Module 1 – Introduction and Evolution of Pharmacovigilance (PV)

Contents

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
DoTS	Dose Time Susceptibility
EMA	European Medicines Agency
EU	European Union
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IND	Investigational New Drug
MAH	Marketing Authorization Holder
NSAID	Non-steroidal Anti-inflammatory Drug
OC	Oral Contraceptives
PV	Pharmacovigilance
SAE	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
UK	United Kingdom
USA	United States of America
VIGOR	Vioxx gastrointestinal outcomes research
VTE	Venous Thromboembolism
WHO	World Health Organization

1. History of Pharmacovigilance

The word Pharmacovigilance (PV) is derived from Greek ‘Pharmaco’ (Medicine) and Latin ‘vigilantia’ (Vigilance, watchfulness).

It can be argued that the history of pharmacovigilance (PV) goes back further but, for practical purposes, the story of modern PV begins with Thalidomide.
In the late 1950s there was little, if any, regulation of medicines outside the United States of America (USA) (where thalidomide was not marketed), and their testing and development was almost entirely in the hands of pharmaceutical companies.

In the case of thalidomide, unjustified claims of safety in pregnancy were made and its use as a sedative was targeted at pregnant women. The drug turned out to be a teratogen, producing a variety of birth defects but particularly limb defects known as phocomelia. Worldwide, about 10,000 foetuses were affected, particularly in Germany where the drug was first marketed. Since phocomelia was otherwise a very rare congenital abnormality, the existence of a major increase in its incidence did not go unnoticed in Germany but the cause was initially thought to be environmental.

In 1961 a series of just three cases associated with thalidomide was reported in The Lancet, the problem was finally recognized and the drug withdrawn from sale. At the beginning of the 1960s, publication of possible adverse effects of drugs in the medical literature was effectively the only mechanism for drawing attention to them.

Thalidomide produced a non-lethal but visible and shocking adverse effect (AE), leading people to ask why so many damaged babies had been born before anything had been done? This question is central to subsequent developments. It is unlikely that anyone will ever be able to predict and prevent all the harms which may be caused by medicines but limiting the damage to much smaller numbers is now achievable. Today we would expect to be able to identify an association between drug and outcome analogous to thalidomide and phocomelia after the occurrence of less than 10 cases, i.e. at least three orders of magnitude more effectively than five decades

ago. The overriding lesson learnt from thalidomide was that we cannot just wait until a drug safety problem, quite literally in this case, hits us between the eyes. So thalidomide led directly to the initial development of the systems we now have, although it is only quite recently (i.e. since the early 1990s) that the term pharmacovigilance has become widely accepted.

Pharmacovigilance has been defined by the World Health Organization (WHO) as '**The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems**'. The European Medicines Agency (EMA) defines PV as 'Preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure and promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public'.

There are other definitions but this very broad one seems to be the most appropriate since there is a clear implication that the process is one of 'risk management'. This is a concept which is applicable to many aspects of modern life but, surprisingly, its explicit use in relation to pharmaceuticals is quite a recent development. Thalidomide is not merely of historical interest since in the last few years it has made something of a comeback. The reasons for this exemplify the point about risk management since the risk of foetal malformation can be successfully managed by avoidance of the drug during pregnancy. It also demonstrates another concept which is central to the practice of pharmacovigilance – **the balance of benefit and risk**. Thalidomide appears to have benefits in some diseases that are otherwise difficult to treat conditions, e.g. refractory multiple myeloma – these appear to outweigh the risk of foetal malformation if there is an effective pregnancy prevention scheme in place.

A further point which thalidomide illustrates well, and is relevant to many other drug safety issues is that:

Not everyone is at the same risk of a particular adverse effect.

In this case, a substantial part of the population i.e. women who are not of childbearing capacity, are not at risk at all.

Main lessons from thalidomide:

- The need for adequate testing of medicines prior to marketing.
- The need for government regulation of medicines.
- The need for systems to identify the adverse effects of medicines.
- The potential relationship between marketing claims and safety.
- Avoidance of unnecessary use of medicines in pregnancy.
- That some risks can be successfully minimized.

The ramifications of the thalidomide tragedy were many-fold but the key lesson for the development of pharmacovigilance was that **active systems** for detecting hazards are needed.

Within a few years this had been taken forward with the introduction of voluntary (or 'spontaneous') schemes for reporting of suspected adverse drug reactions (ADRs). These have stood the test of time as an alerting mechanism or 'early warning system'.

2. Definitions in Pharmacovigilance

The Theory

There have been many variants on the terms and definitions used to talk about safety issues over the years. The terminology is somewhat confusing and is explained below.

The “official” and accepted definitions in most countries are based on the International Conference on Harmonization (ICH) E2A Guideline and are as follows:

Adverse Event (AE)—ICH

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). Any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally the use of any dose of a medicinal product, whether or not considered related to the medicinal product (ICH E2A).

Adverse Event/Adverse Experience—European Medicines Agency (EMA)

Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment (Article 2(m) of Directive 2001/20/EC). An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory associated with the use of a medicinal product, whether or not considered related to the medicinal product, symptom, or disease temporally.

Adverse Experience/Event—Food and Drug Administration (FDA)

The FDA uses the term adverse event/experience and defines it as follows for post marketing cases:

Any AE associated with the use of a drug in humans, whether or not considered drug related, including the following: An AE occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action (21CFR314.80(a)).

For clinical trial cases, the FDA revised the definition effective March 2011 to read as follows (21CFR312.32): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

In practice, most people use the term AE to refer to any “bad thing” that occurs during the use of a drug without implying that the bad thing is due to the drug. The bad thing may be due to the drug substance, excipients, packaging, or storage issues, and may or may not be due to the active ingredient.

Adverse Reaction

In the pre-approval (i.e., not yet marketed, experimental) phase of a product, the definition is as follows: “All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.”

This means “that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out” (ICH E2A).

For post-approval (i.e., marketed) products, the definition is as follows: “A response to a drug which is noxious, unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function” (ICH E2A).

Note that this is one of the few areas where the preapproval definition is different from the marketed definition.

Serious Adverse Event (SAE) and Serious Adverse Reaction

A serious adverse event (experience) or serious adverse reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  Note: The term life-threatening in the definition of serious refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe:
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or

- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse (ICH E2A).

The FDA (21CFR312.32, 21CFR314. 80(a)) and EMA (Good pharmacovigilance practice) definitions are similar but do differ somewhat.

Note that an event or reaction may meet one or more of the criteria for seriousness simultaneously. Only one is needed, however, to consider the event or reaction to be serious. For an individual case safety report (ICSR) to be serious, it takes only one serious AE out of all the AEs present. To be a non-serious ICSR, all the AEs must be non-serious.

The FDA's definition of "serious" for clinical trials (21CFR312.32(a)):

An AE or suspected adverse reaction is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note that this now includes both the investigator and the sponsor. Either may declare an event/reaction to be serious. The FDA also moved the idea of “disability” directly into the definition in the section on incapacity.

A suspected adverse reaction is defined by the FDA for clinical trials is:
Any AE for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug (IND safety reporting), ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Nonserious
An event or reaction that is non-serious (does not meet any of the criteria for seriousness).

Suspected Adverse Drug Reaction (SADR)
A noxious and unintended response to any dose of a drug or biologic product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase “a reasonable possibility” means that the relationship cannot be ruled out (ICH E2A).
The point here is the word suspected, which means some level of causality with the drug in question, is present. It may be serious or non-serious.

Serious, Unexpected, Adverse Drug Reaction
An SADR that is serious and unexpected. See the definitions for serious and unexpected. The FDA does not use this definition formally for cases, though the concept is similar.

Serious, Expected, Adverse Drug Reaction
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Suspected Adverse Reaction—FDA

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the adverse event.

Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21CFR312.32).

Suspected, Unexpected, Serious Adverse (Drug) Reaction (SUSAR)—EMA

An SADR suspected of being due to the drug in question (causality) and unexpected. See the definitions for serious and unexpected.

Unexpected—FDA

The FDA issued new final rules effective March 2011 in which they change and explain their concept of unexpected. Previously the idea was that an adverse event would be unexpected if it was possibly associated with or related to the use of the drug. The FDA has now changed this definition for clinical trial (IND) reporting to read as follows: For a pre-marketed product: An AE or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed….For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure (IB) referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. ‘‘Unexpected,’’ as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21CFR312.32(a)).

For marketed products: Any adverse drug experience that is not listed in the current labelling (Package Insert or Summary of Product Characteristics (SPC)) for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labelling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be

unexpected (by virtue of greater severity) if the labelling only referred to elevated hepatic enzymes or hepatitis (21CFR314.80(a)).

Note that AEs that are “class related” (i.e., allegedly seen with all products in this class of drugs) and are mentioned in the labelling (Package Insert or SPC) or investigator brochure but are not specifically described as occurring with this product are considered unexpected.

Unexpected Adverse Reaction—EMA

An adverse reaction, the nature, severity or outcome of which is not consistent with the SPC (Article 1(13) of Directive 2001/83/EC67). This includes class related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product. For products authorized nationally, the relevant SPC is that approved by the Competent Authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant SPC is the SPC authorised by the European Commission.

During the time period between the Committee for Medicinal Products for Human Use (CHMP) Opinion in favour of granting a marketing authorisation and the Commission Decision granting the marketing authorisation, the relevant SPC is the SPC annexed to the CHMP Opinion.

These adverse reactions, when the SPC is used as the reference document, are referred to as unlabeled. This is quite different from unlisted (see below).

Unlisted Adverse Reaction—EMA

An adverse reaction that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI). This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as occurring with this product.

Expected

As opposed to “unexpected,” any event that is noted in the investigator brochure or labelling (Package Insert or SPC) is termed as “expected”.

3. Evolution of Pharmacovigilance

In the past, the process of PV has often been considered to start when a drug is authorised for use in ordinary practice. Nowadays, it is more commonly considered to include all safety-related activity beyond the point at which humans are first exposed to a new medicinal drug.

The ultimate purpose of PV is to minimise, in practice, the potential for harm that is associated with all active medicines. Although data about all types of ADRs are collected, the main focus is on identifying and preventing those which are defined to be serious. This means an ADR which meets at least one of the following criteria:

- Fatal
- Life-threatening
- Causes hospitalization or prolongs the existing hospitalisation
- Results in long-term disability

Additionally, all congenital abnormalities are considered serious and the definition of 'serious' allows the application of medical judgement such that a reaction may be considered serious, even if there is not clear evidence that one of the above criteria is met.

Non-serious reactions are important to individual patients and health professionals involved in their treatment but they can usually be managed clinically and they impact much less on the balance of benefit of risk and the public health.

Thus, PV may be seen as a public health function in which reductions in the occurrence of serious harms are achievable through measures which promote the safest possible use of medicines and/or provide specific safeguards against known hazards.

Development of PV since the 1960s

In the early 1970s another drug safety disaster occurred – this was the multi-system disorder known as the oculo-mucocutaneous syndrome caused by practolol – a cardio selective beta blocker used to treat angina and hypertension. As in the case of thalidomide, several thousand individuals were permanently damaged before the association was recognised. The fundamental problem in this instance was a failure of timely identification despite having an early warning system in place. Ultimately the system was dependent on doctors suspecting an association between drug and

disease. Probably because of the unusual nature of the syndrome – dry eyes, skin rash and bowel obstruction – and a long latency period (averaging almost two years in respect of the onset of the most serious bowel manifestations), relevant cases were not reported until the association was identified in the medical literature. Around 3,000 cases were then retrospectively reported to the United Kingdom (UK) 'Yellow Card' scheme, an example of the potential effect of publicity on ADR reporting. Subsequent attempts to develop an animal model of practolol toxicity failed, indicating that the problem could not have been predicted from pre-clinical studies.

Main lessons from Practolol

Some adverse effects are not predictable from pre-clinical studies.

- Spontaneous reporting schemes are not invariably effective.
- Long latency effects and clinical manifestations not known to be related to other drugs may not be suspected as ADRs by doctors.
- Additional, more systematic methods of studying post-marketing safety are needed.

The overriding message from practolol was that spontaneous ADR reporting alone is insufficient as a means of studying post-marketing safety.

Thus, in the late 1970s various schemes designed to closely monitor the introduction of new drugs were suggested, but most of them were not implemented. The basic idea was that initial users of new drugs would be identified through prescriptions and monitored systematically rather than waiting for someone to recognize a possible adverse effect. The concept did come to fruition in the UK in the early 1980s with the development of 'prescription-event monitoring', a method which is still in use today.

