

Pharmacovigilance

I. Ralph Edwards • Marie Lindquist
Editors

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Critique and Ways Forward

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Foreword

As an answer to the challenges posed by the thalidomide tragedy in the early 1960s, the World Health Assembly endorsed the concept of an international collaborative project aimed at the early detection of possible drug-related problems. This was a seminal moment. Countries found they could join together and discuss safety problems in an open and collaborative manner and create a world data repository for the collected reports of suspected drug harms.

Starting in 1968, 10 countries were actively involved in the development of what in 1970 became the WHO Programme for International Drug Monitoring (PIDM), under the leadership of Prof. Jan Venulet. Amongst these early pioneers of drug safety, years later ‘rebranded’ as ‘pharmacovigilance’, were Drs. Hans Halbach and Bruce Royall from WHO Headquarters; Professor David Finney, who first had the basic idea of collating international case reports; and Dr. Ed Napke whose ‘pigeon hole system’ was the forerunner of the disproportionality methods used today to find signals based on pooled medical experiences.

By 1978, the operational activities were transferred from Geneva to the WHO Foundation Collaborating Centre for International Drug Monitoring, established for

WHO Programme for International Drug Monitoring

Founding members:

Australia (headed by Dr. Anette Welshe)

Canada (Dr. Ed Napke)

Czechoslovakia (Prof. O. Smahel)

Germany (Dr. G. Homann)

Netherlands (Dr. Leo Canta)

Ireland (Dr. A. Scott)

New Zealand (Dr. G. McQueen)

Sweden (Dr. B. Westerholm)

UK (Dr. W. Inman)

USA (Dr. A. Ruskin)

this purpose in Uppsala, Sweden. This foundation that was to become the Uppsala Monitoring Centre (UMC) has since been responsible for the maintenance of the database and the development of pharmacovigilance science and technology.

The first years to 1985 and even to 1990 were largely concerned with scientific and practical developments, always considering the best ways to harmonise and standardise tools and services, as well as to discuss global drug safety-related issues. Country representatives met at annual meetings organised by WHO, where work tasks for the Foundation Collaborating Centre were discussed and agreed. Any country could appoint a national pharmacovigilance centre to be a part of the PIDM after satisfying basic criteria of competence.

It was the mid-1980s when the pharmaceutical industry became actively involved in pharmacovigilance in a global sense. Two difficult pharmacovigilance challenges were responsible in part – practolol and keratoconjunctivitis plus sclerosing peritonitis and benoxaprofen and persistent skin photosensitivity with renal/hepatic failure. The global involvement of the pharmaceutical industry and regulators was essential, and pharmacovigilance dissolved into several complementary, sometimes dissenting, groups. The Council for International Organizations of Medical Sciences (CIOMS) and the specially created, industry-supported International Conference on Harmonisation (ICH) both served as platforms for industry and regulators to share views and ideas. Initially, both sides (industry and regulators) were suspicious of each other but agreed that, to achieve effective and cost-efficient processes, standards needed to be developed and rules adhered to.

As some of the large countries' databases expanded and there were increasing inflows of reports, the initial careful assessment of each report clinically, as if making a remote differential diagnosis, became too taxing. In essence, this led to a trend in the USA to consider a more and more public health epidemiological approach to drug safety, and the desire for pharmacoepidemiology to perform observational studies on collated data, rather than use clinical manpower on detailed evaluation of individual case reports. To bring together the scientific expertise, the International Society of Pharmacoepidemiology (ISPE) was started, for the first years being almost an entirely US enterprise.

In Europe, to tackle the same challenges, regional centres were created within countries to decentralise the workload. This regional clinical development was most advanced in France, and the natural desire for scientific but particularly joint clinical and pharmacology meetings led, from an annual national meeting in France, to the development of the European Society of Pharmacovigilance in 1984 and finally to the International Society of Pharmacovigilance (ISoP) in 2000.

From this, it is easy to see how two major groups have formed in pharmacovigilance: those with a public health epidemiology perspective and those who are more concerned with clinical analytics. The former rely on pharmacovigilance to deliver the best approximations of truth based on observational studies and a public health perspective; the latter consider collections of clinical cases and do individual case diagnosis and make clinical assessments of collated data on any safety issue.

Logic and experience tells us that both approaches have their place; the pioneers' vision that early signs of previously unknown medicine-related safety problems

would be identified promptly can only be realised by the use of different tools to create and evaluate hypotheses.

The use of pharmacoepidemiological methods has become popular with both regulators and industry because of their apparent robustness. Pharmacoepidemiology gives an apparently accurate numerical relative probability that event occurrence is not due to chance or is different between those exposed and unexposed to the drug, and a probability of real difference is generally accepted as equal or less than 0.05 or 0.01. These conventions are difficult to interpret with small effect sizes, and the probability for error makes it impossible to rule out rare effects. An important question is, 'What is an acceptable level of risk, and when should we stop putting resources into confirming the probability of risk from drug harm'?

For too long, the idea that case reports are the 'worst level of evidence' or 'just anecdotes' has predominated despite most hypotheses, and indeed decisions on regulatory action, being based on such evidence, and that is even considering 95 % under-reporting of suspected adverse reactions.

Where an expert group considers that the harm of one or more adverse effects caused by the drug is greater than the effectiveness, the drug is likely to be removed from public use or from publicly funded systems. Whilst it is clear that such actions are sometimes beneficial, we have little idea of how often or to what extent.

