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Dictionaries and Coding in Pharmacovigilance

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Introduction

For some reason, many professionals working in the field of drug safety do not find the topic of dictionaries exciting. Most would admit, however, that they are of critical importance. The purpose of the dictionary is to bring order to seeming chaos. They are intended to bring some discipline to the vast number of descriptive terms that health professionals and patients use for medical conditions, and to the enormous array of medicines that the former inflict on the latter. By abbreviating the original descriptions and reducing them to some form of code or standard terms, it is possible to record the data effectively and concisely on a computer database, to search for similar medical conditions associated with unique medicinal products and to present the information in summarized format or numerical tables.

The characteristics of the dictionary exert a profound effect on the data. If there are too few terms in the dictionary, then compromises have to be made when coding the data. Details that have been reported may be lost, e.g. staphylococcal bronchopneumonia and acute exacerbation of chronic bronchitis might both just become 'respiratory infection'. If the relationships within the dictionary are not completely valid, then a case reported as 'psychological problems' might be transformed into 'psychotic' in the database – which is enough to drive anyone mad.

At the other end of the scale, it could be that the dictionary accurately reflects the facts, but does not group conditions appropriately. If grouping is not effective, then it might be difficult to find items in the database. For example, if pneumonitis is classed together with some similar conditions as a respiratory disorder, but pneumonias are grouped separately under the heading of infections, then this could result in failure to identify all cases relevant to a particular safety concern about the adverse effects of a drug on the lung.

Another way in which the choice of dictionary could affect one's view of the world is, paradoxically, by being too specific. If a dictionary included 25 different types of headache, then it might be difficult to answer the simple question of whether there were there more reports of headache with the beta-blocker ololol in patients receiving active drug or placebo in a comparative trial with 100 patients in each treatment arm. The answer might be that

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there were: two reports of tension headache, two reports of throbbing headache, four of unspecified headache and three of sinus headache with ololol; and one of tension headache, two unspecified headache, one vascular headache and one headache with flashing lights in patients receiving placebo. If there is no group term for 'headache', then real differences between treatments might be missed. Such 'splitting' might similarly reduce one's ability to detect signals of new adverse reactions in a post-marketing safety database.

Thus, whilst dictionaries may not be held to be universally fascinating, it is worth learning about them if serious mistakes are to be avoided in pharmacovigilance.

Scope of this chapter

This chapter describes some of the medical and drug dictionaries that are used in the safety surveillance of medicines, pre- and post-registration. I have regarded the term 'dictionary' as being synonymous with 'terminology'. The 1994 Collins Shorter English Dictionary gives one definition of 'dictionary' as: 'a reference book listing words or terms and giving information about a particular subject or activity'. A definition for 'terminology' from the same source is: 'the body of specialised words relating to a particular subject'. However, a better term might be 'thesaurus', defined in the Collins Dictionary as 'a book containing systematised lists of synonyms and related words; a dictionary of selected words or topics'.

There are a great many dictionaries currently in use in the pharmacovigilance/regulatory affairs environment. I have only considered those most relevant and widely used for general purposes in drug safety. Thus, specialist dictionaries covering specific disease areas, such as oncology or pathology, are not included; neither are those used for animals (e.g. VEDDRA). I have also ignored the many (sometimes excellent) dictionaries that have been developed in-house (e.g. the Medicine Control Agency's ADROIT dictionary, or Glaxo Smith Kline's MIDAS dictionary), as well as dictionaries used sometimes in medical practice outside the pharmaceutical environment (e.g. Read codes).

In addition to dictionaries, some issues relating to definitions of terms used for adverse reactions are also considered. It may seem strange that the existing dictionaries do not actually define the medical terms that are included – unlike dictionaries used for languages. However, there has been an initiative by the Council for International Organizations of Medical Sciences (CIOMS; Bankowski *et al*., 1999), to provide some definitions, and this topic is also included.

Drug dictionaries

The huge plethora of available medicines provides a challenge for those wishing to store accurate information on databases. When considering all the different formulations, dosage forms, routes of administration, therapeutic and pharmacological classes, manufacturers, approved and proprietary names for each of these, the task becomes daunting indeed. A number of standard classifications have been produced, of which the two most widely applicable are considered below.

Anatomical–therapeutic–chemical classification

The anatomical–therapeutic–chemical (ATC) classification is a system for the classification of drugs according to their site of therapeutic effect, therapeutic indication and pharmacological nature. It is widely accepted as a useful method of categorizing and recording individual drugs. The main ATC groups are shown in Table 12.1 (Anonymous, 2000).

Table 12.1 The main ATC groups

A	Alimentary tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genitourinary system and sex hormones
H	Systemic hormonal preparations excluding sex hormones
J	General anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculoskeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

Within each main group, there is arrangement of classes of drug as sub-groups, according to broad therapeutic area or site of action. Thus, for the Respiratory system there are the following sub-groups: R01 Nasal preparations; R02 Throat preparations; R03 Anti-asthmatics; R05 Cough and cold preparations; R06 Antihistamines for systemic use; and R07 Other respiratory products.

Additional breakdown by pharmacological category is effected under the sub-groups: e.g. under R03, Anti-asthmatics, we have: R03A Adrenergics, inhalants; R03B Other anti-asthmatics, inhalants; R03C Adrenergics for systemic use; R03D Other anti-asthmatics for systemic use.

Further specificity is then provided with additional codes under each category according to pharmacology or chemical structure. Thus: R03CA Alpha- and beta-adrenoceptor agonists; R03CB Non-selective beta-adrenergic agonists; R03CC Selective Beta-2-adrenoceptor agonists; R03CK Adrenergics and other anti-asthmatics. An extract from the Cardiovascular system group is shown in Table 12.2, to further illustrate the logic behind the classification.