The first drug studied by prescription-event monitoring was benoxaprofen, a non-steroidal anti-inflammatory drug (NSAID) which frequently produced photosensitivity reactions, i.e. rashes in light-exposed areas. A published case series of five deaths related to hepatic and renal failure led to withdrawal of the drug in 1982, even though some doubts were expressed as to whether they were caused by the drug, particularly as prescription-event monitoring did not reveal any indication of these effects. Many of the patients who experienced serious ADRs with benoxaprofen were elderly; this

was due to reduced excretion of the drug as a consequence of renal impairment. Even though it is well-recognised that many patients who use NSAIDs are elderly, benoxaprofen had not been adequately studied in this population prior to marketing.
A reduction in the dosage recommendations for the elderly was implemented briefly but it was too late to save the drug. Because the usage of benoxaprofen took off rapidly after launch and an important adverse effect – photosensitivity reactions – was common, a large number of spontaneous reports were received in a short period of time, swamping the primitive computer systems then used and pointing up the need for purpose-designed databases. The issue also illustrated the need for patients to be properly informed about possible ADRs and how to minimise the risk – in this case by avoiding exposure to the sun. It was therefore influential in moving us towards the introduction of patient – these became compulsory in the European Union (EU) during the 1990s.

Main lessons from benoxaprofen

- Uncertainty about cause and effect from individual case reports – further impetus to the need for formal post-marketing studies.
- The need to study a drug in the population that will use it (e.g. the elderly).
- The need for purpose-designed computer systems to handle ADRs more promptly and effectively.
- The concept of intensive surveillance of new drugs, achieved in the UK by the introduction of the Black Triangle scheme.
- The need for patients to be informed about possible ADRs.

As it turned out, benoxaprofen was just the first of a series of NSAIDs withdrawn for various safety reasons in the 1980s. During this decade, pharmaceutical companies started to conduct their own post-marketing surveillance studies and UK guidelines related to their conduct were drawn up in 1987. However, initially, the value of such studies turned out to be limited because they usually lacked comparator groups and often failed to meet the planned sample-size. The UK guidelines were revised in 1993 with the aim of improving the quality of studies. The principles of the revised, so-called Safety Assessment of Marketed Medicines

(SAMM), guidelines also became a blueprint for the first EU level guidance on the topic.

During the mid-1980s, the term pharmaco-epidemiology was first used to mean the scientific discipline of the study of drug use and safety at a population level. The discipline developed strongly during the 1990s with the increasing use of computerized databases containing records of prescriptions and clinical outcomes for rapid and efficient study of potential safety hazards. In some instances prescription records are held in a separate database to clinical events, and linkage between the two databases needs to be achieved through some common identifier in the two sets of data in order to study adverse events at an individual patient level. Towards the end of the 1980s pharmacovigilance eventually recognized and started to deal with the problem of dependence on benzodiazepines – so-called 'minor tranquillisers' such as chlordiazepoxide and diazepam that had been introduced in the 1960s. Advice was issued to limit the dose and duration of such treatments although, even today, such recommendations are widely ignored. The issues brought into focus the problems faced in dealing with the misuse and abuse of prescription drugs. This is another example of a situation where spontaneous ADR reporting failed to highlight an important concern, the issue eventually coming into focus as a result of pressure from advocates for groups of affected patients. As well as the problem of delayed identification of real hazards, pharmacovigilance has suffered from the reverse, i.e. apparent identification of hazards which turn out not to be real. To some extent this is inherent in a system which relies much on clinical suspicions – sometimes these will be wrong.

The consequences are that sometimes a drug may be unnecessarily withdrawn or people become too scared to use it. For example, Debendox, a combination product containing an antihistamine doxylamine, was widely used for the treatment of nausea and vomiting in pregnancy in the 1970s. It was withdrawn in the early 1980s on the basis of concerns that it might cause foetal malformations, a concerted campaign against the drug and impending litigation. At the time, the evidence of a hazard was very weak but it was not possible to exclude a significant risk to the foetus. Subsequently, many studies of this potential association were performed and collectively they provided no evidence of an increased risk of foetal

malformations. This example illustrates the intrinsic difficulty of disproving the existence of a hazard once concern has been raised. A more recent, very high profile example illustrating the same point was the suggestion made in late 1990s that combined measles, mumps and rubella (MMR) vaccine might be a cause of autism in children. Despite there being little credible evidence for this suggestion, it was impossible to completely disprove it and hard to convince worried parents. Vaccine campaigns were damaged and a significant number of cases of measles occurred in the UK for the first time in many years.

The mother of all drug safety scares occurred with oral contraceptives (OCs) in 1995. It was not the first 'pill' scare – this story began in the late 1960s when it was discovered through spontaneous ADR reporting and confirmed in formal studies that combined OCs (containing an oestrogen and a progestagen) increased the risk of venous thromboembolism (VTE). This led to a reduction in the dose of oestrogen to 20–30 μg of ethinyl oestradiol which lessened (but did not abolish) the risk without compromising efficacy. Nevertheless, when the risk of thrombosis became public knowledge many women were scared and stopped taking OCs. It is important to recognize that most women using OCs are relatively young and healthy – this impacts considerably on their perception of the risk. There have been several 'pill' scares over the years related to VTE and also to other safety issues – e.g. a possible association with myocardial infarction and a small increase in the risk of breast cancer. In each instance, many women who stopped using OCs later returned to using OCs but the public health impact of each of these scares in terms of unwanted pregnancies was considerable.

This has been particularly unfortunate since pregnancy itself is fundamentally riskier than using any OC and there may also be compensating health benefits from using them. In 1995 a WHO study of OCs unexpectedly found a two-fold increase in the risk of VTE when use of so-called 'third-generation' (3G) OCs was compared to 'second-generation' (2G) OCs. The difference between these pills was the progestagen component – desogestrel or gestodene for 3G OCs and levonorgestrel for 2G OCs. This was surprising as it had always been considered that VTE risk was simply related to the dose of the oestrogen component of the pill. Another multinational study which could address the relative safety of 3G and

2G OCs was ongoing and a further study was quickly conducted using a UK database. Within about three months the results of three studies were available and their findings were all quite similar. Arguments were put forward that the associations seen in these studies were not necessarily causal and also that it was possible that 3G OCs might have benefits which would compensate for the increase in VTE risk. There was general agreement that the absolute level of risk – VTE is quite rare in healthy young women, even if they take the pill – was not such that 3G OCs should be withdrawn from the market but nevertheless the UK's expert regulatory committee felt that doctors and women needed to know. Despite a clear message being provided that no one should stop taking OCs, many women did, presumably because the media coverage scared them. It did not help that the principal investigator of one of the studies flew from Canada to London to give a press conference criticizing the committee's advice because the public get more worried when experts disagree. At the time, the European Medicines Agency had recently been formed but co-operation on nationally authorized products was in its infancy. Various authorities in Europe and around the world adopted different positions and it was not until 2001 that the EU reached an agreed position on the issue.

Over a period of several years, more studies were done and the effects of the various progestagens on blood clotting investigated. Ultimately, it was shown that there were plausible differential effects of these agents on clotting and there was enough consistency in the risk data to convince most scientists that the observed association was causal. But, despite good intentions all round, it was hard to escape the feeling that more harm than good had been done and that the communication tools used were inadequate. In 1997 the WHO convened a meeting of experts to specifically consider how communication in PV could be improved.

Main lessons learned from the OC safety issues

- Drugs are sometimes marketed at the wrong dose.
- There may be differences in safety between drugs of the same class.
- Harm may result from safety warnings.
- Uncertainty and debate about risks may fuel public concern.

- The power of the media to influence users is much greater than the authorities.
- The need for greater international co-operation in PV.
- There is a need to develop more effective communication tools.

One important point about the OC issues discussed above is that the data on which they were based did not (after the initial signal in the 1960s) come from spontaneous ADR reporting. Despite that, causation was debatable because the studies were not randomized trials but 'observational'. VTE is a sufficiently rare outcome in young women that it would be extremely difficult to conduct a large enough clinical trial to detect a doubling of risk. Later in life, women have also been prescribed female sex hormones – in lower doses and as replacement therapy (HRT). In this age group the baseline risks of VTE, arterial cardiovascular disease and various cancers are much greater and therefore, it is more feasible to study them in clinical trials although they do need to be large and long-term. Therefore observational studies of these outcomes were performed first and, in general, they appeared to show that HRT reduced the risk of arterial disease outcomes, i.e. myocardial infarction and stroke. The HRT was not authorized for the purpose of reducing cardiovascular risk but in the 1980s and 1990s it was quite widely used for this purpose. The fundamental problem in performing such studies is that women using HRT may be healthier to start with, although it is possible to address this, at least to some extent, in the design and analysis. Another important point is that the outcome in question is a benefit (i.e. a reduction in risk) and, because of such biases, observational studies rarely provide convincing evidence of benefit. It is generally accepted that randomized trials are needed to establish efficacy and benefit. Eventually, large randomised trials were set up but they had to be stopped early because they tended to show the opposite of what expected – i.e., an increase in cardiovascular risk. Warnings were issued and, because there is no major downside to suddenly stopping HRT, communication was intrinsically easier than with OCs. Indeed, the intended effect of the warnings was that women who were inappropriately using long-term HRT should stop taking it. However, conveying the right messages was not straightforward because there were multiple

risks involved, and they are time-dependent and cannot simply be expressed as a proportion (e.g. 1 in 100).

However, history is not yet ‘complete’ on any of these issues, indeed one often wonders whether it ever can be – e.g. with the return of previously withdrawn drugs like thalidomide and clozapine. The latter is an antipsychotic drug which was first introduced in the 1970s and then withdrawn following reports of agranulocytosis, i.e. absence of white blood cells. It was reintroduced with compulsory blood monitoring around 1990.

Selective serotonin re-uptake inhibitors (SSRIs) are antidepressants which were brought to the market in the late 1980s and have since largely replaced older, ‘tricyclic’ antidepressants such as amitriptyline. The main reason why they have done so – apart from effective marketing – is that they are less toxic to the heart in overdose, i.e. there is a greater margin of safety in relation to dose. Depressed patients are at risk of taking an overdose and therefore this is potentially an important advantage. There have been two controversial issues with SSRIs – withdrawal reactions and a possible increase in the risk of suicide. Problems experienced by patients when they stop treatments are often quite difficult to assess because they could possibly be related to recurrence of the disease. Nevertheless, the potential for SSRIs to produce withdrawal reactions was identified during their development, and when spontaneous reports were received post-marketing it was hardly a new ‘signal’. There were very large numbers of such reports received but few were serious and the level of usage of the drugs was high. Over a period of years it became clear that the problem was occurring much more commonly than initially thought, particularly in users of paroxetine, a fairly short acting drug. Ultimately, greater care was needed in withdrawing patients more gradually from these drugs. Suggestions have been made that SSRIs are drugs of dependence but most scientists do not accept this because features such as craving and dose-escalation are generally absent. Importantly, it emerged that the nature of some of the more unpleasant symptoms patients experienced – e.g. so-called ‘electric shock’ sensations in the head was being lost in the data processing systems. This was due to inadequate coding such cases often became ‘paraesthesia’, something that hardly conveys how unpleasant such sensations

can be. Thus, it was recognized that we need better ways to capture unusual patient experiences and this gave considerable impetus to allowing patients to report their adverse reactions to the authorities. That approach had been used in the USA for many years but hardly at all in Europe until the early years of the new millennium. The possibility that any drug might increase the risk of an outcome associated with the disease it is being used to treat is invariably difficult to evaluate. Suicidal feelings and actions are relatively common in depressed patients and it is not surprising when they occur in a patient who has recently started treatment.

Nevertheless, around 1990 a clinician in the USA saw several patients treated with fluoxetine who had suicidal thoughts and he published a case series suggesting that the drug might be responsible. This prompted a review of all the clinical trial data for the drug which did not support the proposition, but it was never completely refuted. Over the years more clinical trial data accumulated for various drugs in the class and studies were conducted in children and adolescents, the latter being a high-risk group for suicide. Even in severely depressed patients, completed suicides are rare in clinical trials and therefore the evidence that is available relates mostly to attempted suicide (also uncommon in trials) and thoughts of suicide measured on various scales. Trials of paroxetine in children produced some potentially worrying findings that for some time were known only to the manufacturer. When the regulatory authorities eventually received the data, they issued warnings against the use of this drug in children. The company was investigated, and prosecution considered but the law was found to be insufficiently clear that they were obliged to immediately submit concerning clinical trial data to the authorities when a trial was being conducted outside the authorized indication. This issue again pointed to the potential importance of clinical trials to the assessment of safety and raised concern about a lack of transparency with clinical trial data. Already, considerable steps have been taken towards making clinical trial data publicly available through mechanisms other than publication in the literature which is slow and selective. The jury is still out on whether SSRIs directly increase the risk of suicide but there is general agreement that the early phase of treatment is a high-risk period and that careful monitoring of patients is required.

Finally, what is probably the most important drug safety issue of recent years?