ISoP, amongst others, has taken the view that there are likely to be critical limitations to a system that makes top-down decisions on availability of drugs to a very heterogeneous group of patients in an even more heterogeneous population. It has also been well demonstrated that normative information focussing on public health findings to healthcare professionals or patients has had limited educational value.

ISoP membership is more of the view that the best public health results in pharmacovigilance can be achieved by optimising each patient–health professional interaction about therapeutics and that all aspects of therapy, as well as trust, patient empowerment and good communication practices, need to be considered to achieve this.

Accordingly, too much focus on methodology becomes counterproductive when instead much more effort needs to be put into transforming the results of scientific evaluation and risk assessment into practical information and knowledge that really helps health professionals and patients in their decision making.

Since the early years, pharmacovigilance has evolved from its initial focus on detection of new adverse reaction signals towards the improvement of rational therapeutic practice throughout the world. In order to improve overall public health, improved clinical patient safety should be the prime objective. To reach this ultimate aim, efforts are needed not only in the further development of pharmacovigilance as a science but also in the areas of communication and education.

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Preface

This book arose from a series of discussions of the International Society of Pharmacovigilance (ISoP), culminating in a strategic planning meeting in Berlin in 2012, with the Executive Committee members and all past-Presidents of ISoP present to talk about the future.

From the Berlin meeting, there was a common view that there were movements in society in general and medicine in particular that would affect the practice of pharmacovigilance. A long list of future issues that needed addressing was identified: ranging from the utilisation of richer data sources as a complement to case reports, to anti-counterfeiting measures, and the need for transparency of both assessment and decisions.

It was thought that over the last decade in particular, there had been a great increase in media attention paid to issues of drug safety. Also, there are an increasing number of stakeholders with active interests in different broad aspects of safety: all expressing views that the current system is not delivering optimally to improve therapeutics in clinical practice.

Perhaps the major concern is that a concentration on intrinsic problems with drug products means that there is not enough awareness and activity in improving patient care which will need a much more holistic view of risk and benefit in the use of drugs.

No one can be in any doubt about the magnitude of the tasks and changes needed to achieve better pharmacovigilance practices in the future. On the other hand, there is little doubt that the overall high level of iatrogenic illness must be addressed, nor is anyone complacent about the increasing costs of health care, partly due to medication issues.

Several ISoP members have been critical of the largely public health approach to pharmacovigilance – a top-down approach which respects neither the patients' needs and wishes, nor those of highly trained and much overworked professionals who take huge pains and responsibility to give individual patients the best care.

So it is that the idea of this book was born: Why not ask ISoP members to give their views on where pharmacovigilance should go, and what it should leave behind (at least in part)?

We are grateful to all the members of ISoP who have given up their time to talk to us and give us ideas and support. We are particularly grateful to the ex-Presidents and Executive Committee members of ISoP who have shared their thoughts with us. Most of all we are thankful to the chapter writers who have had the courage and imagination to express their thoughts about how the future might be better in pharmacovigilance, and taken the time to write it all down and to keep to deadlines (more or less!).

One person who deserves our special thanks is Sophie Spence, who is ISoP's administrative heart. Without her efforts in bringing us all together happily in Berlin and then supporting us tirelessly with all the correspondence, a few reminders (!), and general organisation, all would have been chaos and loss (at least for one of us – IRE).

You will see that the contributions vary in length and style, and that is deliberate. We did not want to be in any way restrictive, and we hope that this book is just the start of a dialogue that will bring in many more individuals and groups that can add their contributions to progress. We hope this can be done via a web-based version of this book, so that this work will be living for time to come – for the improvement of clinical benefit and avoidance of harm.

Finally, we would like to express our thanks to our ever cheerful, diplomatic and strong supporter who encouraged us to 'go for it' with this book, who is, of course, Nitin Joshi. Nitin has remained enthusiastic on the sidelines even after he recommended us to go ahead practically with the excellent publishing team from Springer, Prasad Gurunadham, Ellen Blasig and Cameron Wright, whom we also thank heartily. They have kept us on the straight and narrow pathway to the finished product, but miraculously made our job painless as well. David Elek at Springer also has been in the background and we thank him for his general support of this project.

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I. Ralph Edwards

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Vigilantiae, quo vadis ?

Introduction

In this chapter, we have considered the present and future developments of pharmacovigilance. Some of the ideas are our own, but the main purpose is to introduce the concepts and provide a framework around the different chapter authors and the content of their chapters. We cannot realistically do justice to all the contributors' ideas, and our strong recommendation is to enjoy reading them all for yourselves!

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

See Elizabeth Storz and Willibert Franzen; both of these chapters discuss practical difficulties faced in managing work under the current bureaucratic system in the EU.

Pia Caduff talks about the sound scientific work that has been done to improve pharmacovigilance but points to the limitations of the top-down public health approach and the surrounding bureaucracy.

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development and also points to the general need for vigilance – alertness – in all medical practice.

Marco Tuccori and Magnus Wahlberg give an account of the problems associated with evaluating ICSRs and observational studies. They review current work being undertaken and make suggestions for the future.

Giovanni Furlan talks about improvements that can be made to cut down duplication of effort in managing and analysing safety issues.

Bruce Carleton talks about the importance of individualising drug treatment and the need for more information and use of phenotypes and genotypes.

Ulrich Hagemann talks about the 'neighbourhood' of pharmacovigilance concepts and activities to include the medical, drug marketing and supply chain environments, as well as the impact of new drugs and scientific advances.

Emmanuel Okoro talks about the clinical scene and how supply issues, the medical context and other factors affect pharmacovigilance particularly in a resource-poor setting.

Alfonso Carvejal strongly proposes further attempts at global harmonisation of pharmacovigilance efforts with a patient focus but also autonomy for those who work in pharmacovigilance towards prevention.

Bruce Hugman reflects on the culture of pharmacovigilance and need for much more dynamism. He argues that communications outwards reflect the state of inner culture.

Shirley-Anne van der Spuy begins with the general concept of health and states that politics should facilitate the right to health and pharmacovigilance as a part of that. For her, the prime stakeholders are patients, but there are several other important stakeholders as well. The interrelationships are challenging, but she proposes some ways forward.

Souad Skalli talks about the use of traditional herbal remedies making the point that pharmacovigilance is just as important for alternative therapies.

Giampaolo Velo raises the issues of ecopharmacovigilance. The negative effects of drugs are not only felt directly by susceptible patients but also via their appearance in the environment as waste or excreted materials. The risks are both direct and indirect.

Brian Edwards discusses the various aspects of patient safety that are of concern with the use of drugs. He points out many inconsistencies in what is regarded as 'safe'. He argues that we currently have confused practices which are unclear and dysfunctional, perhaps because our basic thinking and processes are unclear.

Luis Alesso and Raquel Herrera talk about education for healthcare professionals and the public. For the former, they cover undergraduate and postgraduate education that must be related to specific healthcare settings.

The Aim of Pharmacovigilance

Definition of Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. [WHO, 2002]

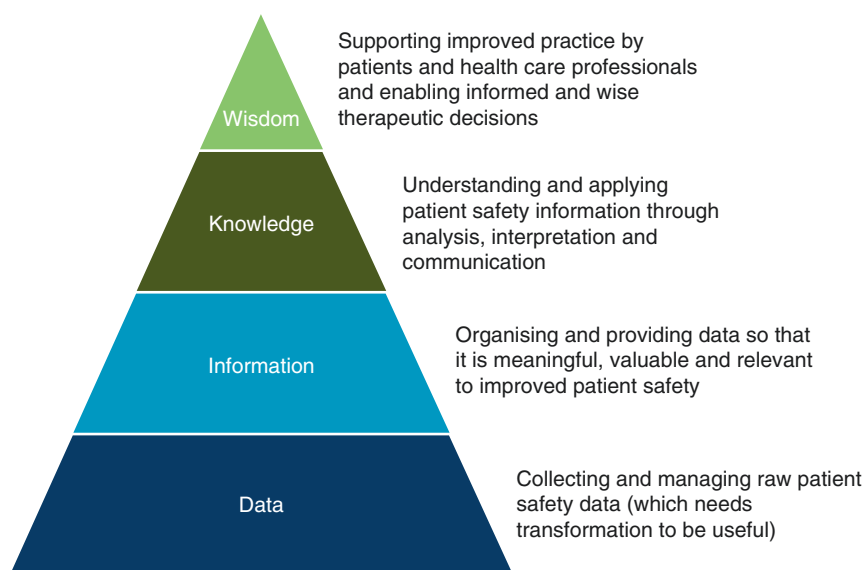
What is the prime objective of pharmacovigilance? Since the early years, pharmacovigilance has evolved from its initial clinical focus on detection of new adverse reaction signals towards the improvement of rational therapeutic

practice throughout the world. Following from this, there is naturally a major public health aspect to pharmacovigilance where the concentration is on improving therapeutic practices, in general, and reducing the overall burden of problems in relation to drug use. To achieve these public health goals, there must be an expressed political will and adequate funding to set up and maintain sustainable and cost-efficient systems for data collection, analysis and communication, and these systems need to be supported by a robust legal and regulatory framework.

Whilst we agree that the public health perspective is important and must be given adequate resources and support, the pharmacovigilance system must never be an end in itself. Our view is that improved clinical therapy for each individual patient should be the prime objective of pharmacovigilance; only if the results of pharmacovigilance activities meet the needs of the individual patient and their health professionals, and support the best possible decision making in each specific therapeutic situation, will there be a real and lasting impact on public health.

To achieve the vision of a world where all patients and health professionals are empowered and able to make wise therapeutic decisions in their use of medicines, we need good-quality data, but that is only the starting point. The key challenge is our ability to transform it into useful, timely and accessible knowledge at the point of care.

In this chapter, we shall concentrate on the scientific and methodological challenges and prospects ahead, but in proposing ways forward, we will also argue that pharmacovigilance can only seriously develop if there is open and constructive debate and a genuine will to work together, across stakeholder groups and borders.



The Starting Point

We need data to be able to determine any unusual clinical features coming during therapy of patients. With this data, we hope to assemble knowledge of any sort that may eventually lead to the better diagnosis, management and prevention of problems with therapy and to better learn about the real-life clinical uses (incl. off-label) of products so that effectiveness risk information will guide therapeutic decisions.

After collecting and collating case data, we need to do causality assessment to determine the likelihood of chance or otherwise spurious associations and so develop hypotheses about the harm that may be related to drug therapy. In order to do that, we need to determine the nature and strength of the causal relationship between a therapy and any clinical event. Such causal relationship will be most often a probability, not a certainty (only a very few medicines and clinical event relationships can be assumed to be near certain).

In essence, the assessment of causation is the same as the process of clinical diagnosis at the bedside. The difference is that the background expertise of the person reassessing the diagnosis is likely to have greater familiarity with causation by drugs and have more time and facilities for checking general information than the average health-care professional or patient. On the other hand, the healthcare professional(s) making the original diagnosis has first-hand information about all aspects of the patient.

In either situation, the individual diagnosis depends upon:

- The relative probabilities of the cluster of signs, symptoms, their evolution and investigations that have been found to point to a pathophysiological diagnosis
- The relative probabilities of various possible competing diagnoses within the patient's community

Clinical diagnosis of apparently serious disorders is an iterative process usually with peer reviews and sometimes involves long periods of follow-up with reassessments noting the evolution of signs and symptoms, any divergent opinions, supporting investigations and more:

- The nature, and particularly the sensitivity and selectivity, of the diagnostic process overall has not had great enough attention in pharmacovigilance.
- Neither have the reasons behind under-reporting of suspected adverse reactions nor possible ways of improving the number and quality of case reports.

In addition to clinical case assessment, we need to quantify the drug/harm incidence to determine the broad public health impact of the possible harm. The usual tools that are used are often variants of the four groups below. Each of them has advantages and disadvantages, so that they must be used according to the needs of each situation:

1. Prospective controlled interventional studies:

- (a) Placebo-controlled double-blind clinical trials
- (b) Comparative post-marketing studies

2. Prospective observational cohort studies with controls:
 - (a) Prospective self-control studies
3. Retrospective case control studies:
 - (a) Retrospective self-control studies
4. Monitored consecutive exposed cohorts with retrospective community data as controls

These are the basic approaches to developing a hypothesis of harm and the first analysis to try to understand the causal attributes of the clinical effect as competing probabilities, as well as quantifying the incidence of the effect.

A view has developed that pharmacoepidemiology can both find signals (raise hypotheses) and validate them (confirm hypotheses). This standpoint must be reviewed critically and in particular must be considered against the numbers of exposed people involved in epidemiological studies and the very nature of epidemiology and proof of causation.

Risks up to ~1:1000 are often seen and evaluated in clinical trials, though that depends upon human exposures during clinical trials and their duration. For exposed groups ~ 1:1000 – 1:10 000 and more rare, spontaneous reporting becomes the main way of first finding signals – and it is often the only way of evaluating the risk. This is because of the rarity of the effect (versus other probable causes – confounding) and the challenges of assembling enough patients with well-documented exposures and other necessary details (e.g. for propensity scoring).

It is clear that new hypotheses can appear, by chance, as a result of epidemiological studies, but that depends upon the data being of good quality, the numbers being sufficient and the observers of the study being alert to new possibilities. On the whole, the number of subjects exposed in even observational studies is too limited to find harms that occur less frequently than around 1:5000. Studies are designed to confirm hypotheses, and the data they use is selected for that purpose. All observational studies have the same problems with data quality as spontaneous reports since the data is collected during the routine work of clinicians; therefore the diagnostic data may be inaccurate and incomplete, particularly those data that are not the focus of the study.

We should therefore not rely on statistical significance: adverse reactions to marketed drugs are relatively too rare. Longitudinal patient healthcare records have the potential to improve this situation, but collection of suitable controls remains a challenge. The process is not short, and the length of time from first signal to public health action causes concerns when serious adverse effects are involved.

At the rarer end of the risk probability spectrum, it seems likely that many, perhaps serious, adverse reactions will remain ‘unverified’ because of lack of power. Instead of trying to find statistical probability as a gold standard alone, we should invest more effort into considering causation using the proposals of Bradford Hill, and so producing a logical argument for causal relationship, and not waiting for a statistic which cannot itself disprove a rare causal association. Also it follows that

any effectiveness – risk evaluations will have limits of confidence that must always be made known to caregivers and patients.

Some Current Problems and What Needs to Be Done

Data and Methodology

The chapters in this book confirm the current status of pharmacovigilance as an almost uniquely public health exercise in which pharmacoepidemiology is considered as the higher level of evidence that is regarded as essential for sound decisions. The collected clinical stories and suspicions that were (and in fact still often are) the basis of both pharmaceutical company and regulatory decisions are derogated to mere ‘clinical anecdotes’. Far more important, the writings confirm the extensive level of bureaucracy that surrounds the collection and analysis of ‘clinical anecdotes’.

It is usually considered that reported case reports of actual experiences of harm with drugs need to be assessed before they are regarded as a ‘signal’ for further attention or regulatory action. This process normally includes an assessment of the plausibility and credibility of the reported association.

The European Medicines Agency (EMA) has in their guidance described the concepts ‘signal validation’ and ‘signal confirmation’. However, it is not easy to understand what exactly is meant by a validated signal and how that differs from a ‘signal’. Should it be interpreted that a ‘signal’ is not a signal but instead a tentative/potential signal? Also, the difference between a ‘validated’ signal and a ‘confirmed’ signal is obscure. If ‘signal confirmation’ means ‘communication via EPITT, within 30 days’, then it is not that the signal has been transformed in the process from one concept to another (from ‘validated’ to ‘confirmed’) but that it is just that the ‘validated’ signal has been posted and made available.

Excerpt from EMA Guidance Document Questions & Answers on Signal Management

Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis. The clinical significance of the signal, its previous awareness, the biological and temporal plausibility and any relevant sources of information supporting the association are taken into consideration. Signals validated by the EMA or Member States are entered in the European Pharmacovigilance

Issues Tracking Tool (EPITT). EPITT is a database developed by the EMA to promote the communication of pharmacovigilance and risk management issues between the EMA and Member States. Signals for which the validation process was not supportive of a new potentially causal association, or a new aspect of a known association, are not entered in EPITT.

Signal confirmation means communication via EPITT, within 30 days of its receipt by the Rapporteur, the lead Member State or a national competent authority that the validated signal is confirmed or not confirmed. Any confirmed signal should be analysed and prioritised by the Pharmacovigilance Risk Assessment Committee (PRAC).

(http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150743.pdf accessed April 4, 2016)

These are the very basic issues that underpin how pharmacovigilance functions. If there are misunderstandings possible at this level, the risk is obvious that the confusion will continue.

The bureaucracy around the reporting of ‘anecdotes’ from industry to regulators and on the development of hypotheses from grossly under-reported clinical experiences seems paradoxical and almost grotesque when little or nothing is done to enhance the quantity and quality of those reported clinical experiences at source. Moreover the bureaucracy around the general evaluation and reporting by industry to regulators and the slow introduction of appropriate and agreed standards has been confusing and unproductive and has led to noticeable inefficiencies and increased workload in industry safety efforts.

For examples, see Elizabeth Storz and Willibert Franzen; both of these chapters discuss practical difficulties faced in managing work under the current bureaucratic system in the EU.

Pia Caduff talks about the sound scientific work that has been done to improve pharmacovigilance but points to the limitations of the top-down public health approach and the surrounding bureaucracy.

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development and also points to the general need for vigilance – alertness – in all medical practice.

Also there are inefficiencies in the separation of functions between pre- and post-marketing groups both in industry and regulators that cause duplications of data and resources.

Giovanni Furlan talks about improvements that can be made to cut down duplication of effort in analysing safety issues.

Under-reporting remains a problem with ICSRs. There are difficulties in getting good-quality data both for ICSR as well as observational studies. There have been many attempts to overcome the problems of the quality of data and the various biases and confounding that affect observational studies. Many improvements have been made but the power of studies remains a challenge. Studies will end up as large, cumbersome, time-consuming and expensive, or they cannot evaluate rarer suspected adverse effects. Certainly evidence from observational studies cannot exclude rare drug causes of harm.

These are areas that are continuously under review and improvement by very many academic and multidisciplinary groups.

See Tuccori and Wahlberg who give an account of the problems associated with ICSR and observational studies. They review current work being undertaken and make suggestions for the future.

New tools and approaches will need to be developed to collate and manage data from different sources and to analyse it for new knowledge. Some of the challenges are listed below and are mentioned in several of the chapters:

- Many harms may be related to medication errors that can in turn be due to environmental and organisational factors.
- Polypharmacy and interactions (this may be reported elsewhere than in the actual cases analysed) (e.g. food interactions and unusual drug interactions).
- Administration device problems (e.g. infusion devices and inhalers).
- Genotype/phenotype differences.
- Substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) product matters.
- Generics (may cause confusions in reporting and may have important differences in the chemistry of excipients and even active ingredients, e.g. biosimilars).

This new knowledge will be novel kinds of signals fulfilling the second part of the WHO definition ‘or any other possible drug-related problems’.

Bruce Carleton talks about the importance of individualising drug treatment and the need for more information and use of phenotypes and genotypes.

The list above annotates more recent areas that have been raised as important concerns that affect safe use of drugs. Given that around half of the adverse effects that are serious enough for hospital admissions are from older drugs and possible medication errors and the other issues mentioned, these should be receiving great attention in the future.

This will need close cooperation with groups involved in broader safety issues in medical practice and certainly the collection, collation and analysis of practices globally that we currently have in place for determining adverse reactions to drugs. We will also have to broaden our current gaze from just drug product data and its regular use to other data (e.g. drug poisoning, misuse, off-label prescribing and fraudulent products) in order to understand how drugs may cause harm and how it can be eliminated or minimised.

There are many more places where critical information about safety issues with drugs is recorded and investigated. Those data sources should be used to gain more information. Some examples are as follows:

- Poison control centres (for more information about human toxicology and pharmacokinetics).
- Drug information services (many adverse drug effects are the reason for queries about a drug).
- Electronic patient/health records contain much information about patients' clinical status that can be linked to the drugs they take by suitable clustering algorithms and useful chronological data.
- Social media/data posted on the web (as yet untested but patient concerns and the impact of drug effects on people are important information).
- Pre-marketing toxicology (links between toxicology and pharmacovigilance should be explored further for its value) and clinical trials data and others, such as the many sources of data in the private domains of health professional and patient organisations.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Main Points

- Knowing what method works for what situation:
 - The importance of good-quality case reports
 - The role of pharmacoepidemiology methods
- Incorporating new data:
 - Vaccines, medication error, SSFFC, patient-reported data, electronic health-care records, active monitoring studies, etc.

- Analysing available data to identify safe use:
 - Influence of demography, drug combinations, diseases, and situations
- Redefining of ‘signal’ to take into account:
 - New types of data
 - That most problems are not ADRs as such but related to drug use
 - Patient outcomes (impact, duration, dose, benefits!)

Risk Management and Decision Support

Balanced Evaluations

In order to make decisions about both individual patients and public health, the good that a medicine can offer must be weighed against the bad. In our view, the correct balances, with explanations, are as follows:

- Efficacy is the result of preclinical work on pharmacology in humans and animals as well as in vitro methods that shows that a drug has a useful pharmacological effect, and hazard is the toxicological and early clinical testing result that indicates a potential for harm in clinical practice.
- Effectiveness is the clinical demonstration of useful effects in real-life clinical practice, just as risk is the probability of harm as assessed from ICSRs and observational studies during the routine clinical use of drugs.
- Benefit is the value of the drug as determined by individual patients, just as harm is the negative way in which a drug may affect them from adverse effects directly caused by the drug or from aspects of its use or misuse. These factors can only be judged by various kinds of outcomes research:
 - The phenomenology of illness and the way in which those matters affect the lives and decisions people make. These are critical factors in improving the care of patients and the possibility of providing decision aids to patients and their carers.
 - Quality-of-life measurement is an essential tool for the vigilance of patients, but so far very little has been done to determine what entities and phenomena the individual patient values most and therefore what should be primary considerations. Development of such a tool is possible:
 - Existential self-assessment by phenomenology.
 - Self-assessment tool should be developed in cooperation with other groups involved in outcomes research.

So far, decisions have been the results of value judgement by groups of experts for broad public health matters and by individual clinicians for patients, and there has been too much focus on harm. The evidence basis for the public health decisions

is obscure or certainly neither made available readily nor much debated. There have been partial attempts made (e.g. NICE in the UK and public hearings in the USA), but little effort has been made to be rigorous about comparisons: efficacy is still often compared with risk and the whole is often labelled ‘benefit/risk assessment’.

Once the basic understanding of the good and bad of drugs is applied more rationally, better decisions will be possible and better tools devised to replace judgements based entirely, or to a large extent, on expert opinion and values.

It will need to be also understood that so-called ‘risk benefit’ evaluations cannot be definitive but have to be iterative to ensure that comparisons between drugs remain current and that new findings and new therapies are incorporated.

It will be important (and always has been!) for the public to better be educated about the ‘risk benefit’ of drugs so that they can learn what to expect. Since this kind of evaluation is relevant for everyone, one could hope that it will be taught from school age. Good communications around drug safety issues, particularly using the media, will be most important.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Main Points

- Improving methods for deciding if (chance of) benefit > (risk of) harm
- Developing decision support for signal action and communication – what is an ‘actionable’ signal?
- Implementing trend analysis strategies and tools to deal with evolving issues
- Devising communication strategies for better understanding of concepts of risk assessment

Management and Prevention of Adverse Reactions

Diagnosis and Management

There are many factors that lead to failures in diagnosis, prescription and drug use. How do those failures affect subsequent management? If a patient has an adverse reaction, will it resolve if the drug dosage regimen is changed? And if a drug therapy is stopped, what alternative treatment is available? Will it have less adverse effects? The off-label use of drugs is another area for investigation: how often do they cause harm? How often do they provide useful information on new indications?

In order to develop a sound knowledge basis to support the best possible treatment options for each patient, we think it is necessary not only to collect more, and better, evidence of patient harm but also to start finding out what it is that works well and why.

Ulrich Hagemann talks about the 'neighbourhood' of pharmacovigilance concepts and activities to include the medical, drug marketing and supply chain environments, as well as the impact of new drugs and scientific advances.

Emmanuel Okoro talks about the clinical scene and how supply issues, the medical context and other factors affect pharmacovigilance particularly in a resource-poor setting.

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Prevention

Despite many developments in pharmacovigilance and drug regulation, drug misadventures are still a major source of death, morbidity and financial burden in society. It has been estimated that about half of the adverse events causing hospital admission are potentially preventable and therefore represent avoidable patient harm. Medication error and drug–drug interactions (DDIs) are well-known causes of preventable adverse reactions, but the size of the problem, both in terms of patient suffering and costs to healthcare systems, is still very much under-researched.

Preventable adverse reactions pose a rapidly growing challenge also in resource-poor nations. Access to better healthcare brings access to more medicines, but inadequate knowledge about medication error and DDIs and their prevention dilutes the health benefits; this is compounded by the effect of SSFFC medicines, which hits already vulnerable populations the hardest but which is a growing problem globally.

This is an extremely important area where there is lack of data, under-developed methodology and even less data on impact. We believe that education and communication is very important at all levels of health professionals and for the public, but much more must be done and learned to prevent the preventable.

Alfonso Carvejal strongly proposes further attempts at global harmonisation of pharmacovigilance efforts with a patient focus but also autonomy for those who work in pharmacovigilance towards prevention.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Main Points

- Develop methods for comparative risk profiles to aid patient and medication management.
- Collect and communicate success stories from data, HCPs and patients on how to mitigate harm, and alternative treatments.
- Establish tools for further research on preventable reactions and how to avoid them.

Regulation and Impact Assessment

In the last decade, as the political and public demand for rapid access to new medicines has increased, the need for more proactive, iterative safety management has been recognised by both regulators and pharmaceutical industry, and efforts have been made to improve regulatory processes and routines.

In resource-poor countries, with previously limited access to medicines, large populations burdened by the endemic scourges of communicable diseases can now be treated thanks to medicine donations. Real-time monitoring of their use for both safety and efficacy is a high priority, of particular importance since some are novel drugs, and others will be used in settings and populations which are very different from those of the original approval.

Withdrawing drugs from the market leads to substitution by others or non-treatment. We know little about the negative effects of such regulatory actions on those that take the drugs without problems and good benefit. We know little about the success or otherwise of the substituted drugs. We know that regulatory communications are not optimal, but there is little suggestion that the changes currently being made are effective.

Given that there is a continued large problem caused by adverse events related to medication, it is essential that the impact of pharmacovigilance should be audited for effectiveness. The emerging role of outcomes research in identifying shortfalls in practice and promoting strategies to improve healthcare is an increasingly important tool for organisations, governments and industry.

The profile of pharmacovigilance has been raised, and its role is under scrutiny and review globally. Both WHO and USAID-financed Management Sciences for Health (MSH) have developed indicators that provide measures that will enable the

assessment of the status of pharmacovigilance and the activities and their impact, nationally and globally, at all levels of the healthcare system with a view to ensuring patient safety. These must now be deployed and fine-tuned as needed and the identified gaps addressed!

Isah and Edwards present ideas of pharmacovigilance performance indicators

Pia Caduff talks about the sound scientific work that has been done to improve pharmacovigilance but points to the limitations of the top-down public health approach and the surrounding bureaucracy.

Main Points

- Establish, evaluate and develop routine assessment using pharmacovigilance indicators.
- Collect data and do research on impact, e.g. changed ADR incidence, changed practices, healthcare and patient-reported outcomes.
- Develop tools and strategies to provide feedback loop pharmacovigilance – healthcare practice.

Communication

Reaching Out to Patients (Communication)

There is a critical need for education and communication between stakeholders in pharmacovigilance. In the past, and currently, there has been secrecy and too much concern about patient privacy issues. That is not to say at all that patient privacy is not of utmost concern and must be protected, but rather it has been used as an excuse in situations where one major party wishes to find an excuse against sharing totally anonymised data. The reasons behind these actions seem to relate to political control, not for the benefit of patients who should be helped by the sharing of group data with experts whose sole intent should be to improve the safety of others who may be exposed to the same drug in the future.

It seems that a rather cynical battle between regulators, industry and other groups with competitive motives that hinder sharing of knowledge about safety has held up the development of pharmacovigilance for decades. Now is the time to begin real, thoughtful communication and education which must be the most important way of

moving forward as a global partnership for the best therapy for patients worldwide.

Luis Alesso and Raquel Herrera talk about education for healthcare professionals and the public. For the former, they cover undergraduate and post-graduate education that must be related to specific healthcare settings.

Main Points

- Develop communication tools and strategies to:
 - Engage with the media, public and decision makers to:
 - Raise the profile and status of pharmacovigilance
 - Enable a public dialogue
 - Get funding
 - Make the best possible information and knowledge available, useful and usable to all stakeholders

What Might We Do Next?

Pharmacovigilance and Rational Therapy

In response to a number of safety issues that the public (via the media) has been concerned about, regulatory agencies have been criticised for delays in regulation and industry for prevarication. Much bureaucracy has resulted from this in order to increase efficiencies in reporting safety problems and in openness to society.

Consequently private enterprise groups have developed for patient reporting, and patient groups have become more and more active. The Internet has also provided more and more information sources on drug safety issues that can be tapped but which need to be evaluated and used carefully. Very many patients are active users registering and communicating their concerns. The use of wearable monitoring devices is also exploding, with the resulting vast amounts of patient-generated data that may add useful information on drug use and responses.

At the same time, there have been a major concerns about the cost and delivery of healthcare – not only safety but effectiveness also. As mentioned above, as a response to these challenges, outcomes research projects have become increasingly practiced, and patient safety projects and monitoring have become more widespread and often performed by independent groups, using approaches and methods that

may or may not be better than those that are current, but there is a great need to investigate and harmonise these methods and to find ways of collating information to produce useful knowledge.

Particularly we need to consider how to measure the balance between efficacy and hazard, effectiveness and risk and benefit and harm using all relevant data and producing results that will be useful for both clinical medicine and public health decisions.

This is particularly so when increases in pharmacological and medical science knowledge have resulted in advances in therapy that make categorisation difficult. Is stem cell therapy a ‘drug’? A biological? How do we consider devices used in drug delivery? How in individual patients do they all interact? Who are the patients who will best benefit from each and how are the treatments best used in combination? What are the negative aspects of combinations of treatment modes? These are the questions that clinicians face daily.

Ulrich Hagemann talks about the ‘neighbourhood’ of pharmacovigilance concepts and activities to include the medical, drug marketing and supply chain environments and includes the introduction of new therapeutic products.

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development. They also point to the general need for vigilance – alertness – in all medical practice.

Successful therapy and good patient outcomes must also take into account patients’ perceptions and expectations – which may be totally different from, and sometimes even seemingly irrational to, those of health professionals or regulators who see things from a different perspective than the patient themselves.

In the overall evaluation of how therapy affects patients, many more questions must be asked and answered: What do patients expect from treatment? What is the best therapy? Is it drugs? Surgery? Physiotherapy? Acupuncture? Herbal medicines?

Medicines are just one mode of therapy albeit the most frequent one used by healthcare professionals. Other therapies need better assessments of their effectiveness and risks; for a single patient, there are good and bad interactions between therapies that need to be better understood, for example, by evaluation of phenotypes and then genotypes of those suffering adverse drug effects.

Souad Skalli talks about the use of traditional herbal remedies making the point that pharmacovigilance is just as important for alternative therapies.

Bruce Carleton talks about the importance of individualising drug treatment and the need for more information and use of phenotypes and genotypes.

Pharmacovigilance is the oldest continuous monitoring system for safer medicines practice and such alertness or vigilance should be a sustained and integral part of safe healthcare practice in general. This is happening as part of the drive to better patient safety, but the methodologies are very variable. This should change towards more harmonised vigilance in all areas, taking into account that all of medical care has overlapping responsibilities and professional territories

It seems very inefficient to have many unrelated and incompatible systems to collect and store data on continuously collected healthcare outcomes. Is there anything we can determine from the current medical treatments of patients and from pharmacovigilance?

Since pharmacovigilance has well-developed approaches to getting information on the negative aspects – and increasing the positive results – of drug therapy, perhaps the same methodology can be used for general therapeutic vigilance. Would it not be wise to broaden what we do in pharmacovigilance and start to record the good and the bad outcomes that patients experience from any of their therapies? Is that not a more rational way of approaching the management of disease? Isn't it so that outcomes research needs to operate in such a way continuously and that we in pharmacovigilance have many of the approaches and tools that will make a huge difference to collecting evidence from the first information on suspected harm and guiding work towards more definitive studies?

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development and also points to the general need for vigilance – alertness – in all medical practice.

All of the above may seem idealistic and out of our reach. It is not – the technology to help us do all of this is available. It is only human will that is required to recreate and develop David Finney's and WHO's idea of a global system for the early warning of problems with therapy and which takes the earliest possible action to improve patients' well-being around the world. Such a cooperative system would be economically efficient as well.

Eugene van Puijenbroek and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

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Why We Need International Collaboration

The chapters in this book, apart from being critical over the status quo, propose ways forward for pharmacovigilance. It is very clear that in the last 10–15 years the interest in the safety of medicines has increased both amongst the public as well as health professionals of all kinds. As a result, there are a number of new stakeholder groupings, some with broad interests and some having specific focus. Much more pharmacovigilance work is now being undertaken by groups outside the global efforts of WHO, CIOMS and ICH.

There is a large overlap in the requirements for long-term, continuous oversight of therapy/management of patients and a need for harmonisation of methods. To do all of this, there is a need of a global, continuous system for assessing the outcomes of healthcare therapy, particularly safety, in a harmonised way that can be used by any domain expert. This is not supplied by any current global organisation.

Global cooperation seems to be essential if we are to find suspicions of problems, investigate them and take appropriate actions. Global cooperation is as necessary now as it was at the start of the WHO programme: we need global data and different ways of looking at it. If we are to be efficient in eliminating or mitigating harm, we need to be sure that all useful information is available, and relevant knowledge transferred, to empower patients and their health professionals worldwide. (*See Alfonso Carvejal.*)

The global coordination of groups concerned with effectiveness and risk in patient care will be essential in the future for the limitation of even greater expansion of healthcare costs.

Main Points

International collaboration is needed to:

- Optimise use of different competencies and resources:
 - Possibility for prompt and open exchange of information.
 - Working towards common goals brings people together.
 - Learning from each other’s experience.
 - Sharing workload.
- Increase understanding and ability to interpret results across countries/regions
- Bring results together instead of duplicating efforts

Conclusion

Our world is full of data of variable quality about virtually the whole of human knowledge but the path from data >>>>information >>knowledge>wisdom is complex. The first and perhaps most extensive/expensive step is to transform data into meaningful information. It has been shown that it is possible to automate data collection satisfactorily for pharmacovigilance (though not with complete agreement) by the work of WHO, CIOMS, ICH and various public–private partnerships to create agreed, usable data sets for information, and there are also methods for knowledge finding within that data.

However, in recent years, we have seen a multitude of new stakeholders taking an interest in pharmacovigilance, and then there is the big data revolution, with vast amounts of patient-generated data and reported outcomes becoming available. From the experience of previous international standardisation work, it would be surprising to have complete global agreement about a single process or formats for collecting, managing and analysing all data. This suggests that repeating the process that took decades, for new clinical data sets and safety purposes, which have links with pharmacovigilance anyway, would be wasteful.

We propose that a better way of expanding our knowledge base is to accept a higher level of heterogeneity in terms of data and information sources and concentrate on collaboration efforts instead of knowledge-finding tools (and those may only need some limited adjustment), better methods for decision support and an open and constructive debate of what the knowledge tells us and how we should use it wisely.

Main Points

- Safer use of medicines for all populations can be achieved.
- New methods and data sources need to be integrated into robust and scientifically sound evaluation processes:
 - There is no one-size-fits-all for evaluation of data, but techniques for data management, outcomes vigilance and data analytical support are common:
 - There is a good case for broad health outcomes vigilance.
- We need to get past our preoccupation with standardisation of data and collection processes and move rapidly towards optimising useful knowledge transferred to patients and their healthcare professionals so that they might make wise decisions that improve peoples' lives.
- Openness, good communication practices and win-win international collaborations are essential for success.

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Pharmacovigilance

Critique and Ways Forward

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