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First Workshop on

Computational Methods in Pharmacovigilance

held during the

Medical Informatics in Europe (MIE) Conference,

Pisa, Italy, 29 August 2012

1. Introduction: First Workshop on Computational Methods in Pharmacovigilance

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Pharmacovigilance is the activity related to the collection, analysis and prevention of adverse drug reactions induced by drugs. This activity plays the fundamental role in monitoring the patient safety during their healthcare process and beyond it. Although this activity relies on a strong surveillance tradition within the pharmacoepidemiological area, some limitations appear and generate uncomfortable cases widely covered by media (such as those related to Mediator or VIOXX). First of all, these are due to the ever increasing amount of the data to collect and to process, and also to the recording and storage of these data in the digital form. Hence, the computational methods may provide with useful and intelligent solutions for a more rapid and systematic management of the data.

The workshop addressed different aspects of the pharmacovigilance process:

Collection of the pharmacovigilance data. Traditionally, the pharmacovigilance cases are narrative documents spontaneously submitted by medical staff, by pharmacists and sometimes by patients themselves. The actual concern is that the collection of these cases is far from being complete. Thus, special efforts are oriented on the computational assistance when collecting and gathering the pharmacovigilance cases and on the corresponding reporting standards and frames.

Analysis of the pharmacovigilance data. This step relies on the encoding of the cases with the dedicated terminologies and then on the semantic and statistical analysis of these cases. The concerns are related to various aspects, such as the semantic correspondence between the cases and the terms, the managing of semantic ambiguity and relatedness between the terms, the exploitation of the SMQs and of the related data.

Prevention of adverse drug reactions. The prevention step aims at facilitating the exchange of information through the well established national and international networks. It manages specifically the grave adverse drug reactions and the guidelines which help countries to strengthen the pharmaceutical politics and decisions.

The first workshop was held in August 2012. It gathered people from industrial, institutional and academic fields working in different areas (statistics, computer sciences, pharmacology, natural language processing, clinical informatics…). The seven selected papers have been reviewed by an international board of experts. They show a strong relevance to the topics of the workshop, cover its various aspects and aim to satisfy the current needs of the pharmacovigilance area.

Two papers address the issues related to the use of terminologies for the description and selection of adverse drug reactions and cases. Thus, the alignment of the Summary of Product Characteristics terms with the MedDRA terms allows to obtain the same representation of several sources of the pharmacovigilance data (Slattery et al.). Besides, the correspondence between terms from terminologies with different granularity may have an impact on the selection of the cases from different databases (Thiessard et al.).

Three papers address the grouping of the pharmacovigilance terms. They are all related to the FP7 IMI PROTECT project. The proposed methods exploit the hierarchical organization of MedDRA (Hill et al.), a specifically built resource onto ADR (Souvignet et al.) or non specific resources and methods (Dupuch et al.).

Finally, two papers are dedicated to the exploitation of bibliographical databases in order to collect relevant literature and to support the information on known and new adverse drug reactions. Machine learning techniques (Toldo et al.) or PubMed-specific queries (Bousquet et al.) are exploited and allow to collect data relevant to the pharmacovigilance survey and analysis.

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2. A Structured Database of Adverse Drug Reaction Based on Information from the Summary of Product Characteristics

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Background: With a vast range of medicines on the market, doctors and drug safety experts are faced with an increasingly complex body of information to consider when making rapid and important clinical decisions. This project addressed the task of converting a part of the available information on adverse drug reactions into a form that can be used in electronic systems to guide decision making. All the textual information from the Undesirable Effects section of the Summary of Product Characteristics of all 391 substances that had current authorizations via the European centralized authorization process was extracted into a structured database. A structured database of adverse drug reactions has multiple uses. It could be used in conjunction with general practice databases to alert the doctor when a patient presents with a reaction to one of their current medications. It can also be used to increase the efficiency of systems designed to identify unknown drug safety problems. Thirdly, it can provide a reference for evaluation of new methods for detecting safety signals.

Methods: The coding involved a three stage process. First, strings of text corresponding to distinct clinical conditions were extracted manually and an exact match to the MedDRA hierarchical dictionary at the Preferred Term level was sought using simple procedures in SQL. Failing this the Lower Level Terms were also searched. If this first matching failed, the European Medicines Agency (EMA) sent the list of unmatched terms to the Uppsala Monitoring Centre of the WHO where an approximate matching algorithm, featuring Porter stemming, stop word removal, synonym replacement and word order permutation,[1] was used to identify potential alternative matches. The algorithm is based on a subset of named entity recognition methods, see de Bruijn.[2] The final resort was to expert evaluation of the remaining codes, this was split between EMA and Bayer Pharmaceuticals.

Results: The approximate matching procedure, previously shown to have a sensitivity of 98%,[1] resulted in a substantial reduction in the number of codes that had to be addressed by expert opinion. 28% of codes did not give exact matches but this was reduced to 2% by the approximate matching. Initially some restricted manual checking of the alternative matches is required but, as the work progresses, a database of agreed matches to non-MedDRA terms results from the

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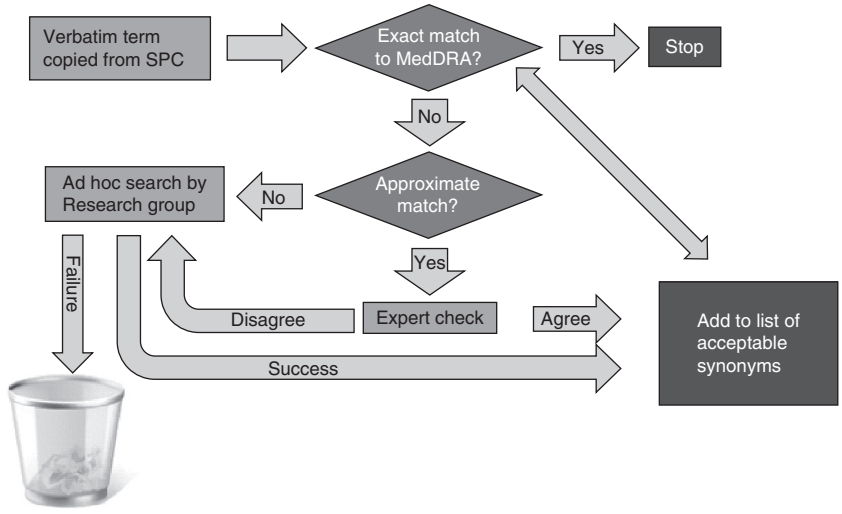

Fig. 1. Mapping process (see abstract no. 2).

matching process. Thus, a resource for still more efficient updating and extension of the database is a byproduct of the process. The database is currently updated to the end of 2011 and the quality assurance and updating processes are being piloted.

Conclusion: This project demonstrated how relatively simple automated matching processes can vastly reduce the effort required to convert simple text into a structured database. This database is a tool for research and pharmacovigilance. It does not have regulatory or legal status but, with this caveat, it is publically available at the PROTECT website.[3]

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The research was conducted as part of the PROTECT consortium. It has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu). The authors declare no conflicts of interest.

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3. Potential Bias Introduced when Excluding Concepts from Different Granularity Terminologies: Application to the EU-Funded SOS Project

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Background: The objective of the SOS Project is to assess the risk of cardiovascular and gastrointestinal events of non-steroidal anti-inflammatory drugs. Seven European databases (DB), containing health records of more than 35 million citizens, are involved in the project. These DB use 4 different terminologies to code events (ICD9, ICD10, READ and ICPC). Homogeneous identification of events was realized using the Unified Medical Language System (UMLS). A UMLS concept describes a single medical notion which can be expressed using different terminologies. Using the UMLS, we provided a list of concepts and all their descendants in the 4 terminologies. Because the terminologies had different granularity and it was decided to exclude concepts – for example when a specified cause was not related to a drug – we faced to a new theoretical heterogeneity if the excluded concept was not present in each hierarchy of the involved terminologies.