The answer is the increased risk of cardiovascular outcomes associated with selective Cyclooxygenase (COX)-2 inhibitors (coxibs). This possibility was first uncovered in basic research but not followed through; the first clinical indication of a problem came from a trial known as Vioxx gastrointestinal outcomes research (VIGOR) which was published in 2000. At the time, two drugs in the class – rofecoxib and celecoxib – had just been authorised. The VIGOR study was a randomised comparison of rofecoxib and naproxen (a standard NSAID) designed to establish whether or not there was a difference in the rates of serious gastrointestinal adverse effects of these two drugs. In that respect, rofecoxib was clearly preferable and the trial results led to rapid uptake of coxibs – on the basis that they were supposedly safer. The VIGOR study also found an important difference in the rate of cardiovascular events such as myocardial infarction – these were five-fold more common in patients taking rofecoxib, compared to naproxen. This information was included in the original publication but lacked prominence and was presented as a five-fold reduction with naproxen rather than an increase with rofecoxib. The paper has since been the subject of extensive criticism. Over the years there have been suggestions that standard NSAIDs might reduce the risk of cardiovascular outcomes (as aspirin does) and one explanation for the finding in the VIGOR study put forward was that naproxen is 'cardioprotective' whereas rofecoxib is not. Ultimately, it took a large clinical trial comparing rofecoxib with placebo to establish beyond any doubt that this was an adverse effect of rofecoxib (rather than a lack of benefit) and the findings of that study led to the drug being withdrawn from the market in late 2004. This event sent shockwaves around the world that are still reverberating leading people to question why such a trial had not been done much earlier, i.e. before millions of people had used the drug. It also left a big cloud hanging over the remaining drugs in the class – some have been withdrawn and some remain in the market. At one stage, the proposition that coxibs might be given to people at high risk of gastrointestinal and low risk of cardiovascular disease seemed reasonable but it has since been discovered that, to a considerable extent, risk factors for these problem overlap in individual patients. To make matters even more complicated, it appears that some standard NSAIDs might also increase the risk of cardiovascular events and, at the present time, our ability to assess the relative safety of drugs in the same class remains rather limited.

Main lessons learned from recent major safety issues

- The need for vigorous follow-up of safety signals with appropriate studies.
- The difficulty of assessing outcomes which are related to the drug indication.
- The potential value of clinical trials in assessing safety and the importance of the choice of comparator drug(s).
- Important safety data may emerge from clinical trials performed for other purposes.
- The need for greater openness about clinical trial data.
- The potential importance of off-label use (e.g. in children) to safety.
- There is a need to evaluate medicines properly in children.
- The need for greater patient involvement in drug safety.
- The complexity of evaluating and communicating multiple risks (and benefits).
- The need for regulatory authorities to have powers to ensure that companies adequately investigate potential risks with marketed products.

Conclusion

The issues discussed above are necessarily selective. The intention is primarily to illustrate that pharmacovigilance has experienced many teething problems and that most of its developments have been in response to quite specific lessons learned from landmark safety issues. This chapter illustrates what PV is and how it has progressed over a period of nearly half a century. Despite that progress, no one should doubt that there is a long way to go yet.

4. Concepts in Pharmacovigilance

The two most important concepts in pharmacovigilance are opposites, i.e. harm and safety. The usual term for harm related to a medicine is an adverse drug reaction (ADR). Since pharmacovigilance is fundamentally about preventing ADRs, this concept will be considered first through a summary of relevant definitions, classification systems which have been proposed, their nature and mechanisms, predisposing factors, and the overall public health burden and costs associated with them.

Classification systems

Since the 1970s, ADRs have traditionally been classified into two broad categories, as follows:

- Type A (Augmented) reactions
- Type B (Bizarre) reactions

The usual characteristics of these different types of reactions are contrasted below, followed by some examples.

Type A reactions are generally:

- Dose-related
- Predictable from drug pharmacology
- Common
- Normally reversible
- May be manageable with dose adjustment.

Classic examples of Type A reactions are bleeding with warfarin, hypoglycaemia with sulphonylureas and headache with glyceryltrinitrate.

Type B reactions are generally:

- Not dose-related
- Unpredictable
- Uncommon
- May be serious/irreversible
- Indicative that the drug needs to be stopped.

Classic examples of Type B reactions are anaphylaxis with penicillins, hepatitis with halothane and agranulocytosis with clozapine.

Additional categories of ADRs have also been suggested, as follows:

Type C (Chronic) – e.g. adrenal suppression with corticosteroids

Type D (Delayed) – e.g. tardive dyskinesia with neuroleptics

Type E (End of use) – e.g. withdrawal reactions with benzodiazepines

In 2003, a system of classification was proposed by Aronson and Ferner based on dose-relatedness, time course and susceptibility; this is known as Dose Time Susceptibility 'DoTS'.

In terms of dose-relatedness, 'toxic' means that reactions occur as a result of drug levels being too high, 'collateral' means that reactions occur at drug levels which are in the usual therapeutic range and 'hypersusceptibility' means that reactions may occur even at very low, sub-therapeutic doses.

The terms early, intermediate and late have not been precisely defined; the main difference between 'late' and 'delayed' reactions is that the latter may occur long after treatment is stopped (e.g. cancer, which may occur years after exposure to a causal agent).

A withdrawal reaction means one that is specifically precipitated by stopping the drug.

If suitable estimates of risk are available, it may be possible to draw three-dimensional DoTS diagrams of the probability of an ADR occurring in sub-groups over time and as a function of dose.

DoTS classification: Examples

a. Osteoporosis due to corticosteroids:

This reaction occurs at therapeutic doses, usually after some months of treatment; females and older people are at the greatest risk. Hence it would be classified as**:**

- Dose: Collateral effect
- Time: Late
- Susceptibility: Age, sex

b. Anaphylaxis due to penicillin:

This reaction may occur with very small doses and within minutes of taking the first dose of a course, but true anaphylaxis only occurs when the drug (or a closely related agent) has been used previously. Hence it would be classified as:

- Dose: hypersusceptibility
- Time: first dose
- Susceptibility: requires previous sensitization

The DoTS approach seems to be gaining acceptance because it addresses the limitations of the A/B scheme into which many ADRs do not clearly fit. Furthermore, it is useful in providing pointers as to how specific ADRs may be avoided**.**

Nature and mechanisms of ADRs

The adverse effects of medicines usually mimic diseases or syndromes which occur naturally and have a variety of non-drug potential causes, e.g. hepatitis or aplastic anaemia. However, there are a few unique syndromes that, as far as we yet know, seem to be caused only by specific drugs.

Four examples of this are:

1. Vaginal cancer in teenagers caused by maternal exposure to stilboestrol
2. Oculomucocutaneous syndrome caused by practolol
3. Eosinophilia-myalgia syndrome caused by some L-tryptophanproducts
4. Fibrosing colonopathy induced by large doses of high-strength pancreatic enzymes in children with cystic fibrosis.

As a general rule, therefore, considering other potential causes is an important part of the assessment of a potential adverse effect.

There are at least four broad mechanisms for ADRs:

1. Exaggerated therapeutic response at the target site (e.g. bleeding with warfarin)
2. Desired pharmacological effect at another site (e.g. headache with glyceryltrinitrate)
3. Additional (secondary) pharmacological actions (e.g. prolongation of the QT interval on the electrocardiogram – many drugs)
4. Triggering an immunological response (e.g. anaphylaxis due to many drugs).

