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Innovations for the Future of Pharmacovigilance

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Abstract

Post-marketing pharmacovigilance involves the review and management of safety information from many sources. Among these sources, spontaneous adverse event reporting systems are among the most challenging and resource-intensive to manage. Traditionally, efforts to monitor spontaneous adverse event reporting systems have focused on review of individual case reports. The science of pharmacovigilance could be enhanced with the availability of systems-based tools that facilitate analysis of aggregate data for purposes of signal detection, signal evaluation and knowledge management.

GlaxoSmithKline (GSK) recently implemented Online Signal Management (OSM) as a data-driven framework for managing the pharmacovigilance of marketed products. This pioneering work builds upon the strong history GSK has of innovation in this area. OSM is a software application co-developed by GSK and Lincoln Technologies that integrates traditional pharmacovigilance methods with modern quantitative statistical methods and data visualisation tools. OSM enables the rapid identification of trends from the individual adverse event reports received by GSK. OSM also provides knowledge-management tools to ensure the successful tracking of emerging safety issues. GSK has developed standard procedures and 'best practices' around the use of OSM to ensure the systematic evaluation of complex safety datasets.

In summary, the implementation of OSM provides new tools and efficient processes to advance the science of pharmacovigilance.

Post-marketing pharmacovigilance is currently a challenging and labour intensive process, not only industry-wide, but also for regulatory agencies.

One of the reasons for these challenges is the complexity and volume of data. GlaxoSmithKline (GSK) typically receives >70 000 spontaneous reports a year. The traditional process has been largely paper-based and focused on individual case reports, which can be challenging with such large volumes of incoming data.

When looking at raw case counts in 'denominatorless' data, it is very hard to discern whether there is an excess of cases. To solve this problem, a number of methodologies, known as dispropor-

tionality analyses (DPA), have come to the fore. These methods assess the frequency of postmarketing reports against a background of all marketed drugs and adverse events.

At GSK, the multi-item gamma poisson shrinker (MGPS) and the proportional reporting ratio data mining, or disproportionality methodologies, were evaluated, and based on the properties of these two methods, we chose MGPS. MGPS is also the method used by the US FDA, and recently, it has been adopted by the UK Medicines and Healthcare products Regulatory Agency.

When we began our work, in early 2002, there were no off-the-shelf tools for quantitative signal detection. In collaboration with Lincoln Technologies Inc., GSK developed a user-friendly and flexible interface able to perform disproportionality analysis in real time.

The first version of the software (Web Visual Data Mining Environment [VDME]) was made available to a restricted number of qualified staff able to make informed use of it as an exploratory tool for hypothesis generation.

Web VDME was used to evaluate specific questions that could not be answered with clinical trials or by epidemiological studies.

The availability Web VDME, a tool that could be used for rapid-in house disproportionality analysis, led to evolution of our company view that disproportionality results should be available to all safety evaluation staff. Initially, we provided these scores to staff using paper-based line-listings. These listings were cumbersome to work with, and required staff to use several other systems to investigate any leads generated with the disproportionality results.

As expected, the paper-based process created voluminous outputs for high case-volume products. In addition, some reviewers were required to look repeatedly at the same signals, with no way to document that they were aware of or had reviewed a particular issue.

These challenges led GSK to design Online Signal Management (OSM), a new pharmacovigilance-systems platform that would enable users to access: (i) a prioritized list of safety issues based on medical significance; (ii) disproportionality scores for all safety issues; (iii) case details and narratives through an easy to use data retrieval and case drill-down; (iv) state-of the-art visualisation tools to identify patterns and trends in the data; and (v) automated alerts to highlight new trends in the data. The tool was also designed to enable in-stream documentation of decision making providing a framework for knowledge and work-flow management that had not previously been possible.

OSM uses automation to filter and prioritise the events based on seriousness, listedness, disproportionality score and trends over time. The aim is for users to receive the information, document/manage the work and knowledge online while giving priority to the new and important safety issues. The interactive visualisation tools permit filtering and ‘drill down’ to individual cases. Non-serious events have less priority than serious events, although they are also screened routinely.

The input given by users throughout development resulted in the creation of a comprehensive process-map, which has been used as a guidance document for training staff. We provided a hands-on training programme, after which staff were able to independently use the OSM tool. In the course of training, we highlighted that DPA results are just one factor to be used in the assessment of safety issues, and that they should be used in conjunction with medical judgment, and other information known about the product.

Early evaluation of the OSM confirms users’ satisfaction with the integrated analysis capabilities in OSM. Preliminary metrics of the time needed to perform routine pharmacovigilance reviews suggest that OSM requires considerably less time than our

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prior methods, without the burden of having to sort through 'reams' of paper.

In summary, GSK has created a powerful new approach to pharmacovigilance, integrating traditional, case-based pharmacovigilance methods with disproportionality and data visualisation tools. These tools exist within a system framework that facilitates in-stream review, tracking of safety issues and knowledge management.

This very innovative tool and the processes that we have developed for its use will help to advance pharmacovigilance by improving efficiency and providing new analytical capabilities that have not previously been available.[1-3]

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