Objectives: To quantify the cases where a bias due to exclusion of concepts appears in real DBs involving different terminologies.

Methods: We linked all the extracted concepts according to their hierarchy using the UMLS and pointed all those with their parents and descendants for which exclusion was not possible in at least one of the terminologies because of its insufficient depth.

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Results: Only five of the seven European DB were used for this study, corresponding to three terminologies: ICD9 (PHARMO, SISR, OSSIFF); ICD10 (GePaRD); READ (THIN). The target population was respectively 11, 14 and 5 million patients. The events of interest and covariates leaded to 15 753 UMLS concepts. Only 76% of the 6 042 ICD9 codes proposed were effectively used in concerned DB; 77% of the 4 960 ICD10 codes and 50% of 9 129 Read codes. The percentage of excluded codes among the effectively used codes in DB was comprised between 1.2 and 2.04%. Most of the excluded concepts were coded with all terminologies, but 58 of them (42%) were coded with only one or two of the three terminologies.

Conclusions: Excluding concepts when using several terminologies introduces new pitfalls that don't exist when all concepts are admitted. The discordances between terminologies when excluding concepts could lead to new algorithms to select the best individual choice to take it into account: (1) excluding the concept and its descendants (exclusions will not be done in certain DB); (2) excluding the ascendant of the initial excluded concept, and all its descendants (some records that should have been kept will be ignored); (3) avoiding any exclusion (some patients will be wrongly selected). Nevertheless, the choice to exclude a concept or not is very dependent of the kind of study, and a very good knowledge of the coding with all the terminologies involved is needed.

Acknowledgements

SOS is a Research and Development project funded by the Health Area of the European Commission under the VII Framework Programme. http://www.sos-nsaids-project.org/ Grant Agreement number: 223495, Health-2007-4.2.2. The authors declare no conflicts of interest.

4. An Attempt to Expedite Signal Detection by Grouping Related Adverse Reaction Terms

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Background: A variety of terms in medical terminologies can describe the same suspected adverse drug reaction. Disproportionality analysis compares the observed report rate of a drug and adverse reaction together to an expected value based on their marginal report rates in the database; a certain number of reports are required before an association can be detected. The objective of this study was to determine to what extent grouping related adverse reaction terms could expedite the detection of disproportional reporting for historical safety signals.

Methods: We carried out retrospective disproportionality analysis for 43 historical European labelling changes[1] each related to one of 13 medical concepts identified as important to monitor and with medium to high probability of being drug-related.[2] The analysis was based on a full extraction from the WHO global ICSR database, VigiBase™, with 4,978,565 reports up until 2010-02-05. We used the Information Component (IC) measure of disproportionality, as in routine screening of VigiBase,[3] but with adjustment for country of origin and year of submission to VigiBase (simultaneously). MedDRA® High-Level Terms (HLT), Standardised MedDRA Queries (SMQ), and Preferred Terms (PT) related to each medical concept were considered. For custom groups (CG) of PTs, for HLTs, and for SMQs, data were aggregated prior to analysis, whereas separate analyses were performed for individual PTs, classifying the medical concept as highlighted at the PT-level if an association was detected for any related PT.

Results: Grouping related adverse reaction terms did not expedite signal detection, on average. Individual PTs highlighted 8 associations earlier than did HLTs and CGs compared to 6 or 7 later, respectively. The corresponding numbers for SMQs were 11 compared to 5. All in all, individual PTs detected 25 of the 43 labelling changes compared to 23 for both HLTs and CGs, and 19 for SMQs. Individual PTs performed particularly well for the 10 labelling changes related to *bullous eruptions* out of which they detected 6. Figure 1 illustrates how individual PTs outperformed groupings in the case of the labelling change for *peripheral neuropathy* with *efalizumab*. The *demyelinating polyneuropathy* and *Guillain-Barré syndrome* PTs are highlighted for *efalizumab* in 2008, whereas the HLT and CG for *peripheral neuropathy* are not highlighted even at the end of the study period; a likely explanation is the low observed and high expected counts for the broader *neuropathy peripheral* PT, which is included in both the HLT and CG.