Particularly at the time they are first identified, the mechanism of many ADRs is unknown or incompletely understood. Some have a pharmacokinetic basis, e.g. impaired hepatic metabolism due to a genetic polymorphism or the effect of another medication taken concurrently, leading to increased plasma concentrations. Understanding genetic pre-dispositions is likely to be an important factor in determining how we might prevent ADRs in the future.

Predisposing factors for ADRs

The main clinical factors which increase the chance that patients will experience an adverse reaction are listed below:

- Age – the elderly and neonates are at greatest risk.
- Gender – women are generally at greater risk.
- Ethnic origin – may affect drug metabolism.
- Impaired excretory mechanisms – reduced hepatic and/or renal function.
- Specific diseases – e.g. asthma and beta-blockers*.
- Polypharmacy– i.e. use of multiple drugs simultaneously, increasing the potential for drug interactions (see below).
- Any previous history of an ADR.

Drug interactions occur when the presence of one drug affects the activity of another. This may occur either because both drugs act through the same pathway(s) – these are called 'pharmacodynamic' interactions – or through effects on absorption, distribution, metabolism or excretion – 'pharmacokinetic' interactions. The result may be an adverse reaction or modified effectiveness.

Some specific examples are given below:

Pharmacodynamic– concomitant use of two drugs with similar effects [e.g. an angiotensin converting enzyme (ACE) inhibitor plus a 'potassium sparing' diuretic may result in hyperkalaemia and cardiac arrhythmias].

Absorption – use of broad-spectrum antibiotics (e.g. penicillin) may, through an effect of bacterial flora in the gut, result in reduced absorption and effectiveness of oral contraceptives.

Distribution – protein-bound drugs (e.g. phenytoin, aspirin) may displace each other resulting in an increased unbound (i.e. active) fraction of drug in plasma.

* This is a very important example since the effect of beta-blockers in patients with asthma is to constrict the airways and to counteract some of the treatments that the patient may be taking (e.g. beta-agonists). Giving a beta-blocker to an asthmatic patient can prove to be fatal.

Metabolism – cimetidine, a drug which reduces gastric acid, inhibits the metabolism of warfarin and thereby increases its anticoagulant effect, leading to bleeding reactions.

Excretion – amiodarone, an anti-arrhythmic drug, reduces excretion of, and therefore the dosage requirements for, digoxin – a drug widely prescribed to patients with cardiac disease.

Many drugs are metabolized by hepatic cytochrome P450 enzymes, the activity of which may be induced or inhibited by a wide variety of drugs. Their activity may also be affected by:

Herbal medicines – e.g. St. John's Wort is an enzyme inducer and may reduce the effectiveness of various drugs including ciclosporin.

Dietary products – e.g. grapefruit juice is an enzyme inhibitor and increases plasma concentrations of some calcium channel blockers, drugs which are used to treat hypertension and angina.

Public health burden and costs of ADRs

Despite the relative safety of modern medicines – compared to those used in the past – ADRs remain an important cause of morbidity and mortality. A study from the UK published in 2004 suggested that about 6.5% of hospital admissions are related to an ADR and estimated the annual cost to the National Health Service to be around £500 million. In 1998, a published study reported that ADRs are among the top six causes of death in the USA.

ADRs are certainly the most important form of iatrogenic (i.e. doctor-induced) disease. Many of the serious reactions that occur are well-recognized and potentially preventable – e.g. bleeding with warfarin, the upper gastrointestinal effects of NSAIDs. In public health terms, it is not newly introduced drugs that are responsible for most of the population burden of adverse drugs reactions but those whose safety profile is 'well-established' (see below).

The concept of safety

Safety may be defined as relative absence of harm. When using the word 'safety' we often mean something else. For example: 'Safety' data often means collection of reports of harm.

Safety departments in the pharmaceutical industry are generally focused much more on harm than safety. And yet how safe something is a key question for the user and one that pharmacovigilance is gradually becoming more targeted at. To establish safety, it is not enough to sit around and hope that nothing much happens. Active processes are required to generate data in large numbers of users –this is one of the main challenges facing people working in the field.

In practice, there is no such thing as absolute safety because, even if something is completely harmless, it is impossible to demonstrate that with complete certainty. For example, if a drug were given to 999,999 people without any problem occurring, it would be very unlikely that the millionth person to use it would be harmed, but it is not impossible. In any case, we know that all pharmacologically active substances have the potential to cause harm. When we say that a drug is 'safe', we mean that there is a low probability of harm that, in the context of the disease being treated and the expected benefits of the drug, can be considered acceptable. Disease context is important because patients with more serious illnesses are much more likely to be prepared to accept potentially harmful treatments than those who have minor or self-limiting illnesses. 'Acceptability' is a subjective judgment which ultimately is made by comparing both the positive and the negative consequences of one course of action (e.g. a drug) with another (which could be any form of treatment or no treatment).

Safety is a moving ball – there is a need to re-evaluate it as experience accumulates. Treatments previously considered acceptably safe may become 'unsafe' in the light of new evidence or the discovery of safer alternatives. An example of the latter was the antihistamine terfenadine which was widely used in the treatment of hay fever until the early 1990s. It was then discovered that it could, very rarely, cause serious or fatal ventricular arrhythmias through the mechanism of prolonging the QT interval on the electrocardiogram. Terfenadine is a 'pro-drug' which is normally completely metabolised on the 'first-pass' through the liver. It is the parent drug terfenadine that prolongs the QT interval (when its metabolism is inhibited) but the metabolite is responsible for the beneficial effects. Thus the metabolite, known as fexofenadine, was developed for this indication and rapidly accepted to be a safer alternative, following which terfenadine became obsolete. To assess how safe something is we need to identify and measure the risks of harm associated with it. Risk is the probability of an adverse outcome. It may be expressed in the following terms:

Absolute risk – An absolute risk must have a numerator and a denominator but it may be a proportion (e.g. 1 in 100) or a rate which includes time (e.g. 1 in 100 per year). The 'null value' is zero.

Relative risk – A relative risk is a ratio and makes comparison with a specified alternative (e.g. a two-fold increase compared to no treatment is a relative risk of 2). The 'null value' is one. Absolute risk is more useful information than relative risk but the latter is often easier to measure. Interpreting a relative risk is difficult without knowledge of the 'baseline' rate, i.e. the background probability of the effect occurring in the absence of any intervention. Several times a very small number is still a small number whereas a small increase in the relative risk of something common could be important.

The fundamental problem with safety is that it is much more difficult to determine that an effect is absent than to measure one that is present. We may be hoping or expecting to observe no effect but if nothing goes wrong, does that mean everything is alright?

The rule of three is a simple and useful tool when zero cases have been observed in a defined population. Simply dividing the size of population by 3 approximates an upper 95% confidence limit. In practice, this is the highest value that, statistically, is reasonably likely to represent the truth.

For example: If 900 patients use a new antibiotic and 0 allergic reactions occur then it is statistically unlikely that such reactions will occur more frequently than1 in 300 patients (i.e. 1 in 900/3).

The rule of three works very well provided the size of the population is at least 30 and thus, in the context of drug safety, it usually is applicable.

Safety in practice

There are two basic components to safety:

- **Intrinsic safety** – Some drugs are intrinsically and obviously safer than others at therapeutic doses. Compare, e.g., the adverse reactions produced by paracetamol and any cytotoxic drug.
- **User-dependent safety** – The safety of a drug usually depends on how it is used. For example, monitoring white blood cell count in users of clozapine can completely prevent progression of a reduction in white blood cells to a level that would potentially have fatal consequences. Using the drug without such monitoring is therefore clearly less safe than following the recommended procedure. Another example of safety being dependent on the user would be giving penicillin to someone who is

allergic to it, perhaps because that information has been ignored or is not available. In such a case, the safeguard (i.e. means of minimizing the risk) is avoidance of a specific drug in a particular individual. Using an appropriate dose of medicine is an example of practicing risk minimisation that applies to most therapeutic situations. The amount of safety knowledge available for a drug depends on how much it has been studied and used. Broadly, there are four categories of safety in respect of the amount of knowledge available, as follows:

- **Well-established** – Drugs which have been widely used for many (> 20) years for which it is unlikely that completely unidentified safety issues will emerge.
- **Established** – Drugs for which there is a substantial body of evidence of safety in clinical use but not enough to meet level 1 above.
- **Provisional** – All newly authorized drugs until they have been used fairly extensively in ordinary practice over a period of at least two years. During this period such drugs should be monitored intensively and their safety in ordinary practice proactively studied.
- **Limited** – All investigational drugs and the following situations where the drug might be authorized on limited safety information:

- Small populations eligible for treatment – 'orphan drugs'.
- Drugs with important benefits or where there is great clinical need, i.e. situations where potentially large risks might be acceptable.

A logical principle following from this categorization is that all use of the drug should be associated with systematic collection of safety information. It is important to recognize that drugs in the 'well-established category' are not necessarily safer than those in lower categories (and so on) – only that more information is available about their safety.

Risk-benefit balance

Since absolute safety is an unattainable goal, the aim is to use medicines with an acceptable level of safety. Various factors need to be considered in judging whether safety is or is not acceptable:

- The level of absolute risk(s) and the potential health consequences
- The benefit (s) expected, also measured in absolute terms
- The seriousness of the disease for which treatment is given
- The risks and benefits of alternative approaches
- The perspective of the individual who is to be exposed

In practice, therefore, whether or not safety is acceptable cannot be divorced from efficacy and expected benefits. The harms and benefits of a medicine are balanced at two levels:

1. **The population level** – this is a regulatory task and a question of whether, overall, the benefits that will accrue from availability of a medicine will exceed the expected harms.

2. **The individual level** – this is made by clinicians and patients and takes into account factors such as the patient's previous treatment, disease severity and preferences.

The process of balancing harms and benefits is a judgment alone and an element of judgment is always likely to remain, despite promising attempts that are currently being made to develop mathematical tools to aid the process at the population level. The term risk-benefit ratio has often been used but is best avoided.

A ratio implies one number divided by another and even if two simple numbers were available to summarize risks and benefits, what would a ratio of, say, 1.5 mean?

Conceptually it is preferable to use an additive process and the resulting balance becomes analogous to a financial balance which is either positive or negative. Ideally, a balance sheet would be constructed and the debits (i.e. the ADRs) would be subtracted from the credits (i.e. the expected benefits), hopefully leaving a positive balance. The problems are that the credits and debits are not usually measurable in the same way and there is often uncertainty about the size of some of the entries.

Nevertheless, the analogy is conceptually helpful – i.e. to achieve these benefits it is reasonable (or not) to accept these risks of harm.

Causation – was the drug responsible?

Deciding whether or not a drug is responsible for an AE is very often the most important question facing scientists working in the field of pharmacovigilance. Yet, it

is rarely completely straight forward whether the matter is being considered at the level of an individual patient or in terms of study data of various types. As in the case of the risk-benefit balance, a judgment is often necessary and there are some principles to be applied. There are some similarities in approach between the two levels mentioned above although they will be considered separately below.

Assessing causality in individual cases

Many causality algorithms and categorization systems have been proposed but none has gained universal acceptance, and the value of assessing this for each individual report of a suspected ADR now seems to be doubtful. It is certainly much more efficient to reserve such assessment for a series of cases which might represent a new and/or important safety issue. Systematic assessment of causality in individual cases occurring in clinical trials is intrinsically a weaker approach to assessing causality than comparison of numerical counts.

When individual case causality assessment is being performed, the following four categories are used**:**

- **Probable –** the balance of information available supports causation**.**
- **Possible –** some of the available information is in favor of and some against causation.
- **Unlikely –** the balance of information available is against causation**.**
- **Unassessable–** a reasonable judgment cannot be made, often because key information is missing**.**

In making such judgments there are four broad areas to consider:

- **Temporal relationships –** What was the time relationship between starting treatment and the onset of the event; if treatment was stopped (‘dechallenge’) or restarted (‘rechallenge’) did the event abate and/or recur?
- **Alternative causes –** are there concomitant diseases and medications or non-drug exposures that could explain the event?
- **Nature of the event –** some clinical events are often caused by drugs and immediately suggest a relationship (e.g. certain types of skin reactions).
- **Plausibility –** is the reaction already recognized with this drug(or similar drugs) or can a mechanism be postulated based on the pharmacology of the drug?

Basic concepts

In terms of temporal association, sometimes causation can be considered definitely excluded – ADRs cannot start before the drug is given (although drugs can worsen existing diseases). On the other hand, a positive rechallenge in the absence of alternative causes is generally considered to be strong evidence for causation. Whilst most ADRs start early on in treatment this is not invariably true, as reflected in the time course element of the DoTS classification discussed above.

Merely because an alternative cause can be identified does not mean that it was responsible. Such potential causes are often called 'confounding factors' and when they are present, cases are said to be 'confounded'. This is rather loose use of the word and best avoided.

The issues of nature of the event and plausibility need to be considered with some caution – these factors may add to the arguments for causation but a clinical event that is not normally known to be drug-related or the absence of any information supporting plausibility is not strong evidence against it.

