ABSTRACT
Issues associated with drug safety continue to make headlines in the media. Combining SAS advanced analytics with new Data Integration and Business Intelligence capabilities yields an efficient way to detect drug safety signals and investigate their cause. The resulting software solution includes:

- data import from drug safety systems
- metadata management
- updates of drug safety data marts
- execution of industry-standard and new signal detection algorithms
- ranked lists of possible safety signals
- drill-down to supporting information and patient detail

During the presentation, Eric and David will discuss a case study using veterinary drug data. They will highlight the architecture, user interfaces, and analytical methods and review them with respect to success and applicability.

INTRODUCTION
SAS has provided statistical and reporting capabilities to pharmaceutical companies and regulators for drug safety analysis for many years. Recent developments have increased the need to expand how SAS software is utilized because of the following changes:

- The FDA and drug companies are under increasing scrutiny and criticism by the public, the media, and government
- More safety data is collected during clinical trials and after approval
- Basic adverse event reporting systems are commonly utilized and working well
- The volume of data is overwhelming
- Reviewers need help focusing on real issues

THE CHALLENGE
To monitor the safety of drugs, safety reviewers traditionally relied on their medical expertise and visual observation. Although this process is still critical, reviewers cannot absorb all of the data or see all subtle emerging trends. To optimize the use of valuable medical and epidemiological resources, companies and regulators need ways to narrow the possibilities or find growing problems sooner.

As a step forward, safety reviewers enlisted programmers to create reports or run queries based on their instincts or hunches. Although better than manually scanning through reams of paper, the process is slow and still requires manual guidance and imagination.

Reviewers need an automated filtering mechanism that improves efficiency by helping to detect growing trends sooner and decreasing time wasted on false signals. Some pharmaceutical companies employ a team that performs regular data mining activities on safety data, but not all companies can justify creating a dedicated analytical team. As an alternative, automated signal detection provides a proactive, yet cost-effective approach for any risk management plan.

DETECTING SIGNALS
According to the Report of CIOMS Working Group IV (1998), a safety signal is defined as:

“A report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance.”
Determining when a report is “worthy” is the challenge. Epidemiologists and medical practitioners make the final call as to “worthiness,” but automated safety signal detection can provide a preliminary prioritization of “worthiness” through advanced analytics and signal detection algorithms. Also, as Hauben and Bates (2007) state,

“Sensitivity is of fundamental importance in achieving these goals, but practical reality dictates that the search for truth in pharmacovigilance requires judicious limitations on the numbers of associations that we investigate.”

Given the number of products that regulators and safety reviewers must monitor, automation is critical for the safety of patients. Based on this fact, it is not the value of automated signal detection that should be evaluated, but the quality, effectiveness, and usability of a particular automated system.

QUALIFYING SIGNALS
Because their workload is already heavy, reviewers aim to minimize the number of less-qualified signals that they must pursue. They look for higher quality signals that lead them to real issues faster. Part of the automation, therefore, must find a signal and perform as much refinement and qualification as possible prior to creating an alert. At a minimum, the signals should be prioritized, so nothing is omitted incorrectly.

UNIQUE CHALLENGES WITH VETERINARY DATA
In this presentation, we discuss a specific case study for a veterinary pharmaceutical company. Because the drugs can be administered to multiple animal species and sometimes accidentally to humans, the signal detection process must enable separate or grouped analysis per species. In addition, the analysis may need to cross the species boundary in order to evaluate the overall effect of a specific compound.

In addition to species, many veterinary reports are submitted for a large herd or flock. For example, one case may describe how a farmer administered a product to a herd of 500 cows and noticed reactions on 10. Signal detection methods must account for this type of case, which does not typically occur with human products.

THE SOLUTION
In addition to the powerful analytics within SAS software, SAS Business Intelligence and SAS Data Integration provide new options for the automation, flexible development, and resulting usability needed for a patient safety signal detection system. SAS Enterprise Miner and SAS Text Miner are recommended optional components. In general, the system uses SAS Data Integration to:

- load new data from the customers safety system into a detailed data store
- clean, standardize, and transform the data
- run signal detection algorithms on predetermined combinations of products or product groups
- create data marts that contain summary results from the signal detection, as well as supporting data marts for exploratory reports

The system uses SAS Business Intelligence to display results, provide logical workflows, and enable exploration of signals. In most cases, SAS Stored Processes enable flexibility and full validation when generating results and displaying web pages and reports.

