Title

The Utilization of Standardised MedDRA Queries in Marketing Applications and their Regulatory Reviews

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The development of a new drug is a time-consuming process, involving considerable human and monetary resources.\textsuperscript{1-3} Safety is a major focus in the development of a marketing application and is assessed, in a large part, through clinical trials with databases containing up to hundreds of thousands of adverse events.\textsuperscript{4-7} Coding safety data into a standardized terminology is important for safety analyses that are essential for product evaluation, monitoring, communication, electronic records exchange, and oversight.\textsuperscript{8,9}

The Medical Dictionary for Regulatory Activities (MedDRA) is a five-tiered hierarchical and multiaxial system of medical terminology.\textsuperscript{8,9} The hierarchical system of MedDRA consists of five levels arranged from the very specific to very general.\textsuperscript{9} The multiaxiality designed in the system allows a term to be represented in more than one System Organ Class (SOC) and to be grouped by different classifications (e.g., by etiology or manifestation site) so as to enable retrieval and presentation via different data sets, as well as the examination of a single medical concept from different points of view.\textsuperscript{9,10}

Standardised\textsuperscript{1} MedDRA Queries (SMQs) are groupings of about 50 to 200 MedDRA terms, ordinarily at the Preferred Term (PT) level that relates to defined medical conditions, such as thrombocytopenia or hepatic failure.\textsuperscript{8,11-13} SMQs are intended to be an aid in the identification and retrieval of potential cases of interest from MedDRA-coded adverse event databases.\textsuperscript{8,11} There are several useful and special features while performing SMQ

\textsuperscript{1} Actual spelling; many MedDRA terms use an English spelling, reflecting its origins.
searches. For example, most SMQs have both narrow and broad scope terms. A narrow search could improve specificity while a broad search incorporating the more specific narrow terms as well as broad terms would enhance sensitivity. Moreover, an algorithmic search is available for some SMQs, which involves a combination of search terms from various sub-categories of the broad search terms so as to have greater sensitivity compared to the narrow search and greater specificity compared to the broad search. As of the time of writing, there are almost 100 SMQ topics available to MedDRA users.

In spite of various merits of using SMQs to screen databases, this methodology is not without limitations. The use of an SMQ to identify subjects with specific diseases or symptom complexes is analogous to fishing by casting a net. While the aim of using an SMQ is to identify relevant cases, irrelevant cases are frequently retrieved, especially while using less specific broad terms. While the application of algorithm search option may help to improve specificity, evaluation and verification of the cases identified may be essential for the analysis of safety profile.

Recognizing the importance and impact of SMQ use in safety analyses, the objectives of the current study are to characterize how SMQs were used in marketing applications submitted to the United States Food and Drug Administration (USFDA) and to evaluate their impact in regulatory reviews. Although previous research has evaluated the performance of SMQs, the present study is the first one, to my knowledge, to comprehensively
investigate the use of SMQs in the review process for marketing applications to the USFDA.

PharmaPendium® was used to search² for the Summary Basis of Approvals (SBOAs) in which SMQ searches were described in reviews of drugs approved by the USFDA between the years of 2005 and 2015.²² 102 marketing applications (both New Drug Application (NDA) and Biologics License Application (BLA)) for which the term SMQ was mentioned in the review documents for more than five times were found in this search and the assessment of 38 of them was completed at the time of this analysis. The reviews from these 38 SBOAs were retrieved from the Drugs@FDA website²² and the documents were searched with an optical character recognition function for the terms “SMQ” and “standardised MedDRA Query”. A database was developed in EXCEL® that contained information abstracted from the publicly available review documents.²² The descriptive statistical analyses were performed with the software program JMP®.

Among the 38 applications reviewed, the numbers of applications and SMQs searched per year are displayed in Figure 1. A total of 597 searches using 75 different SMQs were analyzed. The applications investigated in the present effort encompassed more recent applications, especially from 2012 to 2014.

² Database last accessed August 31, 2015.
The numbers of applications and Standardised MedDRA Queries (SMQs) searched per year. The term, year, meant the year at which the review containing the discussion of SMQs was completed. If there was more than one document for a single application, the earliest year was adopted.

The distribution of the major therapeutic class of the applications is shown in Figure 2. The therapeutic class in which SMQ searches were most common (about 25%) was the antineoplastic agents.
Figure 2. The distribution of major therapeutic class of the applications reviewed. The classification of therapeutic class was based on the Anatomical Therapeutic Chemical (ATC) classification system, second level. However, for some drugs without ATC code or with different indications from that mentioned in the ATC classification system, the therapeutic class was manually designated based on the USFDA labeling and review reports. Only those therapeutic classes accounting for more than five percent of the applications were included.

**How were the SMQ searches done?**

Among the 597 SMQ searches, 307 (51%) searches were initiated (meaning performed or requested) by the USFDA, 178 (30%) searches originated from the applicants, and the origins of 112 (19%) searches were not able to be determined based on the review materials. Among those initiated by the USFDA, 217 (71%) searches seemed to be initially performed at the time of the review and the remaining 90 (29%) searches were requested by the USFDA, mostly (64% of the 90) at pre-NDA/pre-BLA stage and performed by applicants.
These data suggest that both the FDA and industry are familiar with this technique, though it is more frequently used at the FDA. The relatively large number of requests suggests that the method is valued by the FDA review staff as a means of understanding patterns in adverse event data.

Seven of the 38 applications (18% of the applications, 48% of the SMQ searches) involved the use of the MedDRA-based Adverse Event Diagnostics (MAED) while the methods utilized for other applications/searches were unknown. The MAED program has the capability to search adverse event (AE) databases for all of the SMQs by treatment group or any demographic or trial variable found in the datasets. From this analysis, one may note that investigations using the MAED program generate a large number of matches, so verification of the findings by reviewing the cases is imperative.

**Which SMQs were used in analyses?**

The top five SMQs searched are demonstrated in Figure 3. The SMQ *Hepatic disorders* was the most frequently searched SMQ and was discussed in almost half of the applications. The SMQs, *Ischaemic heart disease* and *Cardiac arrhythmias* were investigated in more than one third of the applications. In addition, for the top three therapeutic classes reviewed in the present study, the distribution of the major SMQs searched is compared in Table 1. The distribution of the SMQs searched among different therapeutic classes likely reflects the
safety issues that the applicants or Agency (USFDA) has the most concerns.

Figure 3. The frequency of the most investigated Standardised MedDRA Queries (SMQs) (n=38). Because more than one search could be applied in a single application, the total percentage could be more than 100. A: SMQ Hepatic disorders; B: SMQ Ischaemic heart disease; C: SMQ Cardiac arrhythmias; D: SMQ Angioedema; E: SMQ Cardiac failure; F: SMQ Torsade de pointes/QT prolongation; G: SMQ Anaphylactic reaction; H: SMQ Central nervous system vascular disorders; I: SMQ Haemorrhages; J: SMQ Hypertension; K: SMQ Malignancies.
Table 1. The distribution of the major SMQs searched for the top three therapeutic classes reviewed

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Antineoplastic agents</th>
<th>Drugs used in diabetes</th>
<th>Immunostimulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMQ Haemorrhages</td>
<td>SMQs Anaphylactic</td>
<td>SMQ Ischaemic heart</td>
<td></td>
</tr>
<tr>
<td>(searched in 7 out of 9 applications)</td>
<td>reaction, Angioedema, Central nervous system</td>
<td>disease (searched in 2 out of 3 (67%) applications)</td>
<td></td>
</tr>
<tr>
<td>SMQ Hepatic disorders</td>
<td>vascular disorders, Hepatic disorders, Ischaemic heart</td>
<td>Ischaemic heart disease (searched in 2 out of 4 applications (50%))</td>
<td></td>
</tr>
<tr>
<td>(searched in 6 out of 9 applications)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(67%) applications)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What factors affected the sensitivity and specificity of SMQ searches?

Regarding the balancing between specificity and sensitivity, among 329 searches using first-level SMQs, 285 (87%) searches involved the SMQs with both narrow and broad search options described in the introduction to this paper. Twenty-five (9%) of them applied only broad search option while 152 (53%) of them applied only narrow search option. Another 25 (9%) of the searches utilized both options. The search options for the remaining searches (29%) were unspecified in the review document. Therefore, narrow searches aimed at higher specificity seemed to be a preferred approach when both search options were available.

This practice seems to reflect a preference for practitioners to use SMQs as a specific analytical tool rather than a tool that is very sensitive but requires more extensive verification of cases. Although an algorithm search option is available for six of the 75 SMQs searched, the option was not utilized, which might imply that the simplicity of the search may still play an important role regarding handling and analyzing safety profile or that practitioners are
using more simple search programs since the algorithms for this class of SMQ are more
difficult to program than simply searching for preferred terms.

Some SMQs have a hierarchy, a principal or first level and one or more subordinate
SMQ (sub-SMQ) level(s); this allows for more flexibility and potentially more specificity in
how the database is searched. In the present study, this type of hierarchy is available for
22 (29%) of the SMQs searched, accounting for 382 (64%) searches. Sub-SMQs were used
for 20 different SMQs in 268 searches (70.2%). The use of sub-SMQs was most frequent for
the SMQs Hepatic disorders, Cardiac arrhythmias, Malignancies, Biliary disorders, and
Central nervous system vascular disorders. Among all the available SMQs, the SMQ Hepatic
disorders is stratified with most levels and amounts of sub-SMQs. Nine of the 15 available
sub-SMQs were used in the present study with the sub-SMQ Drug related hepatic disorders
- comprehensive search being the most frequently searched. This finding suggests that the
classification into sub-SMQs is helpful in providing a focused look into the safety profile.

Modification of SMQs was used in 49 searches (8.2%) to retrieve target cases of
interests. The comparison of modification strategy applied by either applicants or the USFDA
is demonstrated in Table 2. Regarding the most often searched SMQ (searched in 17 out of
38 (45%) applications; 68 out of 597 (11%) searches) Hepatic disorders, 9 out of 68
searches (13%) have been modified with a combination of SMQs or exclusion of certain PTs.
For the second most often searched SMQ Ischaemic heart disease, 6 out of 27 searches
(22%) have been modified with addition or exclusion of PTs and combinations of SMQs. The use of modification strategy suggests that there were still some case-by-case considerations for some of the searches since the original definition could not suffice.

### Table 2. A comparison of modification strategies applied by either the applicants or USFDA

<table>
<thead>
<tr>
<th>Modification type</th>
<th>Number of searches (%)</th>
<th>Applicants (n=39)</th>
<th>USFDA (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition^a</td>
<td>12 (30.8)</td>
<td></td>
<td>3 (30)</td>
</tr>
<tr>
<td>Addition and combination^b</td>
<td>10 (25.6)</td>
<td></td>
<td>2 (20)</td>
</tr>
<tr>
<td>Addition and exclusion</td>
<td>1 (2.6)</td>
<td></td>
<td>1 (10)</td>
</tr>
<tr>
<td>Combination</td>
<td>5 (12.8)</td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Combination and exclusion</td>
<td>4 (10.3)</td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Exclusion</td>
<td>7 (17.9)</td>
<td></td>
<td>4 (40)</td>
</tr>
</tbody>
</table>

Abbreviations: USFDA, United States Food and Drug Administration.

^a Addition means the inclusion of more terms.

^b Combination means the combination of more than one SMQ.

^c Exclusion means the exclusion of more terms.

**How were the AE retrievals verified?**

To ensure the representativeness and the correctness of the case retrieval, two major approaches were adopted, which included either direct verification of cases retrieved by investigation of other trial data such as clinical laboratory test results, vital signs or through reading the patient narrative and comparison with other search results, such as that of HLTs and PTs. About 43 percent of the searches applied at least one of these approaches, and about 19 percent of the searches encompassed both. Approximately 35 percent of the
searches applied the direct verification technique. Routine verification seemed not to be a common practice, which is worth noting since matching on only one adverse event term is needed to be considered an “SMQ match”. However, only through verification could the results of an “SMQ match” be comprehensively inspected.

For those searches most frequently performed, verification of the cases retrieved accounted for 26 out of 211 verified searches (12%) for the SMQ Hepatic disorders, 17 out of 211 verified searches (8%) for the SMQ Cardiac arrhythmias, and 16 out of 211 searches (8%) for the SMQ Ischaemic heart disease. For the SMQ Hepatic disorders, the cases were mostly verified with the review of adverse events together with clinical laboratory test results, some with narratives for the cases retrieved. For the SMQs Cardiac arrhythmias, Ischaemic heart disease, Haemorrhages, Cardiac failure, Gastrointestinal perforation, ulceration, haemorrhage or obstruction, the cases were mostly assured by review of adverse events. For the SMQ Hypertension, verification was mostly performed by reviewing adverse events, some with a check on vital signs. The results suggest that the verification methods largely depended on the respective characteristics of the safety issue and whether there were readily available clinical laboratory test results or other markers to utilize.

How were SMQ searches analyzed and reported?

For the reporting of search results, inferential statistics were utilized 43% of the time and
descriptive statistics, such as the number of cases or incidence, were applied in about 57% of the searches. For searches presented with inferential statistics, about 58% of the results were provided with a $p$-value and the relative risk or an odds ratio, in addition to the number of cases and the incidence. The distribution of the reporting methods as well as the verification of cases retrieved are collectively shown in Figure 4. Around 32% of the search results were reported using inferential statistics without direct verification of case retrieval, which might lead to an erroneous estimation of the occurrence of the specific SMQ disease syndromes.

Figure 4. The distribution of the reporting methods as well as the verification of cases retrieved ($n=596$; one search with no results displayed was excluded.) Searches reported with both descriptive statistics and inferential statistics were classified as using inferential statistics.
**Were SMQ searches considered to be a valuable tool by reviewers?**

As for the regulatory application of SMQs, about 15% of the searches seemed to have had direct influence on regulatory decisions, mostly labeling requirements based on the conclusions drawn in the reviews. More than 92% of these searches having regulatory impact were verified, which is a very important finding because the labeling reflects the review team’s final opinion of the safety profile.

In conclusions, efficient and effective use of SMQs is essential for safety profile analysis in regulatory reviews of marketing applications. While SMQs searched were based on case-by-case considerations, the SMQ *Hepatic disorders* was among the most common concerns. Efforts have been made to increase specificity, such as the utilization of narrow searches and by using application-specific modification strategies; however, the option of using algorithmic searching was not applied. Searches were frequently, but not uniformly verified with the review of adverse events, clinical laboratory test results, and/or narratives for the case retrieved. Fortunately, regulatory conclusions were mostly drawn from the searches with verification of case retrieval. Although the study to date has encompassed only a limited number of applications, the trends and practices observed have revealed key issues for more efficient SMQ use. A comprehensive study, involving all of the applications using SMQs, is merited.
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