Assessing causality from study data

One of the main reasons why data from randomized controlled trials are considered to be the 'gold standard' is that, in principle, observed differences between randomized groups should be attributable to the different treatments (i.e. causal). Other explanations are still possible, e.g. differences could simply be due to chance or caused by various biases, particularly in relation to what is being measured. Problems with the randomization may also occur – e.g.it may not have been done properly. Sometimes, as a result of bad luck, randomization may not have worked to produce groups that were adequately balanced at baseline in terms of important factors which may predict the outcome of interest. Whilst all these alternative explanations need to be considered, when a difference that looks important is observed in a randomized trial, causation is the most likely explanation. If the trial has adequate statistical power (and the difference is significant), the groups were well-balanced at baseline and the measurements are objective or blinded, then no great element of judgment is required to accept that such a treatment difference is likely to be real.

For study data which are not randomized, assessing causation requires much more judgment and is often a source of debate. When such studies find a difference, this is known as an 'association'.

In terms of chance, the issues are much the same as for randomized trials but there are many more types of biases that may be relevant. In the real world people tend to do things for a reason and patients who are given particular treatments may be selected according to factors which are relevant to the outcome of interest. Losses to follow-up are more likely than in trials and the reasons why people are 'lost' from studies may not be random.

Aside from the greater problem of bias, there is also the problem of 'confounding'. A confounder has a triangular relationship with an exposure (usually a drug) and outcome (AE of interest).

When it is present, the risk of the outcome is affected and whether or not it is present also varies according to the exposure status. Age is a good example of a perennial confounder – in very simple terms, older people tend to use more drugs and have more adverse outcomes. Therefore, there is a need to be sure that any observed association is not simply a consequence of that. A randomized study will, unless it is small, tend to balance the groups for age – or indeed any confounder – largely circumventing this problem. In principle, confounding can be dealt with – either in the study design (e.g. by matching patients or groups so that relevant factors are balanced) or, more commonly, in the analysis by statistical adjustment. However, to do so requires that all potential confounders are identified and adequately measured. Smoking is another common confounder and knowledge of smoking status in terms of (say) current, ex- or non-smoker is fairly crude given that there may be a close relationship between the precise amount smoked and the risk of the outcome. The possibility that confounding has not been fully addressed is called 'residual confounding' and this is often a possible alternative explanation to causation when the data come from non-randomized studies. When chance, bias and confounding are considered unlikely, causation is possible but still cannot be assumed as an explanation for an association based on non-randomized data. Often there may be a series of studies or various types of data which bear on this question. In this context, nine criteria first described by Bradford–Hill (Hill's criteria for causation) in the 1960s are still used. These may be summarized as follows:

Strength (effect size) – the stronger an association is, the less likely is to be explained by other factors.

Consistency (reproducibility)– repeated observation of an association in different studies and under different conditions support causation.

Specificity – a few ADRs are completely unique syndromes (some examples were given above) and their specificity means that causation is hardly in doubt.

Temporality – exposures must precede outcomes in a consonant manner.

Biologic gradient – is there evidence of dose- or duration related risk?

The final four criteria are: plausibility, coherence, supportive experimental evidence and analogy – these are related by a theme of whether or not the association fits with existing scientific knowledge and beliefs. If so then causation is more likely but newly identified associations may not fit – so absence of any or all of these criteria does not preclude an association being causal.

In general terms, the more criteria that are met, the more likely an association is to be causal. However there is no simple formula for adding up these criteria and coming to a definitive answer. Judgment is required and Bradford–Hill's criteria are merely a conceptual framework for making such judgment. It is worth noting that some of the criteria, e.g. temporality, dose-response, plausibility, are analogous to what was described above for the assessment of causality in individual cases.

5. Stakeholders in Pharmacovigilance

The PV system is meaningless without the contributions of all stakeholders (regulators, MAHs, Health care professionals, patients and their careers and the wider public) to provide the information about a medicine and any potential impact on safety.

Patients and their Care givers:

Patients primarily have the responsibility to comply with the treatment schedules and recommendations in the label and to be aware of important risks. Although much of the focus for ADR reporting has been centred on the regulatory authorities, the manufacturers responsible for the medicines themselves and the reporting healthcare practitioner, PV systems are opening up to more direct input from patients themselves as well as other representative bodies. A good understanding by patients of the potential benefits and risks of a medicine is likely to have a positive effect on reporting of ADRs and compliance with suggested risk minimization activities

MAHs (Marketing Authorization Holders):

The MAHs are the 'owner' of a medicinal product and as such primarily responsible for ensuring that the objectives for PV are being met and that appropriate action can be taken when needed. In many jurisdictions, this responsibility is captured in the law. With respect to bio-therapeutics, MAHs should provide clinical immunology and analytical support to HCPs and patients to help them to identify and manage related ADRs.

Regulators:

The regulators have a dual role in PV activities. On the one hand, they supervise the compliance of applicants with their PV activities. On the other hand, they play a role in facilitating PV activities in their territory (e.g. by facilitating reporting of ADRs or by creating databases that allow pooling of data to facilitate analysis). They can also play a role in proactive safety reviews and data capture that can be organized for cohort event monitoring, linked to a particular healthcare investment or initiative.

Healthcare Professionals (HCPs):

Spontaneous reporting systems are the most common mechanism by which safety reporting occurs, and these systems rely heavily on the direct contributions of all stakeholders who have been involved in the prescription, delivery and use of a medicine by a patient. This includes physicians, pharmacists or other healthcare workers. Their role is to ensure that the patient is sufficiently informed and motivated

to report any untoward effects they may experience. They also have a crucial role in ensuring traceability of the prescribed product by ensuring that all necessary information on the product prescribed and dispensed is included in the patient file, which can be accessed for verification e.g. in case of a reported ADR.

6. Communication in Pharmacovigilance

Communication plays an import role field of drug safety. The communication will be effective only when it is received and understood and resulted in appropriate change or action.

Information, such as ICSR is transferred from HCPs, consumers to regulatory bodies' pharmaceutical company and between regulatory bodies and pharmaceutical industry. The accumulation of reports may be used for information purposes, and to assist in the identification of possible signals. These are then assessed by the analysis of individual and aggregate cases; the latter being exchanged between administrations for multinational analysis at the European level. Once a decision has been made on a possible alert, the decisions and the reasons thereof must be transmitted to administrations and to other correspondents, such as health professionals, the pharmaceutical industry and WHO.

Objectives of safety communication should aim at:

- Providing timely, evidence-based information on the safe and effective use of medicines
- Facilitating changes to healthcare practices (including self-medication practices) where necessary
- Changing attitudes, decisions and behaviors in relation to the use of medicines
- Supporting risk minimization behavior

Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of Pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions and contributing to the protection of patients' and public health.