The detection and evaluation of adverse drug reactions is crucial for understanding the safety of medicines and for preventing harm in patients. Not only is it necessary to detect new adverse drug reactions, but the principles and practice of pharmacovigilance apply to the surveillance of a wide range of medicinal products.

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from a review in E-STREAMS

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Stephens’ Detection and Evaluation of Adverse Drug Reactions

Principles and Practice

Sixth Edition
Stephens’ Detection and Evaluation of Adverse Drug Reactions

Principles and Practice

Sixth Edition

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Foreword

Despite the many therapeutic advances made possible by drug discovery over the decades, experience has shown that all active pharmaceuticals have the potential to cause harm. In the half-century which has now passed since the thalidomide disaster, much progress has been made in developing the concepts and strategies to study the balance of benefits and harms, which determines the clinical utility of a medicine. The scientific methods to do so have become progressively more refined—in the laboratory, in the clinic, and in the population. This book reviews in depth the impact that genetics and toxicology have had on our ability to understand the mechanisms of drug toxicity; the contribution of the randomised control trial to the assessment of both benefit and harm; and the increasing power of epidemiological methods to detect unanticipated adverse events in the treated population.

Allied with these scientific developments has been an expansion of the regulatory system for pharmaceuticals in all developed countries. Two concepts have been particularly fruitful in recent years. The first is that there needs to be a continuous review of the benefit–harm relationship for any pharmaceutical as it passes along the trajectory from discovery to long-established use. As new knowledge accumulates, action may be needed to revise the terms of market authorization and to communicate significant new information to prescribers and to patients. The second is the shift from reactive to proactive pharmacovigilance. The legal and regulatory underpinnings for such a shift are clearly described here, notably the principles of risk assessment, pharmacovigilance plans, and risk management strategies to be specified at the time of market authorization.

That is not to say that spontaneous reporting of suspected adverse drug reactions has lessened in importance. The limitations of spontaneous reporting have long been known: under-reporting, lack of precise denominator information, and preferential reporting of clinically ‘unusual’ events with a short temporal relationship to drug exposure. Yet such reporting, by health-care professionals and increasingly by patients themselves, has an essential role in providing signals to be assessed more rigorously from other data sources. This book describes many recent advances in the capture, aggregation, analysis, and assessment of spontaneous reporting data. The ever-expanding use of information technology in clinical settings, capability to move large quantities of data by the internet, and the use of advanced statistical techniques to ‘mine’ data have all contributed. Although astute spontaneous reporting has generally been thought of as a means to deepen our understanding of the human pharmacology of the drug molecule, it can also serve to detect quality failures in the pharmaceutical supply chain, as was recently seen with the contamination of heparin with over-sulphated chondroitin sulphate.
FOREWORD

The detection and evaluation of adverse drug reactions is pre-eminently a multidisciplinary enterprise and one in which industry, academia, regulatory authorities, and clinicians all have key roles to play. The pace of change since the last edition seven years ago has been truly remarkable. It has been driven by developments in science and by lessons learned from individual drugs that have revealed adverse effects in the course of widespread population use. The aim of a proactive pharmacovigilance strategy must be to ensure that such effects are detected, assessed, and responded to appropriately, with the minimum of delay.

Three particularly challenging areas of pharmacovigilance are dealt with in depth in this volume. Vaccines are perennially controversial, despite their huge positive impact on public health, for complex reasons which are examined. Drugs used in cancer therapy frequently lie at the opposite end of the benefit–harm continuum. Herbal medicines are used by a substantial minority of the population, have a limited evidence base on safety, yet can on occasions give rise to life-threatening toxicity and drug interactions.

Perhaps the greatest challenge we face is the transfer of new knowledge about individual medicines into clinical practice. Here too the impact of the internet in recent years has been profound. It will undoubtedly increase further, offering as it does the essential elements of fast dissemination, accessibility and search function, which printed media cannot match. When important new benefit–harm information becomes available, from whatever source, a regulatory agency should be able to make that available on its web site within hours rather than days. Ideally the information should be tailored separately to meet the needs of three groups of users: prescribers, patients and specialists in the field. The Appendix examining national and institutional pharmacovigilance web sites in a systematic way is a valuable addition to this volume.

