LEADING ARTICLE

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Using MedDRA
Implications for Risk Management

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Abstract

The introduction of MedDRA, the Medical Dictionary for Regulatory Activities, as a standardised terminology may have a major impact on the performance of risk management. Thus, MedDRA is likely to have an important effect on the analysis of clinical trial safety data. Review of the most commonly used terms in clinical trial tables from the labelling of ten products indicated that each adverse event could be represented by many MedDRA preferred terms; this might theoretically lead to failure to identify differences in adverse event incidence between treatment arms. Possible solutions are proposed. The use of MedDRA in spontaneous reporting systems is a regulatory requirement in some countries. Variability in modes of implementation and use of the terminology are discussed; these may impose additional limitations on any use of spontaneous data for comparative purposes. There are important differences in the ways that safety databases interface with MedDRA and uncertainty about the most appropriate way to manage version changes. The characteristics of MedDRA must be taken into account when establishing methods for signal detection and its use will affect the retrieval of similar cases as required for signal evaluation. The use of MedDRA in the periodic safety update report is discussed. The possible use of MedDRA in pharmacoepidemiology is highly relevant to risk management, and some issues are briefly outlined. With regard to communication of risk, if MedDRA is introduced into existing product labelling, care must be taken that the change itself does not cause misunderstanding; the most appropriate use of MedDRA in this regard remains to be determined. There is a need for careful evaluation of MedDRA in fulfilling its various functions in pharmacovigilance, followed by definitive regulatory guidance on its use.

MedDRA[1], the Medical Dictionary for Regulatory Activities, is a structured terminology for recording information relevant to all stages in the development and use of medicines.[1-3] MedDRA is utilised in the EudraVigilance safety database held by the European Agency for the Evaluation of Medicinal Products (EMEA) and in the US FDA Adverse Event Reporting System (AERS) database. It is required for electronic exchange of information on suspected adverse reactions between industry and regulatory authorities after drug registration in the European Union (EU).[4] At the time of writing, the Japanese regulatory agency and the FDA are in the

1 MedDRA is a registered trade mark owned by the International Federation of Pharmaceutical Manufacturers Associations.

process of making use of MedDRA mandatory for similar purposes.[5,6]

While at present there is no regulatory requirement to use MedDRA for clinical trials, its use is recommended in the Common Technical Document, devised by the International Conference on Harmonisation (ICH), in presenting safety analyses from clinical trial programmes in the course of product registration.[7] It will probably be needed for submission of serious adverse events from post-authorisation studies in the EU.[4] Guidance from the European Commission suggests that the use of MedDRA will be necessary in the future for the submission of expedited reports from all clinical trials with centres in the EU.

It is the objective of this paper to consider what the implications are for pharmacovigilance and risk management when MedDRA is used for recording adverse events.

MedDRA is a hierarchical structured vocabulary, which includes terms for diseases, diagnoses, syndromes, signs, symptoms, qualitative findings of laboratory and clinical investigations and social circumstances. It comprises five levels: lowest level terms (LLTs); preferred terms (PTs); high level terms (HLTs); high level group terms (HLGTs); organised within 26 system organ classes (SOCs). Individual terms may be located in more than one SOC – the terminology is multiaxial – but one SOC is designated as the primary location for each term, other location(s) being referred to as secondary. The scope and architecture of MedDRA have been described in detail elsewhere[1-3] – a simplified diagrammatic representation is shown in figure 1.

1. MedDRA and Safety Data from Clinical Trials

The pharmacovigilance specification and plan for a new medicine will be based on the findings from preregistration clinical and preclinical studies.[8] These determine the initial safety information on the product, in respect of adverse events and/or suspected adverse reactions in the labelling. MedDRA use will affect the analysis and interpretation of clinical safety data[9,10] but the impact is likely to be greater on type A ('augmented') adverse reactions than on type B ('bizarre') reactions; it would be unusual for there to be a high frequency of type B reaction from a clinical trial programme[11] and their identification is less reliant on numerical comparisons between treatment arms.

