work implies that companies' commercial interests may differ from the interests of public health.[34]

In most countries the precise data and considerations underlying regulatory benefit-harm evaluations remain unpublished. Occasional announcements or press releases do not meet the needs of patients, health care providers or drug bulletins. Details of known and new ADRs and relevant background information are missing.

At the time the authority and the pharmaceutical companies consider and discuss the available pharmacovigilance data, little or no information is publicly available. Even for indisputable ADRs, it may take months or years before information is included in the official product information. Summary of Product Characteristics (SPCs) and patient information leaflets are therefore often outdated and incomplete, and there may be inconsistencies between SPCs of different brands of the same drug.[35]

2.2. Conflicts of interest

EU law obliges the member states to promote the protection of human health and of consumers of medicinal products (for discussion about the word 'consumer' see annex). EMEA, however, is attached to the Enterprise Directorate General (DG) of the European Commission, the primary concern of which is industrial performance, and not under the DG Health and Consumer Protection (DG Sanco), which would seem the more proper umbrella.

Conflicts of interest may arise, because drug regulatory authorities are, to a growing degree dependent on fees from the pharmaceutical industry.[5] On the other hand the fees keep the drug regulatory agencies more independent of shrinking public budgets. But, in many countries, those who advise regulatory authorities often have substantial links with, and sometimes direct funding from, pharmaceutical companies.[36] For example, of the 38 members of the national UK Committee on Safety of Medicines in 2002, 19 received payment directly ('personal interests') from pharmaceutical companies, and of the 19 who did not have personal interests, 10 declared receiving monies indirectly ('non-personal interests').[37]

In the pre-approval stage, regulators and their scientific advisers tend to weigh the balance of scientific doubts about drug safety in favour of the drug's promoters in order to facilitate early licensing. In the postmarketing phase, they also take this approach to the interpretation of spontaneous ADRs and other safety data.[34]

It may be a hindrance for appropriate action, if the same authority which is responsible for clearing products for approval also has the task of monitoring their safety and, under given conditions, has to remove them from the market. That creates an inherent conflict of interest.[38] Measures may be delayed because they could signal poor quality of approval decisions and the authority may have to explain why it allowed the drug to reach the market. The unwillingness to disclose the information is intensified by the fear that disclosure may threaten a product, affect company profits and share prices, and be followed by litigation.

Even when an authority has issued a warning about a product, or has ordered its withdrawal from the market, it often does not disclose the data which led to the action, perhaps because decisions that are not explained are harder to dispute. But, for drugs following the centralised procedure, drug companies must now inform the European agency of their reasons for withdrawing their application, and the agency must make this information available to the public.

2.3. Problems of organisation

Pharmacovigilance data obtained nationally and internationally are not yet sufficiently integrated and mostly not adequately accessible. Knowledge obtained in one country may not be shared with other countries. On the other hand, larger (international) databases and greater speed in generating and analysing signals does not seem to have led to faster communication by regulators or improvement in surveillance of drugs.

Several years of active pharmacovigilance are necessary to get a clear picture about ADRs of new drugs, of little-used drugs, of new combinations of active substances and of new indications which may alter the established benefit-harm profile of that drug. Although new drugs/indications imply particular risks they are mostly not marked as new (with the exception for instance of the black triangle symbol used in the UK).

Long-term use of drugs in chronic diseases or for prophylaxis is normally introduced without appropriate long-term studies. Thus, long-term safety is unknown and late unexpected ADRs may affect many patients before being recognized and acted upon.

The 'compassionate' use of unlicensed drugs for patients with chronically or seriously debilitating disease, or whose disease is considered to be life-threatening, and who cannot be treated by an authorised medicinal product, creates a particular risk of unexpected ADRs because of the paucity of knowledge of harm and benefit at the time of use.