Communication is a key factor in pharmacovigilance. As it becomes increasingly multidisciplinary, from genetics and toxicology to statistics and law, we risk the Tower of Babel problem: specialists engaged on a joint enterprise being unable to understand each others’ language. Stephens’ Detection and Evaluation of Adverse Drug Reactions will greatly mitigate that risk, to the benefit of patients.

Sir Kent Woods
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Preface to the Sixth Edition

As were previous editions, this book is designed to be both read and used as a reference work. The raw statistics of its contents reflect how widely it spans the whole range of pharmacovigilance activities: its 15 chapters and two appendices contain over a quarter of a million words, 125 tables, 55 figures, and over 2000 references. It is aimed at all those who work in pharmacovigilance or have an interest in adverse drug reactions, whether in regulatory authorities, pharmaceutical companies, or academia.

However, this new edition is significantly different from the previous one. We have retained several chapters and authors from the fifth edition, but they have been joined by new co-authors, and their chapters have all been extensively revised and updated. The introductory material in Chapter 1 has been completely rewritten to reflect modern advances, and there are several new and highly relevant chapters, such as those on pharmacogenetics, proactive risk management, societal considerations, assessing the safety of drugs used in oncology, and the pharmacovigilance of herbal medicines. The former appendices have been replaced by two new ones, one on pharmacovigilance web sites and the other on guidelines and a checklist for reporting suspected cases of adverse reactions in journals. We have also modified the title, to Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice, to reflect the fact that pharmacovigilance is not just about detecting new adverse reactions and to stress that while many of its principles apply generally, practices can differ, for instance in the surveillance of biologics, vaccines, herbal medicines, and drugs used in particular circumstances.

We thank all our contributors for their diligence, and Fiona Woods and her colleagues of Wiley-Blackwell for their hard work, encouragement, and patience throughout the lengthy process of assembling this new edition.

JT, Bisbrooke, Rutland
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I would also like to thank Lucy Sayer, formerly of John Wiley, for persuading me to commit to producing a new edition and her support during the early stages of the project.

JKA—When John Talbot invited me to join him as co-editor of Myles Stephens’ textbook, I accepted with alacrity. His vast experience in pharmacovigilance in the context of drug development and his deep understanding of the importance of so many matters of practical relevance complemented my own academic approach, and preparing the book with him has been an exceptional educational experience. We are both deeply indebted to Myles Stephens, whose wide-ranging scholarship laid the foundations of what has become a standard text in the field of pharmacovigilance and one that we feel honoured to have been able to advance.
1

Adverse Drug Reactions: History, Terminology, Classification, Causality, Frequency, Preventability

Jeffrey K. Aronson

1.1 Introduction

No therapy that is effective is free of adverse effects. The detection of adverse effects of drugs and adverse reactions to drugs and other therapeutic interventions, the scientific basis of which has been delineated since the 1960s is more important than ever before, as therapy becomes increasingly complex and is used in increasingly ageing populations. Figure 1.1 shows the increase in the numbers of publications, culled from Pubmed, that have contained the terms “side effects” or “adverse effects” since 1965. There has been a steady increase in the number of publications from year to year, and the rate of increase has grown since the start of this century and shows no signs of abating (top panel); in the years before 1985–90 the rate of increase even outpaced the rate of increase in the total number of papers published (lower panel).

1.2 Defining pharmacovigilance

The term “pharmacovigilance” first appeared in French in the late 1960s, when the terms “pharmacovigilance intensive” and “pharmacovigilance spontanée” were contrasted [1]. 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 possible drug-related problems” [2]. Its scope includes not only the small molecules that are found in traditional medicinal products, but also biologics, vaccines.
ADVERSE DRUG REACTIONS

Figure 1.1 The numbers of publications containing the terms “side effects” or “adverse effects” from a Pubmed search 1965–2010

and other cellular products, blood products, herbal medicines, traditional and complementary medicines, and medical devices.

In a directive of the then European Economic Community (EEC) a pharmacovigilance system was defined as “a system [that is] used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically” [3]. The directive specified that the purpose of such systems is “to ensure the adoption of appropriate regulatory decisions concerning the medicinal products authorized within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use” (implying postmarketing surveillance) and that “such information shall be collated with data on consumption of medicinal products”. An amendment to this directive, published in 2000, specified that “[the] system shall also take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks” [4].
Pharmacovigilance has in the past been regarded as being synonymous with postmarketing surveillance for adverse drug reactions. For example, it has been defined as “the study of the safety of marketed drugs under the practical conditions of clinical usage in large populations” [5] and “the process of evaluating and improving the safety of marketed products” [6]. However, it is now recognized that pharmacovigilance goes further than that, since it also includes premarketing surveillance [7], and this facet has been specifically incorporated in another definition, which states that pharmacovigilance “involves the monitoring, detection, evaluation and responding to drug safety hazards in humans during premarketing development and post marketing” [8].

The aims of pharmacovigilance are:

- the identification and quantification of previously unrecognized adverse effects and reactions;
- the identification of subgroups of patients at particular risk of adverse reactions;
- the continued surveillance of a product throughout the duration of its use, to ensure that the balance of its benefits and harms are and remain acceptable;
- the description of the comparative adverse reactions profile of products within the same therapeutic class;
- the detection of inappropriate prescription and administration;
- the further elucidation of a product’s pharmacological and toxicological properties and the mechanism(s) by which it produces adverse effects;
- the detection of clinically important drug–drug, drug–herb/herbal medicine, drug–food, and drug–device interactions;
- the communication of appropriate information to health-care professionals;
- the confirmation or refutation of false-positive signals that arise, whether in the professional or lay media, or from spontaneous reports.

1.3 The modern history of pharmacovigilance

Physicians have been aware that medicines can have unwanted effects since they first started using them therapeutically, and before that recognized the poisonous effects of many other substances; for a detailed account of the history of early developments see [9]. The modern history of the development of pharmacovigilance can be considered to have begun with the German toxicologist Louis Lewin, who published the first book devoted entirely to adverse drug effects in 1881, Die Nebenwirkungen der Arzneimittel [10]. Three subsequent editions appeared in 1893, 1899, and 1909. In 1883 a translation of the first edition in cumbersome English appeared in a so-called “second edition” as The Untoward Effects of Drugs, translated by J J Mulheron, Professor of the Principles of Medicine, Materia Medica, and Therapeutics in the Michigan College of Medicine in Detroit [11].

Also in the 1880s, UK doctors, supported by Ernest Hart, editor of the British Medical Journal, started to campaign against the marketing of patent medicines that contained useless or toxic ingredients, but the Patent Medicine Bill of 1884, which sought to control them, failed because of pressure from the Society of Chemists and Druggists. However, the campaign
ADVERSE DRUG REACTIONS

continued. In America, concern about adulterated and misbranded foods and drugs at the start of the twentieth century culminated in the publication of 11 articles by Samuel Hopkins Adams in *Collier’s Weekly* in 1905, titled “The Great American Fraud,” in which he exposed many of the false claims made about patent medicines. This led directly to the 1906 Pure Food and Drugs Act, which established the forerunner of the Food and Drug Administration (FDA) [12].

The British Medical Association, likewise concerned, started to publish a series of articles in the *British Medical Journal* in 1905 under the general title “The Composition of Certain Secret Remedies”, dealing with drugs used to treat epilepsy, headache, kidney diseases, and other conditions. In 1906 it started to reprint similar articles from the *Deutsche Medizinische Wochenschrift*. These articles were then published in a volume titled *Secret Remedies* in 1909; a second volume appeared in 1912, after the first had sold 62,000 copies [13]. In 1915 the Medical Research Committee (later to become the Medical Research Council), which was established in 1913, called for prescribers to report “therapeutic efficacy and the presence or absence of special incidental symptoms” in relation to formulations of salvarsan [14].

Also in 1915, Otto Seifert published his textbook on adverse drug effects, *Die Nebenwirkungen der modernen Arzneimittel* [15], a 278-page volume, to which a supplement was added in 1928. The problems with salvarsan in the UK eventually led to the establishment of The Therapeutic Substances Act of 1925 [16], which was later superseded by the Medicines Act of 1968.

In 1951 Leopold Meyler published a 192-page book in Dutch, titled *Schadelijke Nevenwerkingen van Geneesmiddelen*, which was entirely devoted to descriptions of adverse reactions to drugs [17]. An English translation, *Side Effects of Drugs*, appeared in 1952. The book was a success, and a few years later Meyler started to publish what he called surveys of unwanted effects of drugs (labelled as volumes rather than editions), each of which covered a period of 2–4 years. In September 1973, after the publication of Volume VII, Meyler died unexpectedly, and Graham Dukes edited the last four-yearly survey, Volume VIII. After that, annual volumes began to appear (Side Effects of Drugs Annuals, SEDA), each surveying a year’s literature. At the same time an encyclopaedic version was prepared (the so-called ninth edition). Since then another six encyclopaedic editions have appeared, the latest (the 15th edition) in six volumes [18], and the SEDA series now runs to 33 volumes. A further eight volumes dealing with specialties (such as cardiology, psychiatry, cancer and immunology, and endocrinology and metabolism) appeared in 2009–10.