1.1 Study of the Use of MedDRA for Recording Clinical Trial Adverse Events

In order to evaluate the likely effects of MedDRA on clinical trial data, a small two-part study was performed. The hypothesis to be tested was that MedDRA PTs are much more specific than the terms that have generally been used to record adverse events in clinical trials until now and that this could affect the results of safety analyses. The objective of the first part of the study was to identify adverse events that commonly occur in clinical trials by examining tables included in product labelling. In the second part of the study, MedDRA PTs were identified that corresponded to the concepts represented by these adverse events.

1.2 Methods

Twenty-five tables published in the Physicians Desk Reference (PDR) monographs[12] on ten medicinal products (selected at random) were examined (see table I). MedDRA terms corresponding to the most commonly recorded events were identified

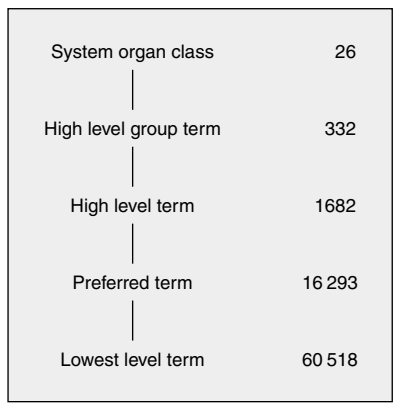

Fig. 1. MedDRA (the Medical Dictionary for Regulatory Activities) hierarchy: levels within the terminology and number of terms at each level (version 6.1).

Table I. Products selected from the *Physicians Desk Reference*[12]

Adalat CC® (nifedipine)
Allegra® (fexofenadine)
Ambisome® (amphotericin B)
Aricept® (donepezil)
Imitrex® (sumatriptan)
Mobic® (meloxicam)
Paxil CR® (paroxetine)
Prevacid® (lansoprazole)
Zocor® (simvastatin)
Zofran® (ondansetron)

and counted, using MedDRA version 5.1. For the more specific terms (such as headache, nausea, vomiting) all corresponding MedDRA LLTs were identified together with their corresponding PTs, followed by a search for other relevant PTs in their primary or secondary MedDRA SOC location under the respective HLTs and/or HLGTs.

For more general concepts (likely to be associated with very many MedDRA LLTs) different approaches were used. For example, for pain, MedDRA was searched at the PT level only for PTs containing the words 'pain' or 'discomfort' or with the suffix 'algia'. For infection, no attempt to identify individual LLTs or PTs was made. Rather, HLTs located in the 'Infections and infestations' SOC were counted.

1.3 Results

Although most of the selected product monographs from the PDR do not state the terminology used, it appears that these were probably mostly customised versions of Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) or the WHO's adverse reaction terminology (WHO-ART) or were in-house developed (company specific) terminologies. The tables (together with any associated text that described adverse event frequency in clinical trials) contained 134 adverse event terms in all. The most commonly occurring medical concepts (occurring in four or more tables in the selected PDR entries) are shown in table II. Some combination of terms was performed to achieve this table – for example, 'pain' in the PDR tables included the terms 'Pain', 'Pain-location specified', 'Pain various locations', and 'Pain and other pressure sensations'.

Table II shows the number of MedDRA terms that could have been used to code the 21 most common medical concepts represented in the PDR tables, had the patient reported more specific complaints. It may be seen that many terms could be used to represent the most commonly occurring adverse events.

Table II. Most commonly occurring adverse events (AEs) in clinical trials on ten products, with corresponding numbers of the Medical Dictionary for Regulatory Activities (MedDRA) HLTs and PTs

AE term	HLT	PT
Headache	1	12
Nausea	1	4
Vomiting	1	9
Dizziness	1	4
Abdominal pain	2	9
Sedation/somnolence	1	4
Constipation	2	4
Diarrhoea	6	12
Fatigue/asthenia	3	6
Insomnia	4	11
Pain[a]	65	168
Back pain	4	6
Rash[b]	17	32
Anorexia	2	4
Sweating	1	3
Dyspepsia	1	4
Flatulence	2	3
Infection[c]	154	Hundreds
Upper respiratory tract infection[d]	3	72
Oedema[e]	1	13
Pruritus	1	24

a PTs for LLTs containing *'pain', 'discomfort'* or ending in *'algia'* were identified.

b Only PTs containing '*rash'* were identified.

c Only includes HLTs with primary or secondary location in the 'Infections and infestations.' SOC.

d There were four PTs referring specifically to 'Upper respiratory tract infection'; the remainder are specific types of infection or relevant symptomatology.

e Only PTs (excluding 'Allergic oedema NOS') under the HLT 'Oedema NEC' were included.

HLTs = high level terms; **LLT** = lowest level term; **NEC** = not elsewhere classified; **NOS** = not otherwise specified; **PTs** = preferred terms; **SOC** = system organ class.

1.4 Discussion on Study Findings

The assumption has been made that the dictionaries used to construct the tables in the PDR did not include more specific terms so that, for example, many different ways of recording pain or discomfort would all be subsumed under the term 'Pain'. This assumption may be correct for dictionaries such as COSTART, but when these dictionaries were customised by users they may have been expanded to include more specific terms. In addition, some of the terms used in the PDR tables are probably group terms – for example 'Pain and other pressure sensations'. The number of terms at the PT or HLT levels shown in table II is based on a subjective selection by the author of terms considered relevant to each adverse event in the PDR tables. For example, many terms that could be represented simply as 'Oedema' were excluded because they appeared more relevant to the concept of angioedema.

Despite these uncertainties, examination of table II shows the large numbers of possible different MedDRA PTs in clinical trial adverse event tables. This might hinder the detection of differences in event incidence between treatment arms of studies.

Using MedDRA in a clinical trial table, instead of seeing 15 reports of 'headache' in 100 patients treated with active drug and five reports in 100 patients treated with placebo, we might see more specific types of headache, if these had been experienced and reported by trial subjects. For example, in 100 patients receiving active drug we might see six reports of 'Headache'; three reports of 'Sinus headache'; one 'Drug withdrawal headache'; four 'Tension headaches'; and one 'Post-ictal headache'. On placebo, in 100 patients, we might see four reports of 'Headache' and one report of 'Tension headaches'. Hence, a simple comparison cannot be readily made between the two treatment arms of the study. By contrast, if MedDRA HLTs were to be used, in this example there would be a 15% incidence of 'Headaches NEC' (not elsewhere classified) on active drug and 5% on placebo.

As another example, if there were reports of different types of infection in a comparative study, it might be problematic to use MedDRA PTs because of their high specificity; even HLTs might be too specific for useful numerical comparisons between treatments. It may thus be necessary to combine different levels of MedDRA within the same table, in order to make the analysis meaningful, and so that the findings can be expressed in a way that can be incorporated in a product information/labelling document.

While it may be helpful to use higher levels of MedDRA to represent conditions in clinical trial adverse event tables, this is not without potential difficulties. As has been pointed out for signal detection,[13] MedDRA HLTs and HLGTs are not homogeneous in content. For example, if HLTs were included in a table, it would not be appropriate to compare the frequency of adverse events between arms of a study for the HLT 'Carbohydrate tolerance analyses (incl diabetes)', as this HLT includes PTs representing normal, abnormal, increased and decreased blood glucose.

The use of group terms in clinical trial tables may also fail to provide a satisfactory solution because of the dispersal of PTs for a medical condition among several HLTs and HLGTs. For example, PTs for diarrhoea may be found in primary locations under the HLTs: 'Diarrhoea (excl infective)'; 'Intestinal infections'; 'Gastrointestinal infections, site unspecified'; 'Sugar intolerance (excl glucose intolerance)'; 'Gastrointestinal spastic and hypermotility disorders'; and 'Gastrointestinal infections – pathogen class unspecified'.

The effects of the high specificity of MedDRA PTs on clinical trial safety data are difficult to predict. The circumstances will vary from study to study and according to the nature of the particular adverse events reported and the way that investigators record them. Thus, it hardly matters that MedDRA has nine PTs for vomiting if patients complain only of vomiting itself and if there were no reports of more specific types of vomiting such as represented by the PTs 'Post-procedural vomiting', 'Vomiting psychogenic' or 'Self-induced vomiting'.

It is also the case that using nonspecific terms, as necessitated in some legacy terminologies, may also cause difficulties – for example coding torsades de

pointes as 'Arrhythmia' could mask the occurrence of this specific and important event.

If the use of MedDRA for safety analyses in clinical trials does indeed prove problematic, there are a number of possible solutions. For example, clinical trial sponsors could impose an industry-wide and standardised limitation on the range of LLTs (and hence PTs) permitted for use in clinical trials. However, this would not be easy to implement and would lead to a loss of information that would negate one of MedDRA's main advantages and might lead to problems of integration of clinical trial safety data with that from other sources.

Another option would be to revise the groupings of PTs under HLTs, such that homogeneous concepts are represented at the HLT level, in contrast to the existing HLTs, which are not homogeneous with regard to their contents. The principal level for comparison of adverse events between treatment arms in a clinical trial would then become the (new) HLTs, with secondary analyses being performed on PTs in addition. Again, this would not be easy to implement and could cause significant disruption to existing databases.

A third option might be to create study-specific groupings of PTs *post hoc*, if considered necessary. While this solution would be relatively simple to put into effect, it might lay sponsors open to criticism that they could have manipulated the data to their own ends.

Alternatively, it would be possible to extend this study to encompass actual clinical trial results recorded on a wide range of medicines. From these clinical trials, the task would be to identify the most common medical concepts recorded as adverse events, propose individual new terms to represent each of these concepts, and to map existing MedDRA PTs to these new terms. The new terms would then function as novel group terms. Analysis would be performed at this level without any need to change the MedDRA hierarchy. The existing MedDRA LLTs (and respective PTs) would still be available in the database for future use.

Finally, recourse could be made to the use of extended/modified versions of legacy terminologies (such as the International Classification of Disease, version 10 [ICD-10], COSTART or WHO-ART) in presenting clinical trial safety data. If these have been found to function adequately for representing clinical trial adverse event data in the past (whatever deficiencies they may have had in other respects) – they could still be employed for this purpose. However, for clinical trials the respective terms (such as WHO-ART PTs or expanded COSTART codes) would be used only for purposes of safety data tabulation and analysis. Adverse events would be coded using MedDRA LLTs and the respective PTs mapped to the appropriate WHO-ART or COSTART term which would then be used for purposes of quantitation and comparison.

The advantage of this last approach is that the beneficial specificity of MedDRA LLTs and PTs would be retained, and these terms would be recorded on the database. Mapping to COSTART or WHO-ART terms would be standardised and these familiar legacy terms used for presenting the data in tables and for summary safety analyses, thus overcoming possible over-specificity of MedDRA PTs. The MedDRA terms that were present in the database would still be available for more detailed analyses and the clinical trial data could be integrated seamlessly with safety data from non-study sources.

1.5 Conclusions of the Study

Firm conclusions cannot be drawn from this small study, although it does suggest that a plethora of MedDRA PTs might be generated in the course of a clinical trial programme and that some flexibility may be needed in the way that MedDRA is used for tabulating clinical trial data. Thus, care would be needed when making comparisons between treatment arms and statements regarding frequency of adverse events should take into account the high specificity of MedDRA PTs and the lack of homogeneity of the group terms. If there are indeed problems that result from these features, there are various pragmatic solutions that might be applied.

2. MedDRA and Spontaneous Reporting Systems

The use of MedDRA for recording suspected adverse reactions in the postmarketing environment was one of the principle motives for its development. The capability to accurately represent the suspected reaction within the safety database and to transmit data electronically using a unified standard dictionary are considered to be major benefits of MedDRA.

The FDA has decreed that it is the MedDRA PT that should be communicated in expedited reporting, while the EU regulatory authorities require the LLT. The EU regulatory guidelines require that MedDRA is used for recording and electronic transmission of more than just the adverse event terms: other data including medical history, investigation findings, cause of death and the effects of rechallenge are all required in MedDRA. At least some of these data may be relevant to the identification of risk factors or subpopulations at risk of specific adverse reactions.

The establishment of the EudraVigilance database and the AERS database, together with the use of common methods of coding will provide an opportunity for comparing safety data across products and geographical regions, although there are significant problems with such an exercise. Regulators and others may believe that, because companies are using the same terminology for adverse events, that there is a unified approach to coding. However, there are several sources of divergence in the way that data are handled by different companies (and sometimes within the same company). These are summarised in table III and discussed below.

3. Variability in the Use of MedDRA

In the absence of regulatory guidance, different methods of implementing MedDRA have been used. Some companies have recoded their legacy safety data based on the verbatim, or reported, terms. Others have taken the terms already coded with WHO-ART, COSTART or other legacy terminology and simply identified and used the corresponding MedDRA term.

Table III. Some sources of divergence in the use of Medical Dictionary for Regulatory Activities (MedDRA)

Differences in implementation
Re-code legacy data verbatim terms or map coded terms to MedDRA
Differences in coding and data entry practices
Auto-encoding or use of browser
Choices permitted by term selection guidelines
Code exact verbatim words or adjust for the context of the case
Selection of secondary SOC location in preference to primary SOC
Use of non-standard coding policies or 'Points to Consider' guidelines
Differences in database/software functionality
Capability of the MedDRA browser to search the MedDRA tree
MedDRA levels and linkages stored by the database
Capability to display/output the data at different MedDRA levels
Differences in version management
Re-coding terms in database with new MedDRA versions, or leaving existing terms intact
Freezing MedDRA versions for the duration of clinical trials, changing version with each release, or changing at study or project end
Changing linkages in database with new MedDRA versions, or leaving the architecture intact
Differences in data retrieval/database searches
Experience, medical understanding and training of user
Use of special search categories, standardised MedDRA queries or *ad hoc* searches
Capability for multiaxial searches or primary SOC locations only
Differences in data analysis and presentation
Use of primary or secondary SOC locations in tables
Presentation of PTs, HLTs or other levels in tables
Differences in data transfer
Requirements for expedited submission of LLT and/or PT level

HLTs = high level terms; **LLT** = lowest level term; **PTs** = preferred terms; **SOC** = system organ class.

Differences in coding practice may significantly affect the apparent safety profile of drugs. The 'Points to Consider' guidelines endorsed by the ICH, while recommending certain methods of term selection and coding with MedDRA, nevertheless allow choices that may result in major differences in practice between users of the terminology.[14,15] For example, some companies code signs and symptoms in an adverse event as well as any diagnosis that has been recorded; others would code the diagnosis only. While the 'Points to Consider' guidelines recommend the latter approach, they clearly permit the use

of the former as an alternative. Another example is the variation in coding used to modify pre-existing conditions. In the absence of a suitable term indicating the change (such as 'Asthma aggravated'), it is permissible to either code asthma alone (while capturing the modification in some other manner) or to use two terms, one for asthma, the other for the aggravation of the condition.

In the process of coding, many companies follow the recommendation of the 'Points to Consider' guidelines with regard to the allocation of terms to primary MedDRA SOC. Hence, they do not select which SOC is primary and which is/are secondary; they follow the allocation already fixed within the MedDRA hierarchy. Other companies choose which should be the primary SOC, based on the context of the case, the clinical trial or the product used. This will affect tables and counts of adverse events, as well as affecting the process of searching the safety database and retrieving similar cases.

Coding is also fundamentally affected by the software used – whether this is a browser or auto-encoder – and its specifications, for example whether it is capable of identifying non-current LLTs, or of displaying the MedDRA hierarchy for 'top-down' searching.

At the time of writing, there is uncertainty among users of MedDRA as to the best way to handle the changes in version that occur twice yearly. Although regulatory guidance in Europe[4] requires the use of the most recent version of MedDRA for purposes of expedited reporting of new cases, that guidance does not indicate how companies should manage the data that already exist. In particular, it is not clear whether it is necessary to revisit adverse events that have been coded with an earlier version of MedDRA in order to update the coding that has been performed. The matter is complicated by differences in the ways that safety databases handle the MedDRA data model and on how many levels of the hierarchy and what elements of the architecture are stored.

The way that data coded with MedDRA are searched in order to identify cases with similar medical conditions is open to great variability, depending on methods used, system capability and the expertise and medical knowledge of the individual performing the search. The result is that a single enquiry about product safety could produce widely differing responses.

Other sources of variability result, on the one hand, from lack of guidance about the level of MedDRA to be used to generate adverse event (or other) numerical tables and on the other, from conflicting regulatory requirements between Europe and the US concerning the level to be used for expedited reporting of adverse reactions, as already mentioned.

4. MedDRA and Periodic Safety Update Reports

The periodic safety update report (PSUR) in the format described in the ICH E2C guideline[16] provides an opportunity for review of the safety profile of a product and the detection of changes to benefits and risks. MedDRA is used in the line listings and in the tabulations of adverse event data. However, no official regulatory guidance is provided on the way that MedDRA should be used.[4,6] Line listings are commonly organised by primary SOC, and each case should only be presented once under the SOC that is relevant to the most important adverse event for that case. However, there is no guidance as to whether MedDRA LLTs or PTs should be used to represent each adverse event in the line listing. In this regard, it is probably appropriate to use the same level of MedDRA as used in the numerical tabulations, to facilitate cross-reference between the tables and the line listings.

In the numerical summary tabulations, the use of MedDRA LLTs is likely to cause fragmentation and dispersal of similar medical conditions, impeding identification of possible signals. Even with PTs, it is necessary to exercise caution, with review of data across and within SOCs, if clusters of similar conditions are not to be missed. This is compounded by the separation, within tables, of serious and non-serious adverse events. For example, there may be adverse event terms relevant to thrombocytopenic purpura distributed among the 'Blood and lymphatic disorders', 'Investigations' and 'Skin and subcuta-

neous tissue' SOCs, further subdivided into serious and non-serious events, and perhaps according to report source also. In this way, it is possible that a threshold for signal identification may be inadvertently missed. If the adverse event terms are presented under MedDRA HLTs or HLGTs, it is important not to be misled by the names of these groupings into thinking that these are comprehensive collections of all terms relevant to a particular medical condition.[17] This point is considered further below (see section 6). It is conceivable that, when a range of Standardised MedDRA Queries (SMQs) become available (see section 6) these could be applied in analysing summary tables, in order to consider together all the events relevant to a specific medical condition. However, it is unlikely that there will be sufficient SMQs to identify all potential signals residing within the PSUR summary tables. A partial solution might be to generate a subsidiary table that includes all PTs presented in both their primary and secondary SOC locations. While this could lead to duplicate counting of events, it might act as an aid to identifying clusters of similar events. However, it would not be applicable to the 'Investigations' SOC (which has no secondary linkages) and in general, the secondary SOC linkages are unlikely to be comprehensive.[17]

5. MedDRA and Signal Detection

The effects of MedDRA on post-authorisation signal detection based on (mostly) spontaneous reports have not been extensively documented in the published literature. However, this is the principal reason that safety data are collected in the post-authorisation period. As with clinical trial data, the effects of MedDRA on signal detection are likely to vary from event to event.

Methods of detecting signals of new safety issues depend on event recognition and on quantification of events. Both of these may be affected by the use of MedDRA.[13] Quantification is involved in identifying when a certain number of reports of an adverse event has been attained – when some threshold, such as three reports of a new suspected adverse reaction has been reached.[18] Other methods involve mathematical/statistical approaches looking for reports of a suspected reaction that stand out as constituting a greater proportion of the total reports for the product than would have been expected from consideration of the database as a whole.[19-21]

The issue then becomes one of how many cases of a particular condition have been reported. If the analysis is performed at the PT level, there could be failure to identify a signal because of the specificity of these terms. For example, MedDRA version 5.1 has 13 distinct PTs for pancreatitis. Suppose the database contained one report each of: 'Pancreatitis NOS' (not otherwise specified), 'Pancreatitis acute', 'Pancreatitis necrotising', and 'Pancreatitis haemorrhagic'. If a proportional reporting ratio was calculated as a means to detect possible signals, based on each of these PTs separately, the fact that there are actually four reports of pancreatitis could be missed. The corresponding HLT might have been appropriately employed for this purpose.

On the other hand, there could be false-positive signals if there was a single report of a case coded with a term that has not been used elsewhere in the database. With the example of pancreatitis, a single report coded as 'Pancreatic phlegmon' might stand out as being unexpectedly common for a product when compared with the total database that contained no such reports. Had the event been reported as 'Pancreatic abscess', it might have been just one of many such cases.

6. Retrieving Data and Identifying Cases

When a putative signal has been identified it is necessary to count the relevant cases in the safety database and to examine the individual cases. Both of these tasks depend on accurately identifying the cases, based on the constituent adverse events, as coded with MedDRA. Because of the size and complexity of MedDRA, searching safety databases is likely to be complicated, with some potential traps for the unwary, leading to the possibility of cases being missed.[17,22-24]

Searches on databases might be based on all terms at a given level (probably PTs) in MedDRA, or limited to the terms that are present in the safety

database for the product under review.[17] It will be important for identifying, interpreting and managing risk that the methods used for searching and the version of MedDRA are recorded and that the basis for each search is transparent to the recipient of the information.

A Council for International Organizations of Medical Sciences (CIOMS) working group is in the process of producing guidelines on searching safety databases coded with MedDRA and is generating around 70 standard searches for specified medical conditions based on the terms derived from the whole of MedDRA that can then be applied to any product. The lists of MedDRA terms (SMQs) that the CIOMS group produces will greatly facilitate data retrieval. However, it is not conceivable that they will produce sufficient SMQs within a short time to cover all requirements for case identification and retrieval and it is likely that companies and regulatory agencies will have to generate their own searches for specific purposes. At the time of writing, the first SMQs, for anaphylaxis, rhabdomyolysis/myopathy and torsades de pointes/QT prolongation are about to be released for user-testing.

7. MedDRA and Pharmacoepidemiology

The planning and initiation of pharmacoepidemiology studies is a central element of risk management activities and MedDRA may be an important consideration here also. The scope of MedDRA includes terms for medical conditions in general, not only adverse reaction terms, hence it may lend itself to studies that examine the broader medical aspects of patient experience following drug exposure. The main advantage to using MedDRA for pharmacoepidemiology studies is that it would probably facilitate the integration of findings with safety data from a variety of sources. It may be foreseen that it will be used in prospective observational cohort studies, in much the same way as it will be used in interventional clinical trials, and that it may be of value for recording previous medical history as well as for events arising during the study. The same concerns regarding the specificity of PTs as described above for clinical trials are likely to apply.

The use of MedDRA in other situations is likely to depend on the nature of the study. Thus, if a retrospective cohort design is employed, it would depend on the format of the records that are accessed; existing coded terms present in databases might be employed rather than re-coding these using MedDRA. However, if patient records are accessed directly and data are not already coded with a suitable terminology, MedDRA could be used. For record linkage the source data are likely to already have been coded, using one of the ICD, or perhaps the Systematized Nomenclature of Medicine (SNOMED). Many ICD-9 and ICD-9-CM (clinical modification) terms are already in MedDRA, and this could be readily employed. At the time of writing, a map between ICD-10 and MedDRA has been proposed. However, mapping MedDRA and SNOMED would be a formidable undertaking and unlikely to be available in the foreseeable future; no plans for such mapping have been announced.

As an example of the way that MedDRA may be relevant to the performance of pharmacoepidemiology studies, it may be noted that the UK General Practice Research Database (GPRD) has created a map linking Read Codes, which are used specifically in the UK clinical environment, and MedDRA. On the other hand, the UK Drug Safety Research Unit has its own dictionary that, at the time of writing, is not mapped to MedDRA. Hence, prescription event monitoring studies performed in the UK will not provide MedDRA-compatible information, in contrast to studies using GPRD data.

8. MedDRA and Product Information

Package inserts, product labelling or Summaries of Product Characteristics (SPC) are seen as an important element in the communication of safety information and these documents will certainly be affected by the use of MedDRA.[25,26] Regulatory guidance on the use of MedDRA for standard product information is limited at the present time to volume 2 of the EU's 'Notice to Applicants, Guidelines on Summaries of Product Characteristics'.

These require that the 'Undesirable Effects' section of the SPC (Section 4.8) should include: "a table of adverse reactions according to a standard system organ class such as in MedDRA.…within each system organ class, the ADRs should be ranked under headings of frequency…". The guidelines go on to specify that, if MedDRA is used, adverse reaction descriptions should be based on the most suitable representation within the terminology.[27]

Companies have interpreted this requirement in different ways. For example, some consider that the guideline mandates the allocation of the MedDRA terms in the SPC to the primary SOC locations assigned in MedDRA. Thus, a drug that is known to be associated with hepatic encephalopathy, abnormal transaminase levels and hepatitis would have these conditions located in the SPC under the separate headings 'Nervous system disorders', 'Investigations' and 'Hepato-biliary disorders', respectively. Other companies take a more pragmatic view and would include all three conditions under 'Hepato-biliary disorders'. Certainly this latter approach is more meaningful for the prescriber, who may not be familiar with the vagaries of MedDRA.