3. Pharmaceutical industry

3.1. Misinformation

Pharmaceutical companies are primarily interested in sales and turnover, while patients are interested in health and wellbeing. To capture market share pharmaceutical companies emphasise the drug's efficacy in their "information" and minimize the significance of ADRs, e.g. classifying them as unproven events (AE). Anything to do with harms tends to remain buried, because of the commercially sensitive connotations. Thus, while the VIGOR trial raised concerns about the cardiovascular toxicity of the non-steroidal anti-inflammatory drug rofecoxib, Merck Sharp & Dohme proposed – in the absence of any evidence – that the explanation of the observed worrying increase in the risk of myocardial infarction was the "cardioprotective potential" of the comparator drug used in VIGOR, naproxen.[39]

Playing down problems may be considered 'natural', given that pharmacovigilance activities may unearth problems that otherwise do not come to light. Drug representatives may hesitate to forward ADR reports because they could harm the company, or because their own income depends on sales figures. Financial liabilities can be so important that when ADRs lead to a drug crisis the company may primarily inform the stock market rather than health professionals and the public, as Bayer did in the case of cerivastatin (Baycol/Lipobay)[40] and Merck Sharpe & Dohme in the case of rofecoxib (Vioxx).[41]

3.2. Lack of transparency

Till today there is no free public access to all clinically relevant data. Over 300 clinical trial registers currently exist.[42] But they are hard to use, not comprehensive (e.g. no details from clinical trials in registers run by industry for drugs that failed to gain approval) and have limited accessibility. The European Clinical Trials Database EudraCT registers all clinical trials on medicinal products that take place in the 25 member states and started on or after 1 May 2004. However, the database itself is confidential. The information is mainly accessible for EU regulatory authorities and concerned drug companies and not for the public. But health professionals, patients and the institutions that pay for health services all need such data in order to make good choices and to use the drugs in the best ways, maximising their benefits and minimising their harms. Systematic reviews of treatments are bound to be biased if studies are kept secret, and future research is misrouted or impeded if lessons from hidden studies cannot be assimilated.[42] Systematic reviews are also biased because of multiple publication and because of selective reporting, e.g. by publishing only the more favourable per-protocol results instead of intention to treat analyses.[43]

Pharmaceutical companies are unwilling to disclose information that might threaten a product and indirectly favour competitors' products. In addition, scientists who have spent years working on a drug are too close to the drug to give objective information.[44]

Companies collect spontaneous reports and forward them to the drug regulatory authorities to comply with the regulations and to protect themselves against law suits. The use of different codes for the same clinical findings can hide alarming signals, e.g. when 'attempted suicide' is classified as 'non-accidental overdose'.

Drug companies sometimes wage aggressive campaigns against those who voice safety concerns.[45] Some pharmaceutical companies have used litigation against researchers, editors and publishers in attempts to suppress the publication of information that casts doubt on the safety (or effectiveness) of their products.[46]

If drug companies compensate victims of ADRs the payment is commonly settled out of court with a secrecy clause, so that other people suffering a similar ADR remain unaware of the settlement.

3.3. Discouraging ADR reporting

Complex ADR questionnaires discourage ADR reporting. Many drug companies send out overlong and overcomplex ADR questionnaires which are time consuming to complete and which give the reporters the feeling that they don't know enough about the reported case. Although they appear to be thorough and scientific, in reality, such forms can actually hamper the goals of pharmacovigilance.[47]

3.4. Failing to conduct important studies

Pharmaceutical companies have little interest in conducting long-lasting and expensive epidemiological studies to clarify the risks of particular drugs or to establish long-term safety. It appears that fewer than half of the postmarketing studies that companies have made commitments to undertake as a condition of approval have been completed and many have not even been initiated.[48] If companies conduct postmarketing studies at all, they prefer a design that demonstrates some economic benefits of the drug in question, creates product awareness for market-penetration or provides data for their own use as defence in any litigation rather than for safety interests.[49] Promotional studies, in which treatment is changed merely to recruit the patient into a post-marketing study, expose patients to the unforeseen hazards of new drugs in numbers that are far too large to be adequately monitored by individual doctors.[50]

4. Doctors

4.1. Under-reporting

Physicians are reluctant partners in ADR reporting. Physicians fail to report an estimated 95% to 98% of all adverse events for varying reasons[51-54]

- they don't think about it because they have not been educated to do so
- they think the features of ADRs are already well known, especially when the suspected drug is old
- they interpret ADRs as minor or irrelevant
- they lack the interest to listen to the patient
- they have doubts about the causal role of the drug(s) involved and wrongly assume that causality has to be established
- they suspect that the ADR has never been previously discussed and fear that their suspicion might therefore be wrong
- they suspect that the ADR has already been reported by a colleague
- they lack the time
- they fear a lot of extra work, because of time-consuming requests for additional information
- they are concerned that the ADR might subject the reporter or others to disciplinary action or a lawsuit
- they fear they could be sued by the company for 'false' statement and compensation
- reporting is thought to be ineffective
- they are ignorant of the requirements for reporting
- they plan to collect and publish a personal series of cases
- they lack understanding of what types of ADR should be reported
- the ADRs simulate a common spontaneously occurring disease or simulate the symptoms of the treated disease
- relevant information is missing such as drugs prescribed by other physicians or medicines taken without prescription (patients rarely tell physicians about their use of alternative medicines)
- they lack financial compensation for the time and effort of reporting
- they lack feedback from authorities or medical professionals in the system
- reporting forms are not to hand

4.2. Lack of training

Besides the lack of education in reporting ADRs, many physicians have lagged behind other professionals in learning how to effectively communicate risk. In other industries, such as aviation and nuclear industries, where risks have to be conveyed to the public this is usually done only by a few specially trained people working on behalf of their organisations. In health care, where the risks are usually far higher and more uncertain and complex, almost every doctor who interacts with patients has to communicate information on risk, yet few have any training.[55]

Physicians tend to report ADRs that they regard as serious rather than those which interfere with the patient's day-to-day life. So ADRs important to patients tend to be neglected.

5. Pharmacists

Patients often use non-prescription drugs without visiting a physician. Thus for many of them the pharmacist is the only health professional the patient comes into contact with. In addition, pharmacists may be in the position to identify problems related to multiple prescriptions from different specialists who don't know or may ignore what is prescribed by others or to collect information unmentioned to the doctor. Most pharmacists, however, are not trained to report ADRs. Thus, ADR information given to pharmacists by a patient is often lost.

Many hospital pharmacists are insufficiently integrated into pharmacovigilance activities, though they have the best knowledge of "pharmaceutical" signals, for example doctors or wards preferring particularly new drugs or frequently using drugs with a high risk profile.

6. Nurses and other health professionals

Nurses, midwives and other health professionals other than doctors and pharmacists, are rarely invited to report ADRs despite the fact that they often alert the prescriber and often give more detailed descriptions of ADRs including minor reactions than do physicians. The quality of reports received from nurses may be similar to those received from doctors.[56-58]

The reluctance of non-physicians - primarily nurses - to report ADRs that may involve doctor error or malpractice is an important cause of under-reporting.

7. Patients

Direct patient reporting of ADRs is not supported by European law. Article 22 of Regulation 726/2004/EC simply states: "Patients shall be encouraged to communicate any adverse reaction to health-care professionals".[10] But, for a variety of reasons (for instance, an unsatisfactory relationship between the patient and the health professional or divergent opinions on the interpretation of an adverse event) patients may not wish the health care provider to fill in the form.

As patients are the only ones who actually experience ADRs, it seems logical to value their experiences. ADRs reported by patients, although often trivial to doctors, can be sufficiently important to patients to make them stop taking the drug. In only a few countries or pharmacovigilance institutions, ADR reports are accepted from patients (pilot schemes are running in Denmark, in the UK and in other European Countries).[59-61] Whether these will not only increase the number of the reports but - as it seems[62] - also lead to a more timely detection of signals of possible ADRs, has to be confirmed. In some fields, it has been shown that patient reporting may be a more sensitive tool than that of health professionals, for instance in detecting withdrawal effects on stopping antidepressants or the risk of antidepressants of enhancing suicidality.[63]

The (poor) quality of patient reporting has been raised as a concern and it may be difficult to categorise such reports without filtering them through professionals. Existing doctor-pharmacist systems cannot easily incorporate this extra task because of the lack of skills to extract useful information from patients' reports and of the time to do it.

In some countries patients generally receive inadequate information about the harm and benefit of drugs, though delivery of information is or should be part of the treatment. While risk perception by patients can easily be manipulated (e.g. by advertorials, advertising or the internet), independent information can encourage more appropriate forms of treatment.

Reports from patients and volunteers during drug trials must also be considered. ADRs experienced by people who drop out from a trial may indicate a special problem and may be missed in the published report of the study.

IV PROPOSALS

Having considered the growing relevance of pharmacovigilance and the many obstacles to undertake pharmacovigilance, the working group makes the following proposals.

1. Basic strategies

1.1. Access to all relevant data

The protocols and results of pre-clinical research (animal studies and toxicology studies) and clinical trials which are registered centrally (nationally or internationally) should be connected to a worldwide register using a unique international numbering system.[64] Registrations should start at trial inception (at the time of ethical approval and/or funding approval) and should cover studies of both drug and non-drug therapies.

The full data must be publicly available from the date of first marketing at latest, whether a product has been licensed through the centralised or a national procedure. The registered trials data have to comply with the CONSORT (**Con**solidated **S**tandards **o**f **R**eporting **T**rials) guidelines including the recommendation about reporting harms-related issues.[15,65] The register must be accessible at no charge. It must be open to all prospective registrants and managed by a not-for-profit organisation. There must be a mechanism to ensure the validity of the registration data, and the register should be electronically searchable.[66]

All scientific journals should require, as a condition of consideration for publication, registration in a public trials register (as announced by the International Committee of Medical Journal Editors).[66]

Current standards for safety reporting in clinical trials have to be revised and information about all adverse events (AEs) or adverse drug reactions (ADRs) per study arm should be systematically included as well as detailed descriptions of cases with previously unknown AEs/ADRs and the specification of numbers and reasons for study withdrawals.

The type and frequency of all adverse events occurring during the development of medicines should be fully declared and mentioned in the Summary of Product Characteristics (SPCs) so that there is no loss of information.

If 'compassionate use' of unlicensed medicines is allowed for patients, all information from preclinical (e.g. animal study data) or clinical trials must be given to the treating physician and on request to the patient and drug bulletins. Reporting of ADRs should be obligatory in compassionate use as with any other use.

1.2. Reporting of ADRs

Reporting of ADRs after marketing should be actively encouraged and should involve all health professionals (including pharmacists, nurses, midwives, healers etc.) as well as patients.

ADR report forms should be widely available (in journals, formularies, compendia, at pharmacies, via the internet, etc.). Their design should be such as to make them easy to complete. The possibility of reporting by telephone, including a toll-free telephone number for this purpose, should be considered and evaluated.

The institutions to which ADR reports are sent should routinely give feedback on information about the recorded data and about other reports on the suspected ADR of the drug(s).

Spontaneously reported ADR data have to be available without restriction (exception: personal data such as identity/addresses of patients and reporters).

1.3. Transparency

Health care providers should be informed promptly about new findings to enable them to inform patients fully to allow them to make informed choices. Information about ADRs should include a description of how such reactions might affect quality of life.

Rules have to be established for 'good pharmacovigilance practice' with special reference to the ethical and legal basis of reporting, and improvement of data availability for health professionals and patients and transparency in pharmacovigilance.

1.4. Evaluation of the effectiveness of pharmacovigilance

Independent research has to be done into the effectiveness of pharmacovigilance, and on how established systems have detected relevant ADRs and protected patients from unsafe drugs. The impact of pharmacovigilance on public health and expenditures should be evaluated.

2. Policy makers and drug regulators

2.1. General strategies

"Activities relating to pharmacovigilance" must "receive adequate public funding". The implementation of this new rule (Article 67-4, Regulation 726/2004/EC)[10] has to be enforced.

The laws and regulations concerning marketing and advertising policies have to be enforced. Advertising that might adversely affect the quality of medical care should be banned. DTCA should permanently be banned. Those advertising prescription-only medicines in the internet should be prosecuted.

A reasonable suspicion of an ADR, or suspicion of a significant increase of a known ADR, requires all concerned to act promptly to protect patients before causality or accuracy of incidence increase is determined, especially if the benefit expected from the medicine may be obtained in another way.

Standardized international methods of investigating drug accidents should be established and implemented for routine use in a way that is equivalent to the procedures developed for the investigation of aviation accidents.

2.2. Transparency

Transparency should be the norm, based on freedom of information legislation. Implementation of Article 73 of Regulation 726/2004/EC[10] concerning public access to documents held by the European Agency has to be looked at by health professionals, patient groups etc. Commercial confidentiality should be confined to details of manufacture and formulation, not to clinical trial data or ADRs. All aspects of drug risks including comparative data have to be openly communicated to all concerned parties (prescribers, suppliers, dispensers, patients etc.).

The pharmacovigilance data should be routinely integrated into the European Agency's public database. Anonymised details of all reported ADRs should be available on the agency's website to improve public access to information on ADRs.

Information about ADRs and their frequency should be given in a patient-friendly and understandable manner. Expressing risk by relative numbers may be misleading and not helpful to the understanding of risk and harm. Absolute numbers and concepts such as "number needed to harm" (NNH) or frequency statements like "three out of every ten patients" should be used.[67] Visual aids should be used wherever possible, to maximise understanding.[55]

Information on all issues of pharmacovigilance including the minutes of pharmacovigilance proceedings should be accessible. Uncertainty about the harm-benefit relation should not be ignored or downplayed. Each time a Direct Healthcare Professional Communication is provided on a safety issue for a drug, a patient-tailored communication should be published by the EMEA or the national agencies.

In the case of specific drug safety concerns, governmental or non-governmental institutions (for instance insurance companies) should initiate or fund appropriate studies like case-control studies or cohort studies, in order to provide optimal information about drug safety. Public hearings during the evaluation process should be introduced. No closed-door expert meetings should be allowed and no reports by "experts" with conflicts of interest.

2.3. Coordination with minimal conflicts of interest

Publicly-funded independent drug safety units monitoring post-approval marketing should be established nationally and in the EU as part of public health apart from the drug approval agencies. Personal funding from pharmaceutical companies should be strictly prohibited for the staff of these units. Physicians with a conflict of interest should not be members of committees that make judgements on harm and benefit of particular drugs or devices. Corresponding article 63 of Regulation 726/2004/EC[10] rapporteurs and experts who participate in pharmacovigilance meetings or working groups of these units should have to declare, at each meeting, any specific interests which would be considered to be prejudicial to their independence with respect to the items on the agenda.

The EMEA should be transferred from the Directorate General (DG) Enterprise to the DG Consumer Protection/Public Health.

Coordination between national and international agencies and pharmacovigilance centres must be improved. The integration of international pharmacovigilance activities has to be ensured. European and national drug safety agencies must develop or strengthen mechanisms for considering pharmacovigilance data obtained by the WHO and non-EU countries.

A network of institutions should be established by individual initiative and medical councils and regulatory authorities to

- help health care providers put pharmacovigilance into practice
- give professionals advice on individual cases
- stimulate ADR reporting, e.g. by giving feedback information
- organize postgraduate training
- plan and conduct studies in pharmacovigilance

In all countries the proposed pharmacovigilance centres should be organized, established and financed as soon as possible.

2.4. New drugs and indications

New drugs/indications should be clearly identified as such to all patients and health professionals. The legislator should instruct the EMEA to list new drugs by generic name (INN; up to five years on the market, with declaration of the year of [local] introduction) or drugs requiring intensive monitoring for other reasons. Substances on this priority list should be identified as such on the packaging and in the patient leaflet inviting the patient to contribute to better knowledge of this drug by reporting any ADR.

For new drugs or drugs belonging to a pharmacological class that has previously given rise to a re-assessment of the harm-benefit balance in the EU or by a non-EU country, use of the EU centralised procedure should be obligatory to ensure that any such assessment is subject to the expertise of all EU member states.[68]

2.5. Long term studies

Given the limitations of spontaneous reporting, well-designed epidemiological studies and other methods of active surveillance are required, such as case-control studies and large cohort studies, to investigate and quantify the risks of drugs including safety in at-risk groups (such as elderly people, children, pregnant women and patients in renal failure) and interactions.

Therapies for chronic conditions or long-term prophylaxis require long-term studies in large, randomised controlled populations with overall mortality as the main endpoint for assessing safety of prophylactic interventions. Long-term studies should be planned and administered in cooperation with pharmacovigilance centres.

2.6. Periodic Safety Update Reports (PSURs)

The Periodic Safety Update Reports (PSURs) which companies have to provide regularly (every six months, every year or every three years, depending on how long the drug has been on the market) and which have to include a scientific evaluation of harm and benefit,[10] should be made available to the public. Once PSURs enter the EMEA they should be considered 'public' as specified in Regulation 1049/2001. Moreover, the PSURs should be written in a way that any new information is clearly identifiable. Outdated products whose "risk-benefit balance is not positive under the normal conditions of use" (article 116 of Directive 2004/27/EC)[9] should be removed from the market.

3. Pharmaceutical industry

3.1. Preclinical and clinical studies

The drug industry needs to strengthen safety monitoring during clinical trials by involving independent pharmacovigilance experts in the early phase of study design. Declaration of conflicts of interest of investigators are now obligatory and should be made public.

Companies should, as far as possible, perform trials that reflect real life situations - with patients who have underlying diseases or take relevant concomitant medications.

Postmarketing surveillance of recently marketed drugs have to be non-interventional: there should be no deliberate change of treatment in postmarketing studies for marketing or promotional reasons merely to recruit the patient into the study.

3.2. Information and transparency

Drug companies must give health professionals and patients full information about ADR reports received nationally and internationally.

Data on drug prescription and utilisation should be available to the public on request so that when there are suspected ADRs, those who wish to make independent evaluations can know how many individuals have been exposed to the drug, in what dose, for how long and under what circumstances. The commercial interests of pharmaceutical companies should not be allowed to restrict access to their data from market research whenever drug safety problems are involved.

When litigation cases (claims of victims of ADRs for compensation) are settled out of court, secrecy clauses should be prohibited.

3.3. Reporting of ADRs

Pharmacovigilance systems of drug companies including the Perodic Safety Update Reports (PSURs), that are used as sources for the identification of new safety signals for changes in the harm-benefit-profile of drugs,[69] should be examined carefully by health authorities, to check that they comply with legislation and provide no misleading information, for instance by inconsistent coding of ADRs.

4. Physicians

4.1. Education

Learning about the harm-benefit concept, pharmacovigilance, effective risk communication and prescribing errors should start early in the professional training of students. Instruction in efficient communication of statistical information should be part of medical curricula and doctors' continuing education. Medication errors may also be reduced by specific education initiatives aimed at prescribers.

Health care providers should be offered basic education in the law and the legal process surrounding ADRs to reduce some of the anxiety about possible legal action.

4.2. Reporting of ADRs

All physicians (and other health professionals) must take responsibility for quality control and optimizing quality of drug therapy. To this end, they should be reminded of their duty to report ADRs as a part of their professional responsibility and daily work. They must be informed about what to report, how to report, to whom to report, and that proof of causality is not a precondition for ADR reporting. Educational programmes in ADR reporting should be established in hospitals in collaboration with the hospital pharmacists. Members of ethics committees should have special training in pharmacovigilance.

Guidelines should be established for reporting anecdotes of suspected ADRs in the literature so that they contain all the necessary information.[70] It should be compulsory to communicate the ADR to a pharmacovigilance centre before preparing and submitting a paper for publication. Editors should not accept anecdotes for publication unless the authors have confirmed that the ADRs are already reported.

4.3. Use of technologies

Health professionals should adopt computerised safety systems to reduce the number of ADRs and prescribing errors. This includes use of drug databases with up-to-date information on harm and benefit of drugs and control functions to check contraindications, doses, interactions etc. Use of computerised prescriber order and implementation of bar-code medication administration should be considered to reduce medication errors.[71,72]

5. Pharmacists

5.1. Education

Pharmacists should be trained in appraisal of harm-benefit evaluation, in pharmacovigilance and in reporting ADRs. They must embrace their growing responsibility for informing patients about harm and benefit of medicinal products, for stimulating patients to speak about ADRs and for reporting ADRs including those of OTC drugs, complementary medicines and food additives.

5.2. Role of hospital drug committees

Hospital pharmacists must be integrated into ADR reporting. They should identify "pharmaceutical" signals suggesting ADRs and investigate them as when they arise. Cases with relevant ADRs should be brought to the agenda of hospital drug committees in cooperation with pharmacovigilance centres where they exist.

6. Nurses and other health professionals

6.1. Education and Reporting of ADRs

Harm-benefit evaluation and pharmacovigilance should be part of the professional training of nurses, midwives, healers and other health professionals. They have to be actively included in reporting of ADRs.

7. Patients

7.1. Information

From the beginning of therapy, patients must be informed independently and fully about the potential benefits and harms of therapy. The factors that influence the ways in which individuals respond to information about health risks and whether patients understand the information supplied should be explored.[73] Patients should be helped to recognise ADRs, and to inform their physician and/or other health professionals about suspected ADRs and other drug problems.

7.2. Reporting of ADRs

Competent authorities, working in accordance with revised EU legislation on medicinal products, should encourage spontaneous reporting of drug-related harm by patients (including volunteers who take part in drug trials), to pharmacovigilance centres, special centres for patients/consumers or directly to health authorities. The use of telephone hotlines or online reporting via the internet needs to be evaluated. Specially written, clear and user-friendly reporting forms should be made available, for instance in pharmacies, to facilitate ADR reporting by patients. Patient reporting systems should periodically sample and evaluate the scattered drug experiences patients report on the internet. Patient organisations reporting ADRs should have in place an appropriate structure to validate reports.

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VI ANNEX

1. Definitions

1.1. ADR/AR = Adverse drug reaction/adverse reaction

WHO defines adverse drug reactions (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function".[74] The causal relation between the drug intervention and the event is at least a reasonable possibility. In this declaration the acronym ADR is used to cover adverse reactions to all products in therapy such as medical devices, natural products, traditional medicines, nutraceuticals, food additives etc. It has also to be considered that an ADR may be the result of intended or accidental poisoning, drug abuse, or errors in administration or compliance.

1.2. AE/ADE = Adverse event/adverse drug event

WHO defines adverse event (AE) as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment".[74] With respect to pharmacovigilance AE and ADR both have their relevance.

1.3. Pharmacovigilance

The WHO defines pharmacovigilance as "... the activities involved in the detection, assessment, understanding and prevention of adverse effects or any other drug related problems ... "[5] or as "analysing and managing the risks of medicinal products".[52,75] Pharmacovigilance is a broad concept, that spans the whole clinical phase of drug development and the postmarketing drug safety surveillance including risk management and preventing of drug errors, communicating drug information, promoting rational drug use and crisis preparedness.

1.4. Signal

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information".[74] Absence of a signal does not mean that a problem does not exist

2. About the word consumer[1]

The word *consumer*, instead of 'patient', is used increasingly in medical publications. In reality a *consumer* is 'a person who purchases goods and services for his own needs' (Collin's dictionary). The word *consumer* therefore is more than a euphemism and a soothing word for 'patient'. Indeed using the term tends to negate the role of doctors and pharmacists and the patient-professional relationship. The term *consumer* assumes the patient is independently and reliably informed, and can choose from the medicines on offer to treat any health problems: this is rarely the case.

The word *consumer* has clear commercial connotations. It puts implicit and sometimes inappropriate emphasis on the role of drug treatments, and tends to overlook non-drug options (surgery, watchful waiting, psychotherapy, etc.). Those with vested interests prefer the term *consumer* since it is consistent with the concept of direct-to-consumer advertising, e-commerce of medicines, and the industrial strategy of bypassing health professionals who are viewed as barriers to expanding drug markets.

Making the patients and the public informed and committed partners in health care is a desirable aim. But the word *consumer* should be avoided when describing the relation between patients and medicines. It should be replaced by 'the public' or 'patients'. Occasionally the word 'individuals' may be more appropriate since those taking medicines to prevent some events (e.g. pregnancy or malaria) are not 'patients'.

VII INDEX

L

M

N

O

P

Q

R

S

T

U

V

W

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