Complementary to the Meyler series, Davies and colleagues have published five editions of a textbook called *Textbook of Adverse Drug Reactions* (1977, 1981, 1985, 1991, and 1998) [19]. Whereas Meyler lists individual drugs or groups of drugs and discusses their adverse effects and adverse reactions, Davies lists the adverse reactions and discusses the drugs that cause them.

1.3.1 Adverse reactions as drivers of change

Over the years, various adverse reactions have led to innovations in pharmacovigilance (Table 1.1). For example, the toxicity of diethylene glycol, a solvent used in a formulation of sulfanilamide, made the news in 1937 in the USA and led to the promulgation of the 1938 Federal Food, Drug and Cosmetic Act, which required evidence about adverse reactions before the release of a new drug, and gave increased powers to the Food and Drug Administration [20]. The story of thalidomide and its effects on pharmacovigilance, particularly the importance of proper preclinical testing of drugs, is well known [21, 22]. Perhaps less well known to the general public is the story of benoxaprofen, which was introduced amid huge
## Table 1.1 Examples of drugs that have been withdrawn or have had their uses restricted because of adverse reactions, or that have had effects on pharmacovigilance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Adverse reaction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvarsan</td>
<td>1915</td>
<td>Toxicity due to impurities</td>
<td>Therapeutic Substances Act, 1925</td>
</tr>
<tr>
<td>Sulfanilamide</td>
<td>1937</td>
<td>Liver damage due to diethylene glycol</td>
<td>Solvent changed; companies required to demonstrate safety; FDA’s powers increased</td>
</tr>
<tr>
<td>Diododithethyl tin</td>
<td>1954</td>
<td>Cerebral oedema</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>1961</td>
<td>Congenital malformations</td>
<td>Withdrawed; Dunlop Committee (later the CSM) established; teratogenicity testing improved</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1966</td>
<td>Blood dyscrasias</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Clioquinol</td>
<td>1975</td>
<td>Subacute myelo-optic neuropathy</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Practolol</td>
<td>1977</td>
<td>Oculomucocutaneous syndrome</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Benoxaprofen</td>
<td>1982</td>
<td>Liver damage</td>
<td>Withdrawed; studies in elderly people required</td>
</tr>
<tr>
<td>Eptomdate</td>
<td>1983</td>
<td>Adrenal suppression</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Zimeldine</td>
<td>1983</td>
<td>Hypersensitivity</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Zomepirac</td>
<td>1983</td>
<td>Anaphylaxis</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Fenclofenac</td>
<td>1984</td>
<td>Lyell’s syndrome</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Indoprofen</td>
<td>1984</td>
<td>Gastrointestinal bleeding/perforation</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Omosin®</td>
<td>1984</td>
<td>Gastrointestinal ulceration/perforation</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>1984</td>
<td>Blood dyscrasias</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1986</td>
<td>Reye’s syndrome (children)</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1986</td>
<td>Seizures</td>
<td>Not marketed in the UK at that time</td>
</tr>
<tr>
<td>Nomifensine</td>
<td>1986</td>
<td>Haemolytic anaemia</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Tocainide</td>
<td>1986</td>
<td>Neutropenia</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Suprofen</td>
<td>1987</td>
<td>Renal impairment</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Spirironolactone</td>
<td>1988</td>
<td>Animal carcinomas</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Flecaainde</td>
<td>1989</td>
<td>Cardiac arrhythmias</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>1990</td>
<td>Eosinophilia–myalgia syndrome</td>
<td>Withdraw from foodstuffs</td>
</tr>
<tr>
<td>Metipranolol 0.6%</td>
<td>1990</td>
<td>Anterior uveitis</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Oxpameterol</td>
<td>1990</td>
<td>Worse heart failure in some patients</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Noscapine</td>
<td>1991</td>
<td>Gene toxicity</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Terodiline</td>
<td>1991</td>
<td>Cardiac arrhythmias</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Triazolam</td>
<td>1991</td>
<td>Psychiatric disorders</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Temafloxacin</td>
<td>1992</td>
<td>Various serious adverse reactions</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Centoxin</td>
<td>1993</td>
<td>Increased mortality</td>
<td>Withdrawed</td>
</tr>
<tr>
<td>Flosequinan</td>
<td>1993</td>
<td>Increased mortality</td>
<td>Withdrawed</td>
</tr>
</tbody>
</table>

(Continued)
ADVERSE DRUG REACTIONS

Table 1.1 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Adverse reaction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remoxipride</td>
<td>1994</td>
<td>Aplastic anaemia</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>1995</td>
<td>Serious allergic reactions</td>
<td>Uses of sulfonamides restricted</td>
</tr>
<tr>
<td>Naftidrofuryl</td>
<td>1995</td>
<td>Cardiac and neurological toxicity</td>
<td>Intravenous formulation withdrawn</td>
</tr>
<tr>
<td>Sotalol</td>
<td>1996</td>
<td>Cardiac arrhythmias</td>
<td>Uses restricted</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>1997</td>
<td>Hepatic disorders</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>1997</td>
<td>Interactions (e.g. with grapefruit juice)</td>
<td>Withdrawn from OTC sale</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>1997</td>
<td>Cardiac valve abnormalities</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>1998</td>
<td>Too many drug interactions</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>1998</td>
<td>Hepatobiliary disorders</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Astemizole</td>
<td>1998</td>
<td>Interactions (e.g. with grapefruit juice)</td>
<td>Withdrawn from OTC sale</td>
</tr>
<tr>
<td>Sertindole</td>
<td>1998</td>
<td>Cardiac arrhythmias</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Cisapride</td>
<td>2000</td>
<td>QT interval prolongation</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>2001</td>
<td>Rhabdomyolysis</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Kava extracts</td>
<td>2002</td>
<td>Liver damage</td>
<td>Withdrawn; method of extraction studied</td>
</tr>
<tr>
<td>TGN1412</td>
<td>2005</td>
<td>Cytokine release syndrome</td>
<td>One study; not pursued; changes to first-in-human studies</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2004</td>
<td>Cardiovascular disease</td>
<td>Withdrawn; class effects investigated</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>2007</td>
<td>Increased mortality; renal impairment</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Benfluorex</td>
<td>2009</td>
<td>Pulmonary hypertension; valvulopathy</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>2010</td>
<td>Cardiovascular disease</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

publicity as a treatment for rheumatoid arthritis in the 1980s [23]. It caused liver damage, which resulted in deaths, particularly in older people, in whom the drug had not been properly tested before marketing. This stressed the need for testing drugs in the populations in whom they are going to be used.

In the late 1990s the observation that prolongation of the QT interval by drugs such as terfenadine and astemizole, particularly when they were given in combination with compounds that inhibited their metabolism, such as grapefruit juice, led to the introduction of mandatory testing of all new drugs for prolongation of the QT interval before marketing [24].

More recently, major changes to the ways in which new compounds are introduced into humans have resulted from the adverse reactions that six healthy volunteers suffered after receiving a novel monoclonal antibody code-named TGN1412 [25, 26] (see also Chapter 4). Further development was aborted and the drug was not given to further subjects.

1.4 Terminology and definitions in pharmacovigilance

Definitions of terms relevant to adverse effects and reactions [27], to medication errors [28], and to other terms in pharmacovigilance have been listed [29, 30] and extensively reviewed and discussed [31–34].
1.4.1 The art of definition

A formal method for deriving definitions in pharmacovigilance has been described in detail [35]. Briefly, it consists of adducing information from etymology, usage, previous definitions, and whatever processes are actually involved. The last of these is derived from the Ramsey–Lewis method (based on an understanding of theory and practice), a method in which a group of terms appearing in a theory can be defined implicitly by the assertions of the theory itself [36]; this can be extended to adduce a knowledge of the practices that are relevant to the term being defined. A fifth method, using dichotomy, is not usually useful in framing definitions of technical terms, although it may occasionally be useful in checking the soundness of a definition [37].

To define something (Latin *definire*) is to determine its boundaries (Latin *fines*), and hence to state exactly what the thing is or to set forth or explain its essential nature; this is what Aristotle called ἄρτο τί ἔχει (to τί ἔχειν, literally, that which is). Thus, a definition is “a precise statement of the essential nature of a thing; a statement or form of words by which anything is defined” [38].

There are different types of definition (see Table 1.2). The simplest is the descriptive definition, such as is found in an ordinary dictionary. Such definitions suffice when all that is needed is to describe what a thing is, to make it recognizable, but they are often inadequate for technical terms. A stipulative definition is one in which one stipulates “what [a term] shall be used to mean”. Such definitions should, if possible, also be what is called “intensional”—they

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive</td>
<td>The simplest type of definition. A diary, for example, can be described as “a book prepared for keeping a daily record, or having spaces with printed dates for daily memoranda and jottings”.</td>
</tr>
<tr>
<td>Stipulative</td>
<td>Definitions that stipulate “what [a term] shall be used to mean”. A stipulative definition of a diary is “a daily record of events or transactions . . . specifically, a daily record of matters affecting the writer personally, or which come under his personal observation”. This definition does not describe a diary in its physical state but stipulates what it is used for and what it contains.</td>
</tr>
<tr>
<td>Intensional</td>
<td>Stipulative definitions come in different forms. Intensional definitions specify the necessary and sufficient attributes or qualities that make a thing a member of a specific set; they describe its essence.</td>
</tr>
<tr>
<td>Extensional</td>
<td>Intensional definitions are not always entirely satisfactory. For example, the second definition of a diary (above) does not describe everything that may be contained in a diary, such as calendars, maps, lists of institutions, and other information. In order to define a diary completely one would need to list all its contents, in what is called an extensional definition, one that consists of a list in which every object that is a member of a specific set is named. An intensional definition should provide an accurate description of the essence of a subject, but will give no information about its range or scope. An extensional definition, which can also be called a scoping definition, does just that.</td>
</tr>
<tr>
<td>Operational</td>
<td>An operational definition is one in which concepts are defined “in terms of the operations necessary to determine them”.</td>
</tr>
<tr>
<td>Ostensive</td>
<td>An ostensive definition gives the meaning by pointing or illustrating.</td>
</tr>
</tbody>
</table>

*All definitions here taken from the OED [38]
should specify the necessary and sufficient conditions that make a thing a member of a specific set. The definitions given here are mostly of this kind.

There are five desiderata for a definition:

- it must describe all the essential attributes of the thing being defined, i.e. it must encapsulate its true essence;
- it should avoid circularity—one should not, for example, define a horse simply as “a member of the species Equus”, nor do as Dr Johnson did in his 1755 dictionary and unhelpfully define a hind as “the she to a stag” and a stag as “the male of the hind”;
- it must not be too wide or too narrow—it should not omit anything of importance, but neither should it include any things to which the defined term does not apply;
- it must not be obscure—one should use commonly understood terms with clear meanings and not terms that themselves need further definition, although with technical terms this may be difficult and even sometimes impossible;
- it should be positive if possible, not negative; one should not, for example, define wisdom as the absence of folly—one should say what it is, not what it is not.

1.4.2 Terms that describe medicines and formulations

1.4.2.1 Medicinal product

The term “medicinal product” was defined in an EU Directive (2001/83/EC) as:

“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

The meaning of “substance” here is further defined as including any matter, irrespective of origin—human, animal, vegetable, or chemical.

Other definitions, such as those used in Australia and New Zealand, are similar, and often refer to the EU definition. However, the EU definition omits some important uses of medicinal products, including as placebos. Confusingly, the term “investigational medicinal product” has been defined in relation to clinical trials for the purposes of the EU Clinical Trials Directive [39] as

“a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.”

However, this definition was constructed with a specific purpose in mind: that of regulating the performance of clinical trials; hence the reference to marketing authorization. This is clearly unsatisfactory for the general purposes of definition [40]. It would have been preferable if the subclass of investigational medicinal products had been defined in terms of a more general definition of the class of all medicinal products.
The following definition and its notes describes what a medicinal product is and what it does: “A manufactured article, intended to be taken by or administered to a person or animal, which contains a compound with proven biological effects, plus excipients, or excipients only, and may also contain contaminants.” Notes on this definition:

- the active compound is usually a drug or prodrug, but may be a cellular element;
- the purposes for which a medicinal product is intended to be taken by or administered to a person or animal are: as a placebo; to prevent a disease; to make a diagnosis; to test for the possibility of an adverse effect; to modify a physiological, biochemical, or anatomical function or abnormality; to replace a missing factor; to ameliorate a symptom; to treat a disease; to induce anaesthesia;
- the term “medicine”, or the more old-fashioned term “medicament”, are acceptable synonyms for “medicinal product”; however, although the term “drug” is often used colloquially to mean a medicinal product (as in “adverse drug reaction”), it is important to remember the distinction between the drug itself (the active component) and the whole product; for definitive regulatory or legislative purposes the more precise term “medicinal product” is preferable; the term “pharmaceutical product” is sometimes used, but this excludes some biological products that are not made pharmaceutically;
- “a compound with proven biological effects” includes chemical compounds, either drugs or prodrugs (which themselves may have no pharmacological activity), or, in racemic mixtures, stereoisomers that may have only adverse effects, or compounds that are used for diagnostic purposes (such as contrast media used in radiology, including ultrasonography); this term also includes cellular elements, such as inactivated or attenuated viruses for immunization, blood products (such as erythrocytes), viruses for gene therapy, and embryonic stem cells;
- “contaminants” includes chemical and biological contaminants;
- the definition does not include food additives;
- the definition does not include medicinal products when they are used to probe systems, such as the use of phenylephrine to study baroreceptor reflexes.

A herbal medicinal product has been defined as “any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations” [41]. Other terms that are used to describe herbal products (herbal substance, herbal preparation, herbal remedy, herbal constituent, herbal ingredient) are defined in Chapter 15, Table 15.1 (p. 646).

1.4.2.2 A pharmaceutical formulation

A pharmaceutical formulation, also called a “dosage form”, is the form in which a medicinal product is presented, for example as a tablet, capsule, elixir, solution for injection, aerosol, transdermal formulation, cream, or ointment. The commonly used term “preparation” is ambiguous, since it can refer to the pure substance itself (for example, as prepared from a plant) as well as the formulation. When formulations are classified according to the time over which
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the active substance is made available to the body, two broad categories can be distinguished: immediate-release formulations and modified-release formulations. Other terms that are subsumed by the term “modified-release” include sustained-release, slow-release, long-release, controlled-release, timed-release, prolonged-release, and delayed-release.

1.4.2.3 Excipient

An excipient is any material, other than the therapeutically active substances, present in a pharmaceutical formulation. Excipients provide bulk, assist in the manufacture of a formulation (for example, by reducing the stickiness of a powder), control the rate at which a tablet disintegrates, provide a protective coating, inhibit degradation of the active substance during storage, mask the taste of a medicine, provide colouring, and control the rate of release of the medicine. They can cause adverse effects.

1.4.3 General terms used in describing adverse drug reactions

1.4.3.1 Benefit-to-harm balance

Benefit

Benefit is a favourable outcome in an individual or a population. In drug therapy it may take the form of successful prevention of an undesired outcome (for example, oral contraception, mass immunization), successful diagnosis (for example, the use of edrophonium to diagnose myasthenia gravis), relief of a symptom (for example, analgesia in terminal care), or reversal of an unwanted outcome (for example, cure of pneumococcal pneumonia with penicillin).

Efficacy and effectiveness These terms are related to benefit. Leaving aside the specific pharmacological meaning of the term “efficacy”, in relation to drug therapy it is “the extent to which a specific intervention produces a beneficial effect under ideal conditions” (for example in a randomized clinical trial) [42]. Effectiveness is “the extent to which a specific intervention, when deployed in the field in routine circumstances, does what it is intended to do for a specified population” [42]. Efficacy does not guarantee effectiveness.

Hazard “Hazard” is the inherent capability of an intervention to cause harm and “a hazard” is a potential source of harm. Harm from a drug hazard is an unwanted outcome that can take the form of symptomatic hurt (for example, pain or discomfort) or organ damage (for example, a rash). Failure of a drug to produce a beneficial outcome has also been regarded by some as a drug-related harm; failure can legitimately be so regarded if it is due to the effect of a drug interaction (for example, failure of oral contraception due to enzyme induction by rifampicin or carbamazepine); in that case the harm is done by the interacting drug.

Risk Risk is the probability that an event will occur during a given quantum of exposure to a hazard [43]. Although some have claimed that the term “risk” can be used to describe beneficial outcomes, it is rarely if ever used in that way. In drug therapy risk is therefore the probability of an adverse or unwelcome outcome. The attributable risk (or excess risk) is the difference between the risk in an exposed population (the absolute risk) and the risk in an unexposed population (the reference risk).