By the same token, it is not helpful, for example, for the prescriber to have to find thrombocytopenia and decreased blood platelet levels in two separate sections of the SPC just because they are represented separately in MedDRA. It would make sense to present these (as is the practice of some companies) in one location, or to combine them as a single term.

The SPC guidelines allow flexibility in selecting the appropriate level of MedDRA for use in describing adverse reactions, although they suggest that "this will usually be at the PT level". In many instances, the PT does not accord with common clinical usage. For example, increased ALT has the PT 'Alanine aminotransferase increased'; permanent deafness becomes 'Deafness permanent'. This inversion of word order has a sound basis for purposes of classification, but might confuse the health professional. However, the SPC guidelines do not stipulate that the exact lexical form of the MedDRA term needs to be used.

In some instances, the MedDRA PT is quite different from the conventionally used expression – for example loss of interest has the PT 'Anhedonia'; Alzheimer's disease has the PT 'Dementia of the Alzheimer's type'. In other instances, there are distinct differences in meaning between the LLT and the PT. Thus, post-prandial hypoglycaemia has the PT 'Hypoglycaemia'; brittle diabetes has the PT 'Diabetes mellitus insulin-dependent'. Hence, the level of MedDRA used could profoundly alter the meaning of the information provided.

At the time of writing, staff within some regulatory agencies in the EU are requiring companies to convert existing SPCs to MedDRA. While this is feasible for the most part, there may be individual terms that cannot readily be converted with suitable precision – especially for therapeutic indications, but also for contraindications, warnings and precautions. If a suitable term can be neither found in, nor added to, MedDRA (the request being refused by the Maintenance and Support Services Organisation), the argument should perhaps be advanced to the regulator concerned that it is more important to present the appropriate message to the health professional who may use the document than to comply with any regulatory diktat for the use of MedDRA.

It is important that the users of product information are not confused by the conversion of labelling documents to MedDRA, or be misled into believing that there are real differences in safety profile between medicines, if these have been artefactually generated as a result of changing the terminology used for recording adverse events. Indeed, preparation of a standard explanation for prescribers, healthcare professionals and other users of labelling information about the effects of changing the terminology might be a useful exercise.

9. Conclusions

This paper has suggested ways in which using MedDRA is likely to affect the identification and management of risk and its communication. However, little work has been published on this topic and it is not clear to what extent regulatory authorities and pharmaceutical companies are aware of the is-

sues and are addressing them. Certainly, data must exist within companies and regulatory authorities that can confirm or refute some of the issues raised here.

The introduction of MedDRA and its acceptance as an international standard provides several potential benefits for risk identification and management: the ability to exchange data effectively between different organisations; electronic data transfer; accurate representation of the medical condition of the patient; a hierarchy and architecture allowing flexibility in searching and case retrieval; and the possibility of extension and revision of the terminology in response to the needs of users. On the other hand, there are some complexities in its use and uncertainties regarding the effects of the high specificity and number of PTs on the quantitative analysis of clinical safety data and on detection of signals. In addition, there have been divergent methods applied to MedDRA implementation that may detract from its benefits as a standard terminology.

Regulatory guidance is needed on the use of the multiaxial structure, especially with regard to the practice of user selection of SOC for PTs. Investigation is also needed of the interface between MedDRA and the various commercially-available safety databases, in respect of their effective use for data retrieval/case identification. A standardised approach to the implementation of new MedDRA versions is required, in order to obviate any untoward effects on data retrieval and presentation. Comparison of the effectiveness of different levels of MedDRA in statistical/mathematical methods used to aid signal detection would also be of value.

MedDRA provides the building blocks for pharmacovigilance and risk-management activities by recording adverse events following exposure to investigational medicinal products and marketed medicines in clinical trials and the suspected adverse effects of medicines after marketing. Its use is pivotal for the definition of the safety profile of new drugs, for identifying possible signals of new adverse reactions for marketed drugs, exploring these signals and for communication of risk in the standard product information.

What is still needed – even at this relatively late stage in MedDRA's evolution – is careful evaluation of the use of MedDRA on real data in fulfilling its various functions, followed by definitive guidance on its use.

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