The signal detection components described here fit within a larger patient safety solution provided by SAS.

WORKFLOW FOR GUIDED ANALYSIS
The solution provides several workflow pathways for reviewing and exploring signals. Figure 1 shows one workflow that provides the reviewer with an overall summary of products and product groupings ranked in descending order of perceived risk. The first page that the reviewer sees is referred to as the Product Signal Summary, whose information is based on a compilation of results from the signal detection algorithms for all products and product groupings. The risk index is based on a weighted composite of multiple signal detection algorithms.
Vet Drug Safety Signal Detection
Sample User Interface Workflow

After the Product Signal Summary page, users drill-down by clicking on various fields to get more detail about signals. In the central flow, users click on a product to see a list of Adverse Events (AEs) for that product or product group along with the associated signal scores. From that page, users either click on scores to see explanatory graphics or continue to drill down to a list of cases for a selected adverse event. For large numbers of cases, the system shows clusters of cases that may be related.

If a user clicks on a case number, the system displays a detailed view of the case information, including any narratives provided by the reporter. Graphic representations are available at all levels of the workflow.

Different workflows are provided so that users can choose how they want to pursue the investigation. Providing “guided analysis”, the system provides high-level indicators backed by supporting evidence and explanation. Because the detailed data store and data marts are permanent structures, reviewers also have the option of performing ad hoc queries directly against the data, outside of the workflow.

In addition, the stored processes that are listed in Figure 1 can be executed from within SAS Enterprise Guide, Microsoft Excel, or other components of SAS.

**ANALYTICAL METHODS**

The system offers pre-built analytical modules and screening algorithms. These modules and algorithms can systematically and independently detect potential adverse drug event signals out of several millions of drug-event combination pairs generated from a spontaneous adverse event reporting database or proprietary safety and clinical trial safety databases. Depending on the entry point your company has implemented, some of the routines can also...
be used to investigate associations involving multiple adverse events (for example, adverse events syndromes and polytherapy), as well as adverse events that may be drug-induced or drug-drug interactions induced.

Analytical methods for screening drug-event associations and for disproportional reporting include industry standard signal detection routines, such as:

- the proportional reporting ratio (PRR) method
- reporting odds ratio (ROR) method
- multi-gamma Poisson shrinker - empirical Bayes geometric mean (MGPS-EBGM)
- Bayesian confidence propagation neural network –information component score method

In the case of spontaneous reporting systems, these algorithms produce statistical scores that quantify the degree or frequency with which a drug occurs with a particular event relative to the expected frequency based on independence model. For clinical trials signal detection, the screening process compares the degree to which patient population on a drug regimen experience adverse events at a rate higher than the patient population on placebo or a comparator drug.

In addition to these methods, the system also employs a statistical detection outlier measure, known as an adjusted residual score, for detecting drug-event pairs with unusually large values that may appear as potential safety signals. The utility of this algorithm is the ability to identify outliers that help point reviewers to the source and the underlying patient reporting population for further investigation.

The signal detection algorithms and process framework implemented in the SAS solution platform also extend the utility of current and industry standard safety algorithms to move beyond signal detection to signal prediction. With the advanced entry point platform, safety professionals are presented with opportunities to build a variety of predictive and risk models for testing different hypotheses involving one or more drugs with specific adverse events and their outcomes. Such models can be deployed to proactively monitor trend and safety profile of the drug product while the drug is still being marketed, as opposed to reacting to unexpected or unanticipated safety issues that may surface (“reacting to the past”).

ARCHITECTURE AND DATA FLOW

The system is based on the multi-tier SAS Intelligence Platform. Most of the heavy lifting is performed with SAS Data Integration, while the presentation relies on SAS Business Intelligence, as shown in Figure 2. The system can also be integrated with SAS Drug Development if that software is in use.
CONCLUSION

Combining SAS analytics with SAS Data Integration and SAS Business Intelligence offers a new opportunity to improve patient safety. Through automation and guided analysis, reviewers can increase efficiency by focusing on real problems rather than false alarms. In addition, reviewers can investigate signals more easily, thereby saving time and increasing the understanding of drug-AE relationships.

REFERENCES


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