The World Health Organization Drug Dictionary

This contains of the order of 45 000 proprietary drug names, with about 2600 being added annually (Uppsala Monitoring Centre, 2002). It is an international classification, giving the names used in different countries, together with all active ingredients with unique reference numbers. Drugs are classified according to ATC code. The dictionary was started in 1968 and includes all drugs mentioned on adverse reaction reports submitted under the World

Table 12.2 Example of ATC codes

C	Cardiovascular system			
	C01		Cardiac therapy	
		C01A		Cardiac glycosides
			C01AA	Digitalis glycosides
			C01AB	Scilla glycosides
			C01AC	Strophantus glycosides
			C01AX	Other cardiac glycosides
		C01B		Antiarrhythmics, class I and III
			C01BB	Antiarrhythmics, class IB
			C01BC	Antiarrhythmics, class IC
			C01BD	antiarrhythmics, class III
			C01BG	Other class I antiarrhythmics
		C01C	Cardiac stimulants excl. cardiac glycosides	
			C01CA	Adrenergic and dopaminergic agents
			C01CE	Phosphodiesterase inhibitors
			C01CX	Other cardiac stimulants
	C02	Antihypertensives		
		C02A		Antiadrenergic agents, centrally acting
			C02AA	Rauwolfia alkaloids
			C02AB	Methyldopa
			C02AC	Imidazoline receptor agonists
		C02B		Antiadrenergic agents, ganglion-blocking
			C02BA	Sulfonium derivatives
			C02BB	Secondary and tertiary amines
			C02BC	Bisquaternary ammonium compounds
			C02C	Antiadrenergic agents, peripherally acting

Health Organization (WHO) Programme on International Drug Monitoring. Drugs from almost 70 countries are represented, and updates are issued quarterly.

Drugs containing the same active ingredient(s) are referred to by *Preferred name* – the international non-proprietary name (INN) in English for single ingredient drugs (or other approved name, if there is no INN). For multiple ingredient drugs, the *Preferred name* is the first reported drug name of a given combination. Drugs are given various designations, as shown in Table 12.3.

Table 12.3 WHO drug dictionary: designation of drug type

N	Single ingredient drug non-proprietary name
T	Single ingredient drug proprietary name
K	Single ingredient drug chemical name
R	Single ingredient drug code number
M	Multiple ingredient drug proprietary name
X	Multiple ingredient drug non-proprietary name
U	Non-specific name, from ATC texts (such as NSAID or benzodiazepine)

The dictionary includes a manufacturer for the drug, although this may in fact be a distributor in a particular country. The manufacturer name is abbreviated to a three- to five-letter code. Drugs are given consecutive record numbers and also two *sequence numbers*, SEQ1 and SEQ2. The first *sequence number* is used for single constituent drugs to distinguish between salts or esters of a substance and the second *sequence number* distinguishes between trade names with the same ingredients. The *Preferred name* has a SEQ2 of 001. An example showing the record number system is given in Table 12.4.

Table 12.4 Example showing the record-number system in the drug dictionary (reproduced by permission of the Uppsala Monitoring Centre)

Drug name	Des	DRECNO	SEQ1	SEQ2
Single ingredient drugs				
1. Ampicillin	N	000005	01	001
2. Ampicillin sodium	N	000005	02	001
3. Binotal for injection	T	000005	02	002
3. Polycillin-N for injection	T	000005	02	003
2. Ampicillin trihydrate	N	000005	03	001
3. Polycillin	T	000005	03	002
3. Austrapen	T	000005	03	003
Multiple ingredient drugs				
1. Ampiclox Ampicillin Cloxacillin	M	001903	01	001
3. Sinteclox	M	001903	01	002

The drug dictionary is available in paper or electronic versions and software is available for browsing the dictionary, which is held as a relational database. This comprises several files, including the drug dictionary itself, the ATC classification, substance names, ingredients, manufacturers, ATC text, sources of drug names and country codes.

Other drug dictionaries

At the time of writing, a new drug dictionary is being developed by the European Agency for the Evaluation of Medicinal Products, based on ATC codes.

Adverse drug reaction dictionaries

World Health Organization Adverse Reaction Terminology: WHO-ART

This dictionary is used by the WHO Uppsala Monitoring Centre for recording suspected adverse reactions on their worldwide database, as well as by many regulatory authorities for their pharmacovigilance activities. WHO-ART (Uppsala Monitoring Centre, 2000) has been extensively used in the past by pharmaceutical companies, but has often been modified by the addition of many new terms within individual organizations, so that these in-house versions are effectively separate terminologies. With regard to the ‘standard’ dictionary, this

is updated at intervals by the addition of new terms and with the release of new versions. Translations are available in several languages, and there are both paper and electronic versions.

WHO-ART has a hierarchical and multiaxial structure. Of the order of 2000 *Preferred terms* are used for data input and represent separate medical concepts. *Included terms* are synonyms to the *Preferred terms* and are used for finding the most appropriate *Preferred term* for coding purposes. However, *Included terms* may also be used for data entry. *High level terms* are used to group qualitatively similar *Preferred terms*, but many *Preferred terms* have no corresponding *High level term*. At the top end of the terminology, there are 32 *System-organ classes*, which provide groupings for the *High level terms* and *Preferred terms*. A *Preferred term* may be assigned to up to three different *System-organ classes*.

Preferred and *Included* terms in WHO-ART are assigned numerical codes that provide information about the level of the term and the *System-organ class(es)* to which it is allocated. Thus, in addition to a unique record number, each *Preferred term* is assigned the number 0100.

The *System-organ classes* are shown in Table 12.5. Each *System-organ class* is associated with a four-digit code, for example 0600 for *Gastro-intestinal system disorders*, 1210 for *Red blood cell disorders*, 1820 for *Application site disorders*. Table 12.6 shows an extract from the *Autonomic nervous system disorders System-organ class.*

Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)

This terminology was distributed by the US Food and Drugs Administration (FDA) and has been widely used by companies for coding adverse events in clinical trials and post-marketing surveillance. However, its small size has resulted in many organizations producing their own customized versions, by the addition of new terms. At the top of the COSTART (Food and Drugs Administration, 1989) hierarchy, there are 12 *body systems*, as shown in Table 12.7.

At the next lowest level in COSTART, there is a *mid-level classification* for retrieval purposes based on pathophysiology. A classification for the *Cardiovascular System* is shown in Table 12.8. The subordinate *Coding symbols* for *Coronary Vessel Disorders* are shown in Table 12.9. As may be seen, these comprise abbreviated text. *Coding symbols* are associated with one or more *Glossary terms*, which are used to assist in selection of the *Coding symbol* when coding. For example, for the *Coding symbol ANGINA PECTORIS*, we have *Glossary terms* including *Angina at rest Prinzmetal's*; *Angina attack*; *Angina of effort*; *Angina pectoris*; *Angina pectoris aggravated*; *Anginal pain*; *Anginal syndrome*; *Effort angina*; etc.

The status of COSTART is tenuous, in view of the adoption of MedDRA® by the FDA (see below). In time it is likely that it will be completely superseded by MedDRA®.

Disease classifications

In this section, some of the classifications that are used in the drug safety environment are reviewed. Although International Classification of Diseases 10 (ICD10) is the current version, many organizations still use its predecessor, ICD9. Hence, both these classifications are considered.

The classification of diseases is defined in ICD10 as 'a system of categories to which

Table 12.5 WHO-ART System-organ classes

Skin and appendage disorders
Musculo-sleletal system disorders
Collagen disorders
Central & peripheral nervous system disorders
Autonomic nervous system disorders
Vision disorders
Hearing and vestibular disorders
Special senses other disorders
Psychiatric disorders
Gastro-intestinal system disorders
Liver and biliary system disorders
Metabolic and nutritional disorders
Endocrine disorders
Cardiovascular disorders, general
Myo-, endo-, peri-cardial & valve disorders
Heart rate and rhythm disorders
Vascular (extracardiac) disorders
Respiratory system disorders
Red blood cell disorders
White blood cell and RES disorders
Platelet, bleeding & clotting disorders
Urinary system disorders
Reproductive disorders, male
Reproductive disorders, female
Foetal disorders
Neonatal and infancy disorders
Neoplasms
Body as a whole – general disorders
Application site disorders
Resistance mechanism disorders
Secondary terms – events
Poison specific terms

morbid entities are assigned according to established criteria' (World Health Organization, 1992). The International Classifications have widespread application, and are accepted as worldwide standards. In the pharmaceutical environment, as elsewhere, they are used for epidemiological purposes. They have also been used for coding baseline medical history and diagnoses in clinical trials and for recording adverse events. However, they were not really designed for this purpose, and the description of conditions and their groupings is not ideal for this function. They are available in printed format as books and can generally be found in medical libraries in academic institutions and hospitals.

ICD9

In ICD9, there are 17 *chapters* plus two *supplementary classifications*: *External causes of injury and poisoning* and *Factors influencing health status and contact with health services* (World Health Organization, 1977). The chapter headings are similar to *System-organ*

Table 12.6 Extract from the WHO-ART autonomic nervous system disorders System-organ class

High level term	Record no.	Preferred term	Included term	System organ no. 2	System organ no. 3
Vasodilatation	0207	Flushing	Skin hyperaemia	1040	
Vasodilatation	0207	Flushing	Skin vasodilatation	1040	
Vasodilatation	0207	Flushing	Skin warm	1040	
Vasodilatation	0207	Flushing	Skin flushed	1040	
Vasodilatation	0207	Flushing	Blood flow sensation	1040	
Vasodilatation	0207	Flushing	Flushing aggravated	1040	
Vasodilatation	0225	Vasodilatation	Hyperaemia	1040	
Vasodilatation	0225	Vasodilatation	Vasodilation	1040	
	0202	Accommodation abnormal	Accommodation disturbance	0431	
	0202	Accommodation abnormal	Accommodation disorder	0431	
	0202	Accommodation abnormal	Distance accommodation disorder	0431	
	0202	Accommodation abnormal	Accommodation paralysis	0431	
	0202	Accommodation abnormal	Accommodation spasm	0431	
	0780	Anticholinergic syndrome		0410	
	0208	Bradycardia	Sinus bradycardia	1030	
	0208	Bradycardia	Pulse rate decreased marked	1030	
	0208	Bradycardia	Sinus arrest	1030	
	0203	Cholinergic syndrome	Parasympathomimetic syndrome	0410	
	0211	Hypertension pulmonary	Hypertension pulmonary aggravated	1010	1100

Table 12.7. COSTART body systems

Body as a Whole
Cardiovascular System
Digestive System
Endocrine System
Hemic and Lymphatic System
Metabolic and Nutritional Disorders
Musculo-skeletal System
Nervous System
Respiratory System
Skin and Appendages
Special Senses
Urogenital System

Table 12.8 COSTART mid-level classification

Cardiovascular System
Cardiac disorders
Arrhythmias
Conduction abnormalities
Coronary vessel disorders
Endocardial disorders
General, functional and NEC*
Myocardial disorders
Pericardial disorders
General and NEC*
Vascular disorders
Arterial and arteriolar disorders
Blood pressure disorders
Capillary disorders

* Not elsewhere classified.

Table 12.9 COSTART coding symbols under Coronary vessel disorders

Coronary vessel disorders
ANGINA PECTORIS
CORONARY ART DIS
EMB CORONARY
OCCLUS CORONARY
THROM CORONARY

Classes, for example '*II Neoplasms*', '*VIII Diseases of the Respiratory System*', '*XIV Congenital anomalies*', etc. Each *chapter* is divided up into sub-groups represented by discrete three-digit codes, each code delimiting a more specific group of medical conditions. Thus, *Neoplasms* are covered by the codes 140 to 239 and *Respiratory disorders* by codes 460 to 519.

Within the *chapters*, diseases are grouped and classified with these three-digit codes. For example, in the *chapter Diseases of the Respiratory system*, we see six sub-headings: *Acute*

respiratory infections; *Other diseases of upper respiratory tract*; *Pneumonia and influenza*; *Chronic obstructive pulmonary disease and allied conditions*; *Pneumoconioses and other lung diseases due to external agents*; and *Other diseases of respiratory system*.

Grouped under the sub-heading *Pneumonia and influenza* 480–487, we see the three-digit individual medical conditions, as shown in Table 12.10. Additional digits are use to represent more specific diseases. The four digit codes ending .8 refer to '*other*' related conditions; the four-digit codes ending in .9 refer to conditions that are '*unspecified*'.

Table 12.10 Example of three- and four-digit terms in ICD9

PNEUMONIA AND INFLUENZA (480–487)	
480	Viral pneumonia
481	Pneumococcal pneumonia
482	Other bacterial pneumonia
483	Pneumonia due to other specified organism
484	Pneumonia in infectious diseases classified elsewhere
484.0*	Measles (055.1†)
484.1*	Cytomegalic inclusion disease (078.5†)
484.2*	Ornithosis (073†)
484.3*	Whooping cough (033†)
484.4*	Tularaemia (021†)
484.5*	Anthrax (022.1†)
484.6*	Aspergillosis (117.3†)
484.7*	Pneumonia in other systemic mycoses
484.8*	Pneumonia in other infectious diseases
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified
487	Influenza

The use of the *asterix* and *dagger* system is demonstrated in Table 12.10. The † symbol is attached to the code showing the underlying disease, whilst the * is attached to the code in the organ system where the disease is manifested. For example, if we consider *Measles* 055, its four-digit codes include: 055.0† *Postmeasles encephalitis*; 055.1† *Postmeasles pneumonia*; 055.2† *Postmeasles otitis*, etc.

ICD9 clinical modification (ICD9-CM)

ICD9-CM provides additional specificity by having five-digit codes, so that, for example, *Mastoiditis* and related conditions are coded as 383, *Acute mastoiditis* is 383.0, *Acute mastoiditis without complications* is 383.00, whereas *Subperiosteal abcess of mastoid* is 383.01 (see Table 12.11) (Anonymous, 1994). This modification of ICD9 tends to be used more in the USA than in Europe.

ICD10

Published in 1992 (World Health Organization, 1992), this version of the International Classification has gained widespread acceptance, especially for the recording of national morbidity and mortality data and of health service resource utilization.

Table 12.11 Structure of ICD9-CM

320–389 Diseases of the nervous system and sense organs
330–337 Hereditary and degenerative diseases of the central nervous system
335 Anterior horn cell disease
335.2 Motor neurone disease
335.2 0 Amyotrophic lateral sclerosis
335.2 1 Progressive muscular atrophy
335.2 2 Progressive bulbar palsy
etc.

The main innovation was the use of an alphanumeric coding scheme of one letter followed by three numbers. At the end of some chapters, there is a category for post-procedural disorders. Additional three-digit codes are available to capture dual sites for aetiology and manifestation.

The classification is again divided into *chapters*. Thus, *Chapter I – Certain infectious and parasitic diseases*; *Chapter II – Neoplasms*; *Chapter III – Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism*; *Chapter IV – Endocrine, nutritional and metabolic diseases*; *Chapter XXI – Factors influencing health status and contact with health services*, etc.

Each *chapter* in the classification is prefaced with a rubric describing the inclusion and exclusion criteria for that chapter. For example, *Chapter IX, Diseases of the circulatory system*, excludes '*certain conditions originating in the perinatal period* (P00–P96); *certain infectious and parasitic diseases* (A00–B99); *complications of pregnancy, childbirth and the puerperium* (O00–O99); *congenital malformations, deformations and chromosomal abnormalities* (Q00–Q99) . . .' etc.

Within each chapter, there are sub-headings or '*blocks*'. For example, *Chapter IX* includes *blocks* for *Acute rheumatic fever*, *Chronic rheumatic heart diseases*, *Hypertensive diseases*, etc., as shown in Table 12.12. Within each *block* there are grouped related conditions, distinguished by three-character codes. In this way, for example, I20 *Angina pectoris* is distinguished from I21 *Acute myocardial infarction* within the *Ischaemic heart diseases block*, as shown in Table 12.13.

Again, the *blocks* may provide inclusion and exclusion criteria. Thus, the *block Ischaemic heart diseases* (I20–25) may include mention of *hypertension*, which may be represented by

Table 12.12 Blocks included in ICD10, Chapter IX, Diseases of the Circulatory System

Acute rheumatic fever
Chronic rheumatic heart diseases
Hypertensive diseases
Ischaemic heart diseases
Pulmonary heart disease and diseases of pulmonary circulation
Other forms of heart disease
Cerebrovascular diseases
Diseases of arteries, arterioles and capillaries
Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
Other and unspecified disorders of the circulatory system

Table 12.13 Three-character conditions classifying Ischaemic heart diseases in ICD10

Ischaemic heart diseases (I20–I25)	
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease

an additional code, if desired. There are notes provided on the way that terms are used – so, in this instance, it is stated that, for morbidity, duration refers to the interval elapsing between onset of ischaemic episode and admission to care, whereas for mortality, duration refers to the interval between onset and death.

Under the three-character *blocks* are presented four-character terms that add specificity to the disease descriptions. For example, under I20, *Angina pectoris*, I20.0 *Unstable angina* is distinguished from I20.1 *Angina pectoris with documented spasm*: see Table 12.14.

Individual chapters include refinements of the coding system. For example, in *Chapter XX*, *External causes of morbidity and mortality*, there are subdivisions by fourth character to indicate the place of occurrence of the external cause: .0 for the home; .1 for residential institution; .2 for school, other institution and public administrative area; .3 for sports and athletics area, etc. Each of these is provided with options for describing the detailed

Table 12.14 Four-character conditions specifying type of angina in ICD10

I20.0	Unstable angina Angina: • Crescendo • *De novo* effort • Worsening effort Intermediate coronary syndrome Preinfarction syndrome
I20.1	Angina pectoris with documented spasm Angina: • Angiospastic • Prinzmetal • Spasm-induced • Variant
I20.8	Other forms of angina Angina of effort Stenocardia
I20.9	Angina pectoris, unspecified Angina • NOS • Cardiac Anginal syndrome Ischaemic chest pain

location, such as baseball field, basketball court, cricket ground, etc. Other subclassifications in this chapter cover the activity during which the injury was sustained, such as sports activity, leisure activity, again with optional detailed descriptions.

Multiaxiality is accommodated within individual blocks in each chapter, with the site indicated by an asterisk. For example, I32* *Pericarditis in diseases classified elsewhere* includes I32.0 *Pericarditis in bacterial diseases classified elsewhere*, which covers four causal types of infection. The causal organisms are indicated by a dagger (†). These are shown under *Pericarditis in diseases classified elsewhere* as: *Gonococcal pericarditis* (A54.8†); *Meningococcal pericarditis* (A39.5†); *Syphilitic pericarditis* (A52.0†); and *tuberculous pericarditis* (A18.8†). In turn, if one refers to A18.8†, this is the block *Tuberculosis of other specified organs*, covering *tuberculosis of endocardium* (I39.8*), *myocardium* (I41.0*), *oesophagus* (K23.0*), *pericardium* (I32.0*), *thyroid gland* (E35.0*) and *tuberculous cerebral arteritis* (I68.1*).

Combination terminology

Medical Dictionary for Regulatory Activities, MedDRA®

Background and development

MedDRA® is a structured thesaurus of medical terms that has been adopted as an international standard by the International Conference on Harmonization (ICH), for use together with other standards (E2B, M2) in the electronic exchange of data between regulatory authorities and between companies and regulators (Wood, 1994; Brown *et al*., 1999). MedDRA® was first made available for general use in March 1999.

MedDRA® scope

The dictionary includes terms that are relevant to all phases involving man in the development and post-authorization safety surveillance of medicines and to the health effects of medical devices (Maintenance and Support Services Organization, 2002a). The terms in MedDRA® cover medical diagnoses, symptoms and signs, adverse reactions, therapeutic indications, the names and qualitative findings from laboratory, radiological and other investigations, surgical and medical procedures, and social circumstances.

MedDRA® does not include a drug or device nomenclature, nor does it include terms covering study design, pharmacokinetics or patient demographics. It does not allow for adjectives such as those describing disease severity or frequency, although qualifiers such as acute, chronic, recurrent are included in terms when clinically relevant. There is a restricted range of terms for describing aggravation or exacerbation of medical conditions.

In the pre-registration phases of a product's life cycle, MedDRA® may be used, for example, for recording adverse events and baseline medical history in clinical trials, in the analysis and tabulations of data from these and in the expedited submission of adverse event data to government regulatory authorities. It may be used in constructing standard product information, such as summaries of product characteristics (SPCs) or product labelling (Brown and Clark, 1996; White, 1998), and in registration files in support of applications for marketing authorization/new drug applications. After licensing, MedDRA® is used in

pharmacovigilance for the continuing evaluation of drug safety, for both expedited and periodic safety reporting.

The structure of MedDRA®

The structure of MedDRA® may be represented diagrammatically as having a five-level hierarchy, as shown in Table 12.15. As will be explained below, MedDRA® is multiaxial as well as being hierarchical, so that *Preferred Terms* (PTs), with their associated *Lowest Level Terms* (LLTs), may be represented under more than one of the 26 *System Organ Classes* (SOCs). Table 12.16 shows the MedDRA® SOCs.

Table 12.15 MedDRA® hierarchy

MedDRA® hierarchy	Number of terms	Example (primary location)	Code
System Organ Class (SOC)	26	Skin and subcutaneous tissue disorders	10040785
High Level Group Term (HLGT)	332	Skin vascular abnormalities	10047065
High Level Term (HLT)	1683	Purpura and related conditions	10037555
Preferred Term (PT)	15 709	Purpura NOS	10037559
Lowest Level Term (LLT)	55 638	Purpuric rash	10037566

Table 12.16 MedDRA® System Organ Classes (SOCs)

Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Social circumstances
Surgical and medical procedures
Vascular disorders

Each PT is intended to represent a unique medical concept: it is the term preferred for use in the regulatory environment and is formatted according to MedDRA® conventions. Eponymous terms may be used if recognized internationally. A PT may describe a single syndrome, even though a syndrome represents a collection of signs and symptoms. Each PT is duplicated as an LLT and may have subordinate to it one or more other LLTs that are synonyms, lexical variants or alternative spellings of the PT. In addition, some LLTs describe conditions that are more precise or specific than the PT to which they are linked; whilst not synonymous, they are considered not to warrant PT status from a pharmacovigilance perspective.

For example, the PT *Alveolitis allergic* has LLTs *Pneumonitis allergic* and *Pneumonitis hypersensitivity* which are synonyms; *Allergic pneumonitis* and *Pneumonitis allergic*, which are lexical variants; the LLTs *Bagassosis* and *Baggasosis* demonstrate differences in spelling; and the LLTs *Malt Worker's lung* and *Bird fancier's lung* are different conditions that do not warrant a separate PT from a regulatory perspective, although they may be distinct medical conditions. An example of a PT and some of its LLTs is shown in Table 12.17. Tables 12.18 to 12.20 show the hierarchical structure of MedDRA® expanded to demonstrate the nature of the terms at various levels.

Table 12.17 Hierarchy and secondary linkages for the MedDRA® PT *Purpura NOS*

	Primary SOC	Secondary SOC	Secondary SOC
SOC	Skin and subcutaneous tissue disorders	Blood and lymphatic system disorders	Vascular disorders
HLGT	Skin vascular abnormalities	Bleeding tendencies and purpuras (excl thrombocytopenic)	Vascular haemorrhagic disorders
HLT	Purpura and related conditions	Purpuras (excl thrombocytopenic)	Bruising, ecchymosis and purpura
PT	Purpura NOS	Purpura NOS	Purpura NOS
LLT	Dermatitis haemorrhagic	Dermatitis haemorrhagic	Dermatitis haemorrhagic
LLT	Dermatitis hemorrhagic	Dermatitis hemorrhagic	Dermatitis hemorrhagic
LLT	Haemorrhage purpuric	Haemorrhage purpuric	Haemorrhage purpuric
LLT	Idiopathic purpura	Idiopathic purpura	Idiopathic purpura
LLT	Purpura	Purpura	Purpura
LLT	Purpura NOS	Purpura NOS	Purpura NOS
LLT	Rash purpuric	Rash purpuric	Rash purpuric
LLT	Hemorrhage purpuric	Hemorrhage purpuric	Hemorrhage purpuric
LLT	Purpuric rash	Purpuric rash	Purpuric rash
LLT	Rash hemorrhagic	Rash hemorrhagic	Rash hemorrhagic
LLT	Rash haemorrhagic	Rash haemorrhagic	Rash haemorrhagic
LLT	Purpura symptomatica	Purpura symptomatica	Purpura symptomatica

Each PT is represented only once under a particular SOC, to which it is connected vertically via a single *High Level Term* (HLT), which in turn is fixed in location and represented only once in that SOC under one *High Level Group Term* (HLGT). It is a rule that there is only one route from LLT to PT to HLT to HLGT within the SOC. Thus, for example, the PT *Alveolitis allergic* includes LLTs *Farmer's lung* and *Malt worker's lung*. The PT is located under the HLT *Lower respiratory tract inflammatory and immunologic conditions*. It might

Table 12.18 Structure of a MedDRA® HLGT, showing its HLTs

HLGT	HLT
Skin vascular abnormalities	Capillary conditions Purpura and related conditions Skin haemorrhages Skin ischaemic conditions Skin vascular conditions NEC Skin vasculitides etc.

Table 12.19 Structure of a MedDRA® HLT, showing its PTs

HLT	PT (primary location)	PT (secondary location)
Purpura and related conditions		
	Ecchymosis	Idiopathic thrombocytopenic purpura
	Henoch–Schonlein purpura	Application site bruising
	Increased tendency to bruise	Injection site bruising
	Majocchi's purpura	Petechiae
	Purpura neonatal	Thrombotic thrombocytopenic purpura
	Purpura NOS	etc.
	etc.	

Table 12.20 Structure of a MedDRA® SOC, showing its HLGTs

SOC	HLGT
Skin and subcutaneous tissue disorders	Angioedema and urticaria Cornification and dystrophic skin disorders Cutaneous neoplasms benign Epidermal and dermal conditions Pigmentation disorders Skin and subcutaneous tissue disorders NEC Skin and subcutaneous tissue infections and infestations etc.

equally well be located under the HLT *Occupational parenchymal lung disorders*, also present in the *Respiratory* SOC. However, that would require two HLTs for a single PT within the one SOC, which is not permitted.

Every PT has a fixed location in one SOC, which is referred to as the 'primary' location. However, the parallel vertical SOC axes are not mutually exclusive; hence, a PT may also be found in so-called 'secondary' locations in one or more additional SOCs, in which it is again placed under a specified HLT and HLGT, whilst retaining all its associated LLTs. Having multiple locations for a PT within the terminology, known as 'multiaxiality', has the advantage that the term may be found when searches are carried out on any of the relevant

SOCs. The principle is similar to that seen above for WHO-ART and to the asterix and dagger system in ICD. The multiaxial linkages for a MedDRA® PT are shown in Table 12.17.

Thus, for example, to look in a database for cases that might be relevant to a new safety signal of heart failure, one would search in the *Cardiac* SOC for all the associated terms (probably PTs) that will lead to identification of the required cases. However, the PT *Paroxysmal nocturnal dyspnoea* is (appropriately) grouped with other types of dyspnoea under the *Respiratory* SOC as its primary location. This symptom of acute left ventricular failure is clearly relevant to the search, and it has a secondary location under the *Cardiac* SOC. Hence, if the search encompassed both primary and secondary locations, it would find cases with paroxysmal nocturnal dyspnoea even if the search was restricted to the *Cardiac* SOC.

The detailed MedDRA® user guide (Maintenance and Support Services Organization, 2002a) explains the development of the terminology and defines hierarchical levels and the rationale and conventions for their use. It is distributed on the MedDRA® CD-ROM, and updates are provided with new versions of MedDRA®.

A noteworthy convention applies to investigations. These are represented only in the *Investigations* SOC; there are no secondary linkages. However, terms describing clinical conditions, e.g. hypoglycaemia, hyperkalaemia, are present only in other SOCs such as *Disorders of Metabolism and Nutrition*. This has important implications for search strategies (see below). In the *Investigations* SOC, there are commonly PTs to describe a high value, normal value and a low value (e.g. *Serum sodium increased*, *Serum sodium decreased*, *Serum sodium normal*. In addition, there are terms for the names of tests themselves (e.g. *Serum sodium*). These are intended to give standard names to fields in databases.

HLGTs and HLTs are designed for data analysis, retrieval and presentation. They provide clinically relevant groupings of terms for drug regulatory purposes. However, the attempts to make the 'contents' of an HLT or HLGT transparent have resulted in some of the names becoming cumbersome; for example, the HLT *Musculoskeletal and connective tissue disorders of trunk congenital (excl spine)* or the HLGT *Miscellaneous and site unspecified neoplasms malignant and unspecified.*

MedDRA® includes data-entry terms from several sources: many of the *Preferred terms* and *Included terms* from the WHO-ART dictionary and its Japanese adaptation, J-ART; COSTART expanded *Symbols* and *Glossary Terms*; Hoechst Adverse Reaction Terminology (HARTS) terms; ICD9 three- and four-digit code terms and ICD9-CM three-, four- and five-digit code terms; there are also terms from the DSM IV psychiatric classification and other standard classifications. These terms are included as LLTs in MedDRA®: some are also PTs.

Vague, obsolete, misspelt or hybrid terms that have been 'inherited' from other terminologies are flagged as *non-current*. These are retained in MedDRA® as LLTs and can be used to preserve historical information, but will not be used for new data entry. Examples of *non-current* terms are given in Table 12.21. These terms, often derived from other terminologies, have been included in order to facilitate the migration of legacy data at the time of transfer to using MedDRA®. However, companies implementing MedDRA® have adopted different approaches to their existing data. Some transfer the previously coded data directly into MedDRA®, as exact matches with the MedDRA® LLTs. Others have recoded the verbatim (original reported) terms from their databases into MedDRA® *de novo.* It should be noted that the location of terms within MedDRA® does not reflect their position in source

Table 12.21 Examples of MedDRA® Non-current terms

Unspecified allergic alveolitis and pneumonitis
EMS
Angioneurotic edema not elsewhere classified
Traumatic amputation of foot (complete) (partial), unilateral, without mention of complication
Malignant hyperthemia
Flatulence, eructation and gas pain
Menopausal or female climacteric states

hierarchies – identical data will appear different when tabulated using MedDRA®, compared with its appearance in tables constructed from the original dictionary used in coding (Brown *et al*., 1997).

Each MedDRA® term has an associated unique numerical eight-digit code but there is no hierarchical sequence or logic to these. These codes are not used for data entry by the coder, but they are intended for electronic transmission of the data.

Regulatory aspects

MedDRA® is being used in the new European Union (EU) safety database, Eudravigilance. From January 2003, MedDRA® has been mandatory in the EU for exchange of post-authorization safety data between marketing authorization holders and regulatory authorities (European Commission, 2001). This includes its use for expedited reports and also for periodic safety update reports. With regard to expedited reports, the Individual Case Safety Reports, the intention is that electronic transmission of data is required, using MedDRA® for adverse reaction terms, but also for other fields described in the ICH E2B guidelines, such as therapeutic indication for suspect drug, patient medical and surgical history, cause of death, etc.

In the USA, the FDA has been using MedDRA® in its Adverse Event Reporting System (AERS) database for some years. They issued an Advanced Notice of Proposed Rule Making in November 1998, stating that the use of MedDRA® would be made mandatory for expedited reporting. A reminder to this effect was published in draft post-marketing surveillance guidelines in March 2001 (Food and Drugs Administration, 2001). However, at the time of writing, there is no knowledge of when a regulation may come into force.

In Japan, the Ministry of Labour, Health and Welfare has requested companies to use MedDRA® for expedited ADR reporting and for periodic reports (Maintenance and Support Services Organization, 2002b). However, the use of J-ART (Japanese WHO-ART) is still permitted and the regulatory authority then recodes submitted data into MedDRA®.

As yet, regulatory intentions concerning pre-registration data and the use of MedDRA® in registration dossiers have not been made known. For the rest of the world, and in respect of post-marketing safety, there seems to be commitment to the use of MedDRA® on the part of the Canadian regulatory authority, and South Africa, Australia and the eastern European countries may adopt it. However, the Uppsala Monitoring Centre still uses WHO-ART, as do the majority of the WHO Collaborating centres. Indeed, the Uppsala Monitoring Centre has indicated that it is developing its own ‘standard’ international terminology, based on WHO-ART and ICD10 (Anonymous, 2002a).

The Maintenance and Support Services Organization

MedDRA® is owned by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA – the umbrella organization for pharmaceutical industries worldwide). Licences for the distribution and maintenance of MedDRA® were issued in 1999 to the Maintenance and Support Services Organization (MSSO) for worldwide activities, and to the Japanese Maintenance Organization (JMO) for Japan. Copies of MedDRA® and licences for its use are only available from the MSSO or JMO. A maintenance framework has been developed to ensure that MedDRA® will be available at a reasonable cost, that it is updated at a frequency appropriate to the needs of users, and that there is evolution in response to advances in medical and scientific knowledge, and to changes in the regulatory environment. The MSSO and JMO are accountable to users and report to a management board.

MedDRA® is provided free of charge to regulatory authorities. Other organizations pay for an annual subscription. The main type of subscription – 'core subscription' – is charged on a sliding scale according to the financial turnover of the subscribing organization. Core subscribers receive a new version of MedDRA® as ASCII files on a CD-ROM every 6 months. Each version of MedDRA® may incorporate up to 9000 changes. Up to this annual maximum for all changes from all users, each subscribing organization may request up to 100 changes to MedDRA® each month.

Changes may include addition of new terms, moving terms, changing their multiaxial linkages, or making them non-current. When a request for a change to MedDRA® is received by the MSSO or JMO, it is considered by a medical review panel. If accepted, the change will be incorporated in the next version of MedDRA® at the time of the 6-monthly update. Notice of acceptance of the term (referred to as a 'transitional term' until it is included in the update) is posted on the MSSO Website, generally within 72 hours of the request being made.

Translations

MedDRA® is available in British English, with American English also present as LLTs, and in Japanese, using Kanji characters. Medically validated translations in French and German down to PT level, and Spanish to LLT level, will be available shortly. Work has commenced on other translations (Dutch and Portuguese – and Greek is under discussion). More translations, including LLTs for French and German, may follow.

Using MedDRA® for data entry

Because of the large size of MedDRA®, the selection of terms for data entry will generally require the use of a software program, referred to as a 'browser' for searching the terminology. Several commercial browsers are available. So too are a number of programs called 'auto-encoders' for automatic selection of MedDRA® LLTs that match the reported or verbatim terms. It is intended that data should be entered at the MedDRA® LLT level in order to capture the specificity of the information on the source document. When an LLT is selected for data entry, there is automatic assignment of PT, HLT, HLGT, and location in primary SOC, together with secondary SOC linkages. It was originally intended that data-

entry staff do not select the location and linkages of the chosen LLT, although some companies have chosen to do this.

Although the large number of LLTs in MedDRA® make the chances of an exact match with the verbatim term likely, there will still be many instances where this is not the case. Under these circumstances, two approaches might be taken. Firstly, one would carry out a 'bottom-up' search for words or parts of words in MedDRA® that are similar to the verbatim term. If this does not produce an acceptable match, then it is possible to search likely locations in the terminology based on suitable HLTs or HLGTs for an appropriate PT and LLT, a so-called 'top-down' search. For example, if we are looking for a term that is equivalent to the verbatim term 'removal of part of the stomach', it would be logical to look in the MedDRA® *Surgical and medical procedures* SOC and, on an intuitive basis, to see what PTs exist under the HLGT *Gastrointestinal therapeutic procedures*, then the *HLT Gastric therapeutic procedures*, and then to choose the 'best fit' LLT, *Partial gastrectomy*, which is under the PT *Gastrectomy partial*.

If a suitable LLT does not exist, then the MSSO may be requested to allocate a new term. However, strict guidance has been provided to the MSSO to prevent the uncontrolled proliferation at this lowest level, and justification for the addition must be provided. Thus, for example, new terms including anatomical location may not be permitted unless there are particular attributes relating to the body site that are important. The objective is to provide a reasonable representation of medical concepts.

Guidance on coding and term selection (Anonymous, 2002b) has been published by a working group, which includes representation from various companies, regulatory authorities and the MSSO. The guidelines are endorsed by the ICH, although they are not formal ICH guidelines. They actually encompass far more than just coding with MedDRA® and have quite major implications for safety databases.

Data retrieval with MedDRA®

One may wish to retrieve data from a safety database for a variety of purposes (Brown and Douglas, 2000):

- to identify the number of reports of similar or associated conditions which constitute a signal of a new adverse reaction and to review the individual case reports;
- to respond to an enquiry from a regulatory authority, or health professional, about numbers of a particular adverse reaction to a product;
- when writing about a new safety issue in the body of a periodic safety update report.

Although no rules or guidelines have been issued, it seems that PTs will be commonly used for identifying cases in a database, each PT being linked through the respective LLTs to individual cases, which may thus be identified.

Display of all the data in a pre-formatted table may produce the required answer for a single drug. Thus, a table might show all the PTs in the database assembled according to SOC, with the numbers of reports of each. Compiling a list of the relevant PTs in the database provides the search criteria for identifying the desired cases.

A disadvantage of this so-called 'data dump' approach is that, for large databases, there

may be many (possibly thousands) of MedDRA® PTs to review, in order to identify those relevant to the query in hand. There are some possible alternative approaches to data retrieval using MedDRA®, depending upon the way that the safety database has been constructed.

If all the levels in the MedDRA® hierarchy are represented in the database, then it may be appropriate to construct a search based on terms at different levels. By reviewing the HLGTs that have cases associated with the subordinate PTs, instead of reviewing all the PTs, the task might be simplified. For example, to identify all reports relevant to a signal that a drug may be causing or exacerbating cardiac failure, instead of searching through large numbers of irrelevant PTs, one could look at what is present in the database as HLGTs. The search would be built on all PTs present under the HLGT *Heart failure*, perhaps adding some PTs occurring under the HLGT *Cardiac disorder signs and symptoms*. It might be helpful to drill down in this HLGT, which is rather broad, and look at the HLTs. The *HLTs Cardiac disorders NEC* (not elsewhere classified) and *Cardiac signs and symptoms NEC* might contain PTs relevant to heart failure, but the HLTs *Cardiac infections and inflammations NEC* and *Cardiac neoplasms* might be ignored. It would be important also to look in the *Investigations* SOC, under the HLGT *Cardiac and vascular investigations (excl enzyme tests),* as there could be cases represented solely by PTs for abnormalities in cardiac function, which might otherwise be missed.

If the database incorporates the full data model for MedDRA®, then it should be possible to search individual SOCs for terms that are present both in primary locations in that SOC and those that are there in their secondary locations. In other words, a multiaxial search could be performed. In the example of searching for heart failure based on the *Cardiac* SOC, this search would then also identify cases with *Paroxysmal nocturnal dyspnoea* as a symptom of acute left ventricular failure, this PT being present in its primary location in the *Respiratory* SOC, but with a secondary location in the *Cardiac* SOC.

If looking for cases with cardiac failure is likely to be a search that would have to be performed repeatedly on different databases, then one might perform a search of the whole of MedDRA® for relevant terms, and then save a list of all the PTs we have identified, to facilitate future retrieval (Fescharek *et al*., 1996; Brown and Douglas, 2000). Unlike the previous search, the parameters for this search – a *Special Search Category* – is independent of the specific data set in question, and can be applied to any database. MedDRA® does include a small number of *Special Search Categories* (SSCs), e.g. for *Anaphylaxis*, *Cardiac ischaemia*, *Haemorrhage* and *Hypersensitivity reactions*. Searching the database for terms included in *Special Search Categories* provides automatic identification of relevant cases. However, the existing SSCs in MedDRA® are of variable quality and specificity, and it is likely that users will construct their own portfolios of searches. An extract from the PTs included in the *Haemorrhage SSC* is shown in Table 12.22.

At the time of writing, a working group of CIOMS had just been established in order to create additional standard searches along the lines of SSCs, which should be of value for pharmacovigilance purposes.

Other aspects of using MedDRA®

Little has been published on the use of MedDRA® for pharmacovigilance purposes. It is not certain at the time of writing what the effect of the high specificity of MedDRA® LLTs and PTs will be on signal detection, for example. WHO-ART has only about 2000 PTs;

Table 12.22 Preferred Terms in the MedDRA® Haemorrhage Special Search Category (partial list)

Abdominal aortic aneurysm haemorrhage
Abdominal haematoma
Adrenal haemorrhage
Anal haemorrhage
Anastomotic haemorrhage
Anastomotic ulcer haemorrhage
Aneurysm ruptured
Antepartum haemorrhage
Aortic aneurysm rupture
Application site bleeding
Application site bruising
Argentine haemorrhagic fever
Arterial haemorrhage NOS
Arteriovenous fistula site haemorrhage
Arteriovenous graft site haemorrhage
Auricular haematoma
Bleeding peripartum
Bleeding tendency
Bleeding time prolonged
Bleeding varicose vein
Blood blister
etc.

MedDRA®, on the other hand, has over 15 000 (Table 12.15). Therefore, MedDRA® PTs may dilute out any signals if many different terms are used to represent associated conditions (Brown, 2002). For example, there are 37 MedDRA® PTs in the *Cardiac* SOC that are grouped under the HLGT *Heart failure*, as well as numerous PTs in the *Investigations* SOC that are relevant to heart failure. If PTs are used in an attempt to identify an excess number of cases over some predetermined threshold in a safety database, or to compare incidences between two treatment arms in a study, then one may fail to show that any one PT qualifies as being greater than the threshold or greater in one arm of the study than the other, despite there being an overall difference present.

It has been suggested that HLTs may be more appropriate for detecting signals and for use in presenting data from clinical trials (Brown, 2002). However, there are some features of HLTs that may make this problematic. Some HLTs contain opposing concepts. For example, the HLT *Platelet analyses* includes the PT *Platelet count increased* as well as the PTs *Platelet count decreased* and *Platelet count normal*. Some HLTs are heterogeneous in respect of the seriousness of the conditions they include. For example, the HLT *Ventricular arrhythmias and cardiac arrest* lumps together the PTs for the serious conditions *Ventricular fibrillation* and *Ventricular asystole* with the usually benign *Ventricular extrasystoles* PT. Hence, if HLTs are to be used for purposes of data presentation, then it will also be necessary to show the subordinate PTs included in the database. For signal detection, some modifications to the existing hierarchy may be beneficial.

MedDRA® overview

MedDRA® is a new international standard, but it is not being implemented by all potential users. The manner of its implementation and use varies between users, and there is a dearth of suitable guidance from regulatory authorities and from the maintenance organization. The result is that there is still much uncertainty about how to use MedDRA® to best advantage.

It is apparent that the large number of LLTs provides specificity, which is something that was lacking in some previous dictionaries. Hence, it will be possible to better capture the actual medical condition as experienced by the patient than was previously the case. However, this very feature may lead to difficulties for finding cases within a database, for detecting patterns of reports that might constitute signals of new adverse reactions, and for presenting comparative safety data in clinical trials.

Further work on standardization of database searches is appropriate, and it is important that further guidance on its use in pharmacovigilance becomes available, so that there will be some consistency of approach. Use of MedDRA® is now required, at least for individual case safety reporting in the EU, but it is apparent that much work still needs to be done to ensure that it can be used effectively for all its intended purposes.

Definition of adverse reaction terms

A CIOMS working group published a series of papers giving definitions of terms used in adverse reaction reporting: these were subsequently collected into a book 'Reporting Adverse Reactions: definition of terms and criteria for their use' (Bankowski *et al.*, 1999). The terms defined cover 21 WHO-ART System-organ classes. The entries for each adverse reaction are generally quite concise, of the order of 200 to 300 words, and comprise a preamble, giving the context, synonyms, the definition itself and the conditions that should be applied for the use of the term.

As an example, the entry for melaena states as a preamble that this usually indicates bleeding in the upper gastrointestinal tract, but may also be due to bleeding in the middle or distal small bowel or proximal colon. The definition is given as 'Melaena is the passage of black stools'. The basic requirements for use of the term state that it should be used according to the definition, but that other causes of black stool, such as oral iron or bismuth medication, or dietary causes, such as liquorice or dark beers, should be excluded. To give an impression of the scope of the definitions, the cutaneous adverse reaction terms covered by the definitions are listed in Table 12.23.

The definitions may be of help when reviewing individual cases, allowing a comment to be added as to whether or not the standard definition has been satisfied by the available information. They are also likely to be of use when exploring a possible adverse drug reaction signal, in facilitating the selection of a sub-group of cases that satisfy standard criteria. However, care needs to be exercised in the way that the definitions are used. Thus, it would not be reasonable to exclude cases from a safety database or from regulatory reporting, simply because the criteria are not satisfied. If a health professional has reported the case as a particular suspected adverse reaction, then this is what should be recorded, whether or not the criteria are met.

Table 12.23 Range of term definitions for Skin and appendage disorders SOC (Bankowski *et al*., 1999)

Dermatitis (eczema)
Dermatitis exfoliative
Fixed drug eruption
Lichenoid drug eruption
Pustular eruption
Urticaria/Angioedema
Erythema multiforme
Stevens–Johnson syndrome
Toxic epidermal necrolysis
Photosensitivity reaction
Phototoxic reaction
Photoallergic reaction

Conclusion

In this chapter, some of the available dictionaries for drug names, diseases and adverse reaction terms have been considered, as well as the application of definitions to the latter. The complexity of some of the dictionaries is notable, as is the way that safety data can be profoundly affected according to the dictionary used and the manner of its employment.

This is a continually evolving area, and we are just beginning the process of standardization in the pharmacovigilance field. If true standardization of dictionaries and their mode of use is ever achieved, then it will greatly facilitate the sharing of safety data and should improve the effectiveness of the pharmacovigilance process.

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