Establishing Case Quality Metrics
The Sciformix experience

Introduction
Measurement of case quality in pharmacovigilance is a relatively new development. Before pharmaceutical companies began outsourcing their case processing operations, the only measure of effectiveness of their internal operations was compliance with regulatory reporting timelines. Now that these operations are performed by vendors, over the last two years vendor management organizations within pharmaceutical companies and Health Authorities have come up with a way to measure the “quality” of Adverse Event (AE) cases. This paper captures our experience and learning in defining and using case quality metrics while working with large and small pharmaceutical companies. The inherent challenge in defining objective case quality metrics arises from the subjective nature of the work and from attempting to balance sponsor expectations vis-à-vis operational efficiencies.

Until about 2009 compliance to reporting timelines of expedited reports by the Marketing Authorization Holders (MAH) was the only valid metric of the effectiveness of an AE processing operation evaluated by global health authorities (such as USFDA, EMEA, UK MHRA). The International Conference on Harmonization (ICH) defined time limits for reporting adverse events which varied from 7 days for death/life threatening adverse events from clinical studies to 15 days for serious, unexpected events from marketed products. This changed in 2009 due to the public focus on drug safety led by recalls of prominent drugs like Avandia, Vioxx etc. The regulators began to look closely at the way the pharmaceutical companies were classifying cases as reportable under the existing guidelines (serious unexpected adverse events) as against adverse events listed on the drug label, which are normally not reported individually but are compiled into aggregate periodic reports. There were instances where pharmaceutical companies used
questionable criteria to “downgrade” reportable adverse events to non-serious, periodic adverse events for which they were cited by the USFDA during inspections. As a consequence, the health authorities began looking closely at “case quality”, i.e., the appropriate disposition of the case, in addition to monitoring that the established timelines for regulatory reporting are met.

Annual reports produced by industry benchmarking organizations also seldom paid attention to case quality until 2009. These reports which summarize the state of AE case processing across large and small/mid-size pharmaceutical companies measured and benchmarked timeline compliance across the industry groups, but never looked at “case quality”. Beginning 2009, when the UK MHRA and EMEA (Volume 9A) provided guidance on what they considered “acceptable” case quality, much of the industry used ad-hoc measures to assess the quality and overall disposition of the cases. More recently (Feb 2011), the MHRA published ‘Best Practice in Reporting of ICSRs’ that outlines quality expectations in the context of E2B submissions. In view of the subjective nature of case assessment and further variability that is introduced in the process when it’s outsourced to third parties, regulatory authorities like the MHRA have defined specific expectations of case quality and of third party case processing. The US FDA has not yet defined what they expect from “good” quality cases.

Over the last three years companies have started to baseline their operations and establish measurement criteria to comply with the newly articulated expectations of the health authorities. There is wide variation in what each company expects as operational metrics to measure quality of the cases they report to the health authorities. This is due to the inherent variability in medical assessment of causal relationship between a reported adverse event and a suspect drug as well as assessment of seriousness of the adverse event given confounding factors such as concomitant medications.

**Sciformix Experience**

A service provider like Sciformix encounters many challenges in managing the expectations of our clients for the following reasons.

**Lack of baseline data**

In the absence of benchmarks for what is considered “good quality”, there are differing expectations about the number of cases without errors and about classifying the impact of errors as critical, major and minor. The threshold for error free cases in a specified time period varies widely. One sponsor expected at least 80% of cases to be error-free whereas another client expected that at least 97% be error-free.
Our experience has been that limited or minimal historical data is typically available with sponsors for use as baseline in defining case quality metrics. While it is possible to retrospectively evaluate old case data if available, it is not always feasible to do so since change in conventions/standards reduces the relevance of historical data and internal quality metrics may be lower than desired.

In some situations there cannot be any historical data available to baseline a process. For example, a client may not have an internal process for cases such as those from Consumer Products, Nutritionals etc. because the regulation that harmonized reporting for prescription and non-prescription products became effective only in 2009.

**Subjectivity in the Process**

- An oft-debated topic is the inherent subjectivity in dealing with complex cases (serious/unexpected, clinical trial cases, cases from legal matters sub judice etc.) given the inherent flexibility provided by the medical dictionary, MedDRA. There could be many accurate interpretations of a specific event. A single adverse event can be coded in three or four different ways in MedDRA all of which may be correct depending on the way the data are interpreted. Trying to apply numerical measures to such a subjective process is fraught with challenges.

- Company specific variations in interpretation of regulations often add another level of complexity to the process. A good example is processing and reporting of adverse events published in literature. Most pharmaceutical companies follow the ICH mandate that a case is considered “valid” if the author of the publication has suggested or established a causal relationship between the reported adverse events and the suspect drug. But some companies adopt a very conservative approach and report all references to a drug in the publication, irrespective of author’s attribution of causality and this can lead to challenges in compliance.

- Companies are becoming aware of regulators’ expectations through inspections and other interactions. For example, after Warning Letters were issued in 2009 and 2010 by the USFDA to Pfizer and Sanofi-Aventis, the industry became aware of the agency’s expectations from Safety Data Exchange Agreements between these companies and their alliance/channel partners who sold their drugs in countries outside of the US and Western Europe. As such events occur, companies interpret and react differently.

Measurement of case quality translates into defining and identifying errors and objectively quantifying error rates of an inherently subjective process. Seriousness of an error is determined from its impact on reporting compliance and
Challenges in standardization of case quality metrics across clients

Some examples of the types of challenges encountered while trying to standardize case quality metrics is mentioned below. These challenges are primarily due to difference in interpretation of regulations across different pharmaceutical companies or differences in the way their safety databases and workflows are organized.

Coding of events while processing literature cases

As part of good pharmacovigilance practices and regulatory reporting requirements, companies monitor published literature for relevant safety information on their products. However there are many questions related to this responsibility. A published paper may not specifically describe or discuss causality and adverse events are often mentioned in passing without further discussion since the purpose of the article may not be to discuss safety data. Unlike the usual spontaneous reports which are prompted by a suspicion of drug-related harm, adverse experience data in publications cannot be presumed to have drug-causality.

Conventions often change over time. For example, the approach that one company adopted to coding suspected adverse events from published literature changed thrice over a four year period, and each time the approach adopted was very different from the approach used earlier.

Submission of late reports based on identification of duplicate cases

Given the varied sources of adverse event reports and the complexity and variability of information received from source documents, duplicate cases get entered in the database despite a meticulous duplicate check process (especially through MHRA ASPRs). These duplicate reports are usually identified while preparing aggregate reports. Such duplicate cases need to be nullified and additional information has to be submitted to regulators under appropriate Manufacturer case ID. In such scenarios there aren’t any specific regulatory guidelines on what should be considered as ‘Day 0’ for re-submission of information identified while deleting a duplicate case. A sponsor may require submission of such cases as late follow-up reports with ‘Day 0’ as ‘Day 0’ of the initially processed duplicate case. However these are not late reports if ‘Day 0’ is considered based on the date when duplicate cases are identified. This practice would lead to late reporting to regulators.
Submission of amended cases

Case amendments are changes made to submitted cases when information is identified as being incomplete or incorrect at a later stage. Since this information is not ‘new’ or ‘additional’, these reports are considered as late reports. A client may require that changes to already submitted cases be made on the basis of internal reviews or aggregate reports. Many such cases do not need re-submission as ‘late reports’ since the changes affecting these cases are not substantive. However, when a client adopts such a practice, it leads to late regulatory reporting due to re-submission of such cases.

Case versioning

The configuration of some safety databases does not allow creation of a new case version when follow-up information is received while the initial case is under processing. Let us consider an example wherein the client processes mandate that all the information received until Day 8 is to be processed as a single life-cycle and that the case needs to be submitted to regulators by Day 10. In such a scenario, cases have to be kept on hold at data entry step until Day 8 in order to accommodate follow-up information allowing only 2 days for QC, medical review and regulatory submission. This could create further operational challenges if Day 10 of the case falls on a weekend. Such a process would reduce the number of submissions, but the inability of the database to support case versioning could stress the process if significant information becomes available on day 8 and could adversely impact case quality.

E2B submission process

Cases could end up being submitted late to regulators despite adhering to the timelines due to E2B bounce backs, where an E2B is initially rejected by the EudraVigilance gateway and the corrected submission is not performed in time. For example, special characters or white spaces in the narrative or capturing the e2b code for reported occupation incorrectly may result in such E2B rejections. Certain errors could arise due to safety database quirks or due to lack of standard conventions about how data are to be entered for E2B submissions.

Case Studies

In view of the subjectivity involved in interpretation of regulations and assessment of cases, expectations around when the providers should use their judgment versus when the Client should be consulted tend to be ambiguous. This impacts case quality and standardization of assessment of case quality. We share our experience of establishing case quality metrics in the following case studies.
Case Study 1

This case study pertains to our engagement with a global pharmaceutical company which has a large portfolio of established products that have been on the market for over ten years. The safety profile for these products is well known and there are but a few events which require significant medical expertise in evaluating. The complexity in the portfolio comes from its geographic spread. As a global pharmaceutical company, it sells directly or through alliance partners in markets across all five continents and the strength/dosage forms (tablet, capsule, suppository etc.) vary across markets. Hence access to up-to-date registration data to assess if our client markets a specific strength/dosage form in a particular market is critical to timely processing of the case.

A set of measures to evaluate performance of case processing was defined a year into the engagement. This included review of individual cases across 150 data fields to determine case quality. The general industry practice is to use about 20 data fields which are important to determine the disposition of a case. Based on the learning from this process, the challenges encountered due to subjective evaluation over a two year period and available industry benchmarking data it was determined that the process for measuring case quality should be revised. The intent was to reduce subjectivity and to simplify the process. A three step implementation approach was identified between the client and Sciformix to simplify the process and to develop quality metrics that would be used to objectively evaluate performance.

Step 1: Over a 3-month period a list of 10 metrics was finalized to measure performance. These metrics pertained to, for example, turnaround time, seriousness assessment, coding etc. Each metric evaluated performance against a defined set of 3 to 20 data fields. This was a long and involved process that required multiple iterations to collaboratively define metrics.

Step 2: Creation of a set of guidance documents specifying how these metrics would be operationalized took about 6 weeks.

Step 3: The team was trained and the process was piloted to resolve any kinks.

Once the process to measure and monitor the agreed metrics was implemented, other aspects such as period and frequency of measurement of metrics were discussed. Sciformix built a probabilistic model to determine the sample size to be used to calculate the error rate and the probability of achieving the quality threshold the Client desired.
The key challenges encountered in this process were:

- Lack of a consensus on which quality measures are acceptable; Understanding the trade-off in attempting to eliminate subjectivity from a process which is inherently subjective; this required developing an exhaustive list of scenarios of high subjectivity and getting agreement on how such scenarios should be handled.

- Discussion on regulatory impact of certain expectations of Clients, especially related to label and seriousness assessment.

- Developing detailed work instructions based on the revised client SOPs to help operationalize the process.

Case Study 2

The Client has a portfolio comprising of consumer and OTC products. Pharmacovigilance for consumer products came into focus when the USFDA harmonized the reporting requirements for prescription and non-prescription products in 2009, thereby mandating that the Consumer product portfolios of companies comply with the same reporting regulations as the Prescription products. The client established new processes and systems to comply with this mandate. In this case, due to lack of baseline data for measuring case quality, a quantitative measure for the first ninety days of operations was established with the expectation that this stabilization period would be used to develop case quality measures. The initial measure was based on rework on cases.

From the experience in the initial period, key data elements were identified and were categorized based on their impact on regulatory reporting. Each category was assigned a threshold expectation. For example, not more than 2% of the cases could have critical errors which impact regulatory reporting. The metrics thus defined were further refined at the end of one year of operations based on learning and process changes. The expectation is that case quality metrics and thresholds would continue to be revised annually as the process evolves.

Case Study 3

We adopted a very different approach for a biopharmaceutical company with a portfolio comprising of complex molecules where the majority of the case volume comprises of adverse events from clinical trials. The Client had evolved a set of metrics and thresholds based on their prior experience of working with service providers. Sciformix and the client then jointly refined the framework based on our collective experience. The framework defined timeline and quality metrics along with the thresholds that
These case studies indicate that the methodology used to measure case quality can vary widely and it may take several months or even years to arrive at a consensus about acceptable quality metrics can take several months or even years.

Defining case quality metrics is an ever-evolving process which needs continuous refinement as processes and regulatory requirements change.

Quality metrics across engagements are seldom comparable as each client desires to measure different aspects of the process.

There is considerable variance in the process, the thresholds and the definition of what constitutes a “good” case. When determining case quality, a sample of cases from a specified time period is typically reviewed by an external Quality Assurance specialist. We used probabilistic models to demonstrate to our clients how the sample size impacts the decision about thresholds for case quality.