Conclusion: No net gain was observed in timeliness from aggregating adverse reaction terms. Time gains did occur when the grouped adverse reactions were closely similar, in a clinical sense, but even then, substantial gains were rare. To the extent that timely detection by individual PTs is due to the inherent multiplicity in screening related terms separately, grouping truly related terms would better protect against spurious associations.

Acknowledgements

The research was conducted as part of the PROTECT consortium. It has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu). The authors declare no conflicts of interest.

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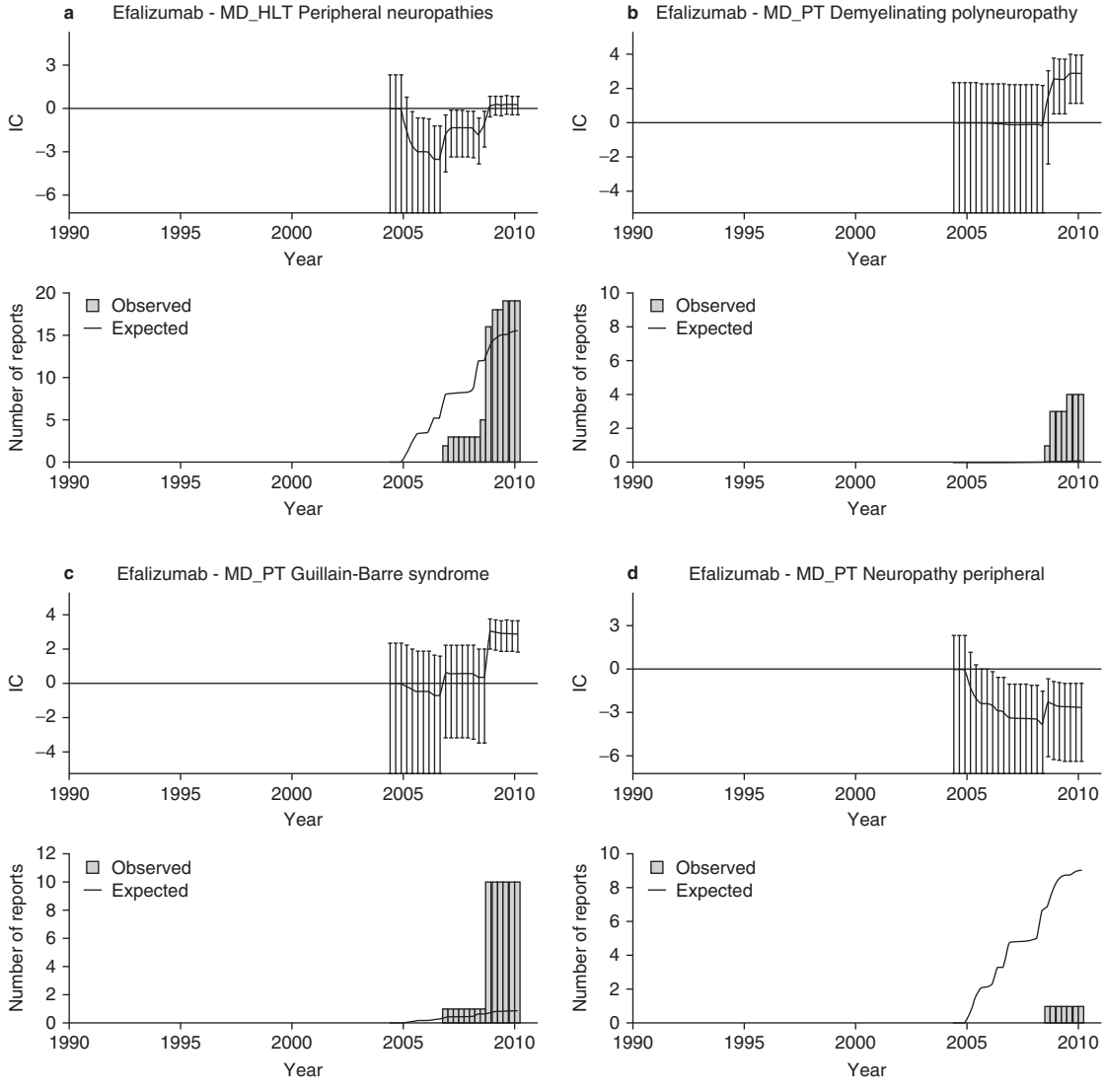

Fig. 1. Peripheral neuropathy with efalizumab is highlighted by individual PTs in 2008 but not at all by the HLT, presumably because of the high expected count for the neuropathy peripheral PT (see abstract no. 4).

5. Evaluation of Automated Term Groupings for Detecting Upper Gastrointestinal Bleeding Signals for Drugs

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Introduction: Case reports are usually coded with the MedDRA® terminology (Medical Dictionary for Drug Regulatory Activities) and stored in databases that constitute putative knowledge on adverse drug reactions (ADRs). Groupings of MedDRA terms already exist and are called Standardized MedDRA Queries (SMQ).[1] They are made manually by experts, but do not cover all medical conditions or may not have the required specificity to cover a safety topic. To support the generation of new SMQs in an automated way, we have developed an

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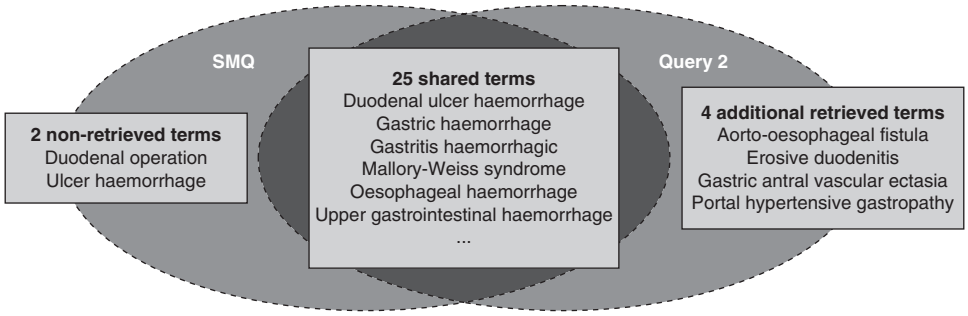

Fig. 1. Venn diagram of SMQ and Query 2 contents (see abstract no. 5).

OWL-DL (Web Ontology Language – Description Logic) representation of MedDRA named OntoADR. The goal of the present study is to compare results between the SMQ and our DL query-based MedDRA terms grouping method by performing an evaluation on the 'Upper gastrointestinal bleeding' safety topic.

Methods: OntoADR contains formal definitions of ADRs based on MedDRA terms and semantic properties from SNOMED-CT® (Systematized Nomenclature of Medicine – Clinical Terms) such as: hasFindingSite (body site affected by a condition) or hasAssociatedMorphology (morphologic changes of a disease). To define OntoADR concepts, we used UMLS (Unified Medical Language System) metathesaurus to extract mappings between MedDRA and SNOMED-CT with a methodology already described by Alecu et al.[2] When the formal definition couldn't be built with this method, it was achieved manually by experts. Two queries were developed to match the safety topic. Query 1 targets hemorrhage in the upper gastrointestinal tract structure.

hasFindingSite some 'Upper gastrointestinal tract structure'
AND *hasAssociatedMorphology* some 'Hemorrhage' (Query 1)

Query 2 aims to add investigations and findings:

{Query 1}
OR
Interprets some 'Occult blood screening'
AND *hasInterpretation* some 'Positive'
OR
interprets some 'Evaluation of stool specimen'
AND *hasAssociatedMorphology* some 'Hemorrhage' (Query 2)

To build the reference grouping (gold standard), we manually selected terms related to the upper part of the gastrointestinal tract from 'Gastrointestinal hemorrhage' SMQ (27 out of 50).

Results: The content of Query 1 and SMQ selected terms was similar (recall: 74.1 %; precision: 83.3 %). Seven terms present in SMQ were absent from Query 1 but five of them where caught in Query 2 (recall: 92.6%; precision: 86.2%) [see figure 1]. Both queries also proposed four additional terms.

Discussion: Almost all MedDRA terms of the SMQ grouping taken as gold standard were returned by Query 2. This result confirms the hypothesis that the modeling of MedDRA terms allows to automatically generate lists of terms comparable to manually grouped terms.

Two MedDRA terms were not retrieved by our queries: 'Duodenal operation' which refers to a procedure possibly related to upper gastrointestinal bleeding treatment; 'Ulcer haemorrhage' which is not semantically defined as a gastro-intestinal-related ulcer in MedDRA. And amongst the four additional terms retrieved by the two queries (see figure 1), only 'Erosive duodenitis' describes a potential ADR. Other terms are not *a priori* related to drugs.

We are currently developing a user interface to assist pharmacovigilance professionals in the creation of such query-based MedDRA terms groupings.

Acknowledgements

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6. Inferring Semantic Relations between Pharmacovigilance Terms with Terminology Structuring Methods

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Background: Surveillance of the adverse drug reactions is the core activity of pharmacovigilance and may modify the conditions of use of medicinal products. To strengthen the signal detection, groupings of related terms are used,[1] such as manually designed SMQs (Standardized MedDRA Queries). We propose an automatic method to assist the creation of SMQs. Few work addressed this aspect. We exploit Natural Language Processing dedicated to the

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terminology structuring methods: detection of synonym (terms with close meanings) and hierarchical (terms with general/specific meanings) relations.

Methods: We exploit the list of MedDRA PTs, 84 SMQs (the gold standard) and linguistic resources. The input knowledge is not specific to the pharmacovigilance area. Steps of our method are:

- *Hierarchical relations* are detected with lexical inclusions. If one term (*hepatitis infectious*) is lexically included in another term *(hepatitis infectious mononucleosis)*, there is a hierarchical relation between them: the short term is the hierarchical parent of the long term.
- *Synonyms* are detected through the compositionality, which accepts modifications in a given syntactic position: if *infectious* and *viral* are synonyms known in lexical resources then the terms *hepatitis infectious* and *hepatitis viral* are considered as synonyms.
- *Morpho-syntactic variants* are detected with Faster transformation rules:[2] insertion (*accessory respiratory muscles, accessory muscle*), derivation (*arterial stenosis, artery stenosis*), permutation (*eye burn, burns of eye*).

Clustering relies on hierarchical relations and is than enriched with synonyms. We perform quantitative (SMQ-based) and qualitative (expert-based) evaluation.

Results and Discussion: The generated clusters are smaller than the SMQs and show their different aspects. Across the 84 SMQs, the specificity reaches 92% (average = 54.7%), although their sensitivity does not exceed 42% (average = 12,8%). Variability in performance is important. The best experience is when lexical inclusions and Faster relations are combined. Hierarchical relations form the core of the clusters (96% of the terms) and show 69% specificity. Faster relations are involved in 50% of clusters and show specificity 75-85%. 30% of the clusters contain synonymy relations (specificity 55-69%). For two SMQs, the impact is null.

Typical situations observed with the expert are:

- Many terms proposed by our methods are included in SMQs.
- Our methods can miss the relevant terms when the semantic regularities are not captured.
- When the SMQs miss relevant terms,[3] our methods can find some of these.

We assume the proposed automatic methods may provide a useful basis for the creation of SMQs, because they systematically collect terms which satisfy given algorithmic conditions.

Conclusion: Our methods exploit resources and methods non-specific to the pharmacovigilance area. They generate small but specific clusters which show different aspects of the SMQs. We expect the methods can be exploited for assisting the creation of new SMQs. Several perspectives are being invested to improve the clusters' quality. Generated clusters are being evaluated through their impact on the drug safety survey.

Acknowledgements

The research was conducted as part of the PROTECT consortium. It has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu). The authors declare no conflicts of interest.

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7. Text Analytics for the Detection of Drug Safety Events from Case Reports

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Systematic high-quality collection of individual drug adverse events from scientific literature is a very tedious, error prone and resource intensive mandatory process in pharmacovigilance. We address how to facilitate this process by considering the three main manual tasks: selection of relevant scientific articles, reading of the articles, filling a database. Table I reports the best choice of machine learning algorithms for each task along with their evaluation in terms of precision and recall. With a recall generally higher than 80% we demonstrate that the performance of optimised supervised learning techniques is comparable to that of humans, thus potentially enabling major savings in time and increasing consistency of the pharmacovigilance process.

Cornerstone of this work has been the creation of a golden standard corpus, comprising of almost 3000 MEDLINE records systematically annotated by two experts[1] with over 80% inter-annotator agreement. For document[1] and sentence classification[2] based on this corpus, we found that the optimal classification performance could be achieved with different types of classifiers and different sets of features. Both commercial (Luxid®) and open source (Mallet, JSRE) technologies delivered similar performances for the classification tasks, whereas the JSRE tool for semantic relation extraction outperformed any other implementation.[3] While linguistic features such as lemmatized tokens and parts of speech were shared by all methods, each task also had some unique features. Further details of this work has been presented by Toldo et al.[4] Detailed performance comparison of various softwares as well as the practical impact on predicting label changes are described elsewhere. Ongoing work includes: handling inter-sentence relations, social media; electronic health records; and extending it to Chinese.

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Table I. Performance of supervised learning methods for AE detection (see abstract no. 7)

Task	Strategy	Method/ Implementation	Precision	Recall
Reduce the reading of irrelevant documents	Document classifier trained and validated on MEDLINE *documents* corpus only	Naïve Bayesian / Luxid® Categorizer Mallet	2%	93%
	Document classifier trained and validated on *EMBASE* corpus		2%	95%
	Filtering with metadata on *EMBASE* corpus		8%	85%
	Metadata filtering + document classifier for *EMBASE* corpus		31%	84%
Facilitate reading by automatic sentence highlighting	Sentence classifier trained on MEDLINE *sentences* corpus using shallow linguistic features	Maximum Entropy / Luxid® Categorizer Mallet	82%	70%
Automatic filling of database	Shallow linguistic relation extraction on MEDLINE *relations* corpus	Support Vector Machines / JSRE	86%	89%

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8. Building a Database of Articles from PubMed for Documentation of Adverse Drug Reactions Related to Antiretroviral Drugs

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Introduction: Medical literature is one of the main sources of information in pharmacovigilance, to detect and analyze adverse drug reactions.[1] Search is primarily based on MEDLINE, the reference database for medical publications that contains more than 22 million citations. In a previous work, we found five publications on the occurrence of 'myeloid leukemia' as an adverse reaction related to 'cyclophosphamide', whereas 1,037 publications mentioned 'cyclophosphamide' as a drug therapy.[2] This example illustrates that an exhaustive search on PubMed may be costly and manually unfeasible. Building a database of articles related to ADRs would improve the efficiency of pharmacovigilance teams in decision making. We focus here on Antiretroviral drugs.

Method: We developed a prototype that first reproduces the pharmacovigilance manual search strategies (VigiPubMed), then automatically extracts relevant information from the MEDLINE abstracts which are retrieved (Luxid®), controls it against a set of terminological resources (MeSH, WHO-ART, MedDRA, etc.), and semantically annotates it (Intelligent Topic Manager®).[3] The extraction period was from 01/01/1989 to 31/12/2006. The query used to extract publications was (''anti-retroviral agents''[MeSH Terms] OR ''Anti-Retroviral Agents''[Text Word]) AND ''adverse effects''[subheading] AND ''chemically induced''[subheading]). This set was evaluated by two senior specialists in pharmacovigilance.

Results: The number of extracted articles with an abstract was 985 with 895 articles classified as relevant by both experts (positive predictive value of 91%) and 24 articles rejected by both experts (2.4%). Kappa (inter-annotator agreement) was equal to 0.407. A third expert evaluated 60 disagreement cases, among which 43 cases were false positives (4.4%) and corresponded to three different situations: (1) ADR related to a concomitant drug: the antiretroviral drug was an innocent bystander and another drug was responsible for the effect (16 cases); (2) Event related to evolution of the disease: the disease and not the drug was responsible for the occurrence of the event (14 cases); (3) Non-clinical study (in-vitro study or animal study) [13 cases].

Discussion: Developments are underway to make the results in operational form for use by regulatory authorities and pharmaceutical companies. Figure 1 shows how drugs and medical conditions are annotated by the Luxid tool. Improved graphical user interface should facilitate decision support for professionals in charge of pharmacovigilance issues. The development perspectives of our project will aim at adding other pharmacovigilance-related data sources (such as Martindale®, Meyler's

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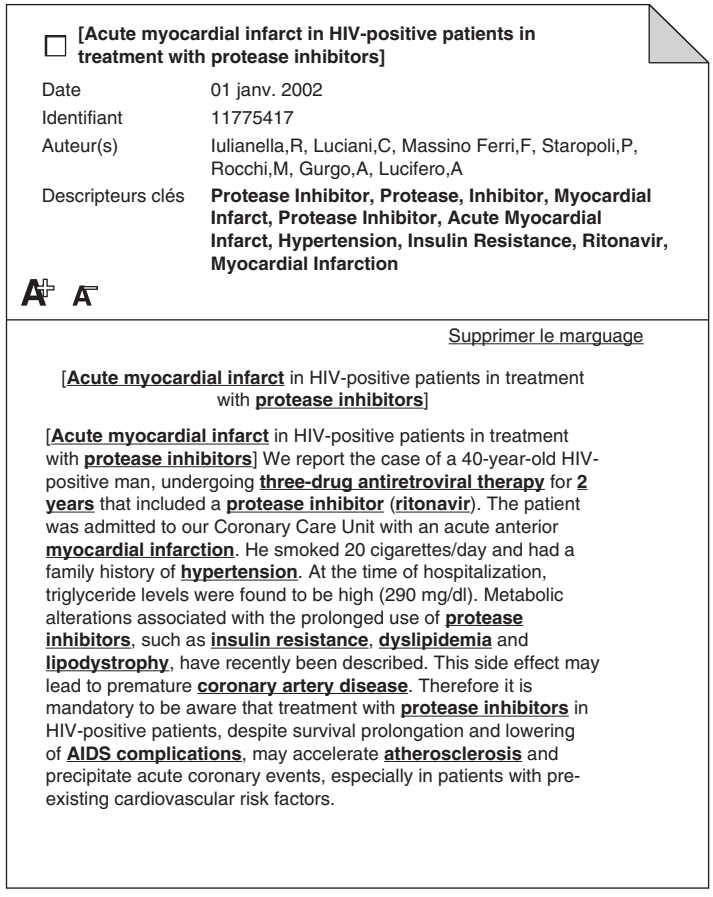

Fig. 1. Annotation of a selected abstract in Luxid (see abstract no. 8).

Side Effects of Drugs®, other databases such as Micromedex®) as a complement to the data extracted from PubMed.

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