A White Paper on

Concise Signal Management & Quality Database: A prerequisite to Signal Detection

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Introduction

"PRO-ACTIVE DETECTION OF A SAFETY WARNING CAN BE A SAVIOR FOR PREVENTABLE HEALTH HAZARDS"

We are indeed grateful to the ultimate offerings in technology. We live in a Virtual world where timely reporting in a predefined format can protect humanity from irreversible damage in addition to ensuring compliance.

Alarming drug/medical device/veterinary safety issues should necessarily be captured in a mechanism where effective analysis and assessment possibly leads to conclusive results and corrective actions.

Pharmacovigilance in the past two decades has been refined to include many sub-topics such as risk minimization, risk management, aggregate reporting, case management, safety assessment, signal detection etc. Furthermore, regulatory offers a set of guidelines in the discipline, compliance to which is an industrial obligation.

Signal management is one such facet of pharmacovigilance system which enumerates number of processes. Streamlining of these processes is vital to detection of a Signal, its transmission to a larger database where it can be archived for future perusal or further processed for making critical decisions based on the analytical tools applied.

KEY OBJECTIVES

Signal management in nutshell

Contribution of stakeholders with special focus on Healthcare professionals and consumers who can ensure quality data for adverse event reporting and eventually signal detection activity…

Salient features of technology so as to optimize work resources for effective signal identification and systematic implementation of procedures.

Signal: a concise review

As per Module IX of Good Pharmacovigilance practices, a 'signal' is:

- ✓ The information that arises from one or multiple sources (including observations and experiments)…
  - which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events
  - Either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

- ✓ Further, as stated by the European Medicines Agency, a safety signal is information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation.

Thus, signal as the term literally suggests, can be an important navigator of the consequences of a marketed drug product to be witnessed, where some action may be necessitated to investigate the signal and avail means to identify and treat potential safety issue(s).

However, as the definition above of signal indicates, it may not always be a safety concern. Instead, it could be a **probable beneficial effect of the drug** and thus, may come as a blessing in disguise.

Signal management summary

The guidance (GVP IX) talks about signal management processes, means to ensure that processes are documented and carried out systematically, and role of MAH and European Union (EU) regulatory network. Every stake holder in the industry has to be aware of the fact that it is a joint endeavor of the industry, HCPs and Regulatory agencies and the task cannot be put to action without ***technology-driven team work approach.***

If we summarize the whole mechanism of Signal management with reference to the guidelines, there are in all six processes involved. **Table 1** gives a macro-overview of the factors to be considered while evaluating each stage.

Usually, though not always it is required that the steps follow the sequence as shown below. As documented in guidelines, the sequence may overlap depending on a number of other affecting factors

Steps in signal management process (table 1)

	Signal Management Stages	Considerable factors
1	Signal Detection	✓ Detailed ICSR review or statistical analyses (rationale method) of a large dataset or both ✓ Quality ✓ Documentation ✓ Period of SD activity ✓ Clinical judgment
2	Signal Validation	✓ Clinical relevance ✓ Extent of previous awareness about signal ✓ Availability of other relevant sources of information ✓ Magnitude and clinical significance ✓ Signal requiring continued monitoring ✓ Robust tracking system to capture the signal validation outcome
3	Signal analysis and prioritization	✓ Impact on public health and/or disease condition ✓ Impact on the benefit-risk profile ✓ Significant clinical association ✓ Novelty of a suspected adverse reaction ✓ Increased frequency or severity
4	Signal assessment (Evaluation of a validated signal)	✓ Assessment of pharmacological, non-clinical and clinical information ✓ Assessment to link the information available to significance of the signal ✓ Potential risk(s) to be timely addressed to prevent/minimize the adverse outcome, if any
5	Recommendation for action	✓ Given by PRAC and published on website in agreement to CHMP (Committee for medicinal products for human use) and CMDh (Coordination group for Mutual recognition and decentralized procedures – Human) ✓ Need may arise to consider(recommendation) intermittently and not necessarily at the end to take a corrective and/or preventive action (CAPA) ✓ Actions followed by a timeframe for compliance to recommendation
6	Exchange of information	✓ Exchange of important information between competent authorities and Marketing authorization holders

1. Roles of individual stakeholders:

Prime focus on the healthcare professionals and patients/consumers

A Signal is generated from a database of adverse events. Accuracy and completeness in collecting single event reports would actually mean accuracy in detecting the appropriate signal from the database. The statistical approaches used for signal detection include application of disproportionality analysis, Bayesian methods or other appropriate methods for signal identification. The HCP and consumer themselves have to have an understanding of importance of Pharmacovigilance to impact upon correct and timely reporting as a pivotal aspect of Signal management.

1.1. Health care professional

1.1.1. Vigilant safety reporting

Health care professional is predominantly responsible for vigilantly reporting any potential serious as well as non-serious adverse events that will find place in the database of MAH/Regulatory and may qualify as a safety signal later on applying data mining techniques. Since they are the first point of contact for the patients being prescribed the newly marketed drug or even when the patient is a part of consented clinical trial study, the onus substantially lies on them to orient and educate their patients to notify them of any adverse event in the immediate stage of occurrence, irrespective of its seriousness.

Patients may not be aware about reporting to a Company or a Regulatory but will definitely inform the prescribers about any atypical symptom or discomfort. It is then the clinician who will analyze this patient verbatim preferably supported by a confirmatory evidence to finalize whether or not this should be reported or is a sheer outcome of disease or other associated factors. One of the online article mentions that FDA considers database as one of the critical element ensuring safety of marketed drugs.

1.1.2. Clinical discretion matters!

The clinical judgment also carries weightage in decision making progress of a signal in its latter stages. Health care professional's view point is also captured in reporting adverse event to Regulatory and Ethics Committees. Spontaneous reporting coming from the medical practitioners hold immense significance as they utilize their sound medical judgment in evaluating causal association between suspect drug and adverse event. HCPs should be accessible to answer any of the queries generated during case processing to capture the event accurately in the database.

Though most of the times, the study criteria are stringently defined based on the pre-

clinical and phase studies in clinical trial of a drug product to cover most of the safety laboratory tests; clinical prognosis is required to analyze the need of any specific laboratory test at a particular visit time or later, in the PMS phase. e.g., periodic diabetes profile may be recommended at the discretion of a clinician if the molecule has shown high blood sugar levels in pre-clinical phase even if it is not demonstrated in the clinical trial study phases. Since, diabetes is a silent killer, practitioner may ask for a diabetic profile tests intermittently as its timely diagnosis is indispensable to assure symptom management and avoid diabetic complications.

1.1.3. Non-awareness of 'What' is reportable

The European Pharmacovigilance legislation necessitate reporting of medication errors resulting into adverse drug reactions (ADRs) to their database. Many a times, the medical and para-medical professionals are unaware about special situations which may also trigger reporting. Such special situations include but are not limited to; lack of efficacy, medication error, over dose, off label use, misuse/abuse etc. Reporter should have clear understanding of what should be reported.

One of the editorial in an online Journal states that pharmacists in United states either did not report an adverse drug event in spite of knowledge and attitude towards reporting or had insufficient knowledge on reporting methodology. Thus, HCPs and para-medics should be acquainted about the reporting criteria as they probably will be first to know of any safety issue. They might have a confirmatory evidence supporting the need to reporting such as a laboratory report, a de-challenge/re-challenge procedure, frequency, severity or rate of occurrence etc. depending upon the drug product class.

1.2. Consumers/Patients

1.2.1. Role of Clinical Pharmacy

Educated and well-informed patients can also be valuable contributors to Pharmacovigilance. Though the practice of clinical pharmacy is still evolving in India, clinical pharmacists in other countries are trained to be patient advisors on medication regime, route of administration, important side effects and other relevant FAQs related to the therapy. Vice a versa, patients in turn want to know in detail about the medicine they are administered and it is this awareness that helps towards effective reporting of adverse events.

In a reported study of spontaneous reporting of adverse drug reactions in United Kingdom, the impact of patients reporting was evaluated. The study did show a significant patient contribution to drug safety if reports from patients were considered in the Yellow card scheme (YCS) in addition to HCP reporting.

In the past few years, the scenario has seen an upside down with pharmacists involving into

community pharmacy, hospital pharmacy, clinical research and direct patient care so as to monitor a drug products life cycle not only until it reaches market but also till its existence in the market. Again, majority patients are no more taking medicines simply prescribed by their family doctors but have serious questions to pose and seek answers for, as the level of education is raised. Again, with the advent of media and internet, they have free access to drug facts just with a finger touch!

1.2.2. PARA-MEDICS: CONTRIBUTORS TO SAFETY REPORTING

Apart from health care professionals, absorption of para-medical professionals in different health care sectors indicates that they can also report adverse events due to drug/vaccine/biologic/medical device that they become aware of, as a part of this inter-related system.

The figure below lists the professionals, who based on their qualifications and experience can willingly contribute to spontaneous adverse event reporting system and hence impact generation of a quality database, ultimately useful for pulling out potential safety data using statistical tools.

One cannot refuse but only reinforce the involvement of ground medical and para-medical professionals in a robust pharmacovigilance pillar built up.

Stakeholders contributing to a Quality Safety Database (figure 1)

Now that the need to reporting is already emphasized and dealt with, we need to sensitize the resources to 'how' we can ensure procedural capabilities with thorough compliance. With the advent of technology, keeping in mind the challenges faced in statistical methods to be employed and the limitations of traditional paper system, the pharmacovigilance system can prove effective if e-solutions are implemented

2. Complexities involved

Shaking hands with technology is the need of an hour!

2.1 Regulation Revolution!

Some years earlier, the stream of pharmacovigilance was just evolving and e-reporting was in its nascent stage. Today, the scenario is dynamic with most of the reporting submissions carried out electronically.

The need arose as a result of globalization and harmonization of the regions to have consistency and uniformity in reporting as well as to eliminate duplication in adherence to regulatory compliance in each of the individual countries where the product is marketed.

The Food Drug and Administration (FDA) has amended its requirement and will be accepting only the electronic format submissions with effect from June 10, 2015. Thus, apart from almost all the Regulatory authorities who have organized themselves for electronic acceptance of data, even Industry segment has to ensure that all the adverse event data is stored, secured, maintained and analyzed on an electronic platform with confidentiality and authorized access. Compliance to audit trails and e-signatures as per the 21 CFR part 11 requirements will have to be assured by technology solution providers.

The Science of pharmacovigilance and technology are two sides of the same coin.

Regulatory adherence, patient safety and risk minimization can be dealt in time if safety reporting is automated

Rigorous safety timelines can be implemented using the tools of technology to accomplish patient safety goals

2.2 Embracing the electronic reporting system

There are two ways to carry out pharmacovigilance activities:

- Paper reporting
- Electronic reporting

The former is now becoming gradually obsolete, time-consuming and prone to errors as new

regulations demand increased reporting fields.

PLUSES: In contrast to above, the electronic reporting facilitated via software solutions is time-saving, instantaneous, meet the current authority norms and is more applicable for a global pharmacovigilance platform.

Hence, sophisticated Software applications are your ultimate answer to deal with adverse event reporting timely, accurately and vigilantly.

PvNET is one such viable software application that eases Industry's requirements to drug safety reporting and knows how to simplify it with minimal need of end-user training.

Its in-built Signal detection module helps identify a signal by quantitative and qualitative signal detection, saving time and manual efforts. The latter can then be invested in other strategic and planned activities.

There lie absolute benefits in shaking hands with technology solutions for pharmacovigilance regulatory compliance especially for complex tasks such as Signal detection, as compared to the conventional and soon to be obsolete paper system:

PROVIDING COMPETITIVE EDGE

- Robust Signal Detection activity embedded in the software solution, unlike other technology solutions which provide a separate module
- Cost effective upgrade option as and when there are major amendments in regulations

MEETING REGULATORY NORMS

- Validated, 21 CFR Part 11 compliant solution facilitate Generic pharmaceutical industry's bulk products pharmacovigilance

PERFORMING COMPLICATED STATISTICAL ANALYSIS

- Complex statistical tools can be applied to investigate innumerable drug-adverse event combinations showing potential safety concern, to detect a signal or evaluate an enhanced

frequency of occurrence.

- The qualitative signal reporting can also be carried using the system applications to evaluate any new and important data with respect to nature of new AE/ADR, severity of AE/ADR or the specificity of AE/ADR

- Customized system generated line listings filter the important data and other pertinent suspect drug information benefiting the medical reviewer to spend more time on analysis and further decision making.

Boon to Generic Pharmaceuticals– Multiple Drug Adverse Event Analysis in ONE SHOT!

- Proportional reporting ratio (PRR) can be simultaneously run for all of the Company's drug products instead of one at a time

- Signal identification, reporting and monitoring through period-wise and cumulative listings is a feasible option

Business driving tool

- Invites lucrative business opportunities using a more technology-savvy approach

- Important to successfully surpass Regulatory inspections and Sponsor's audits

Automated Literature Search - Quick drug-oriented database search

- Literature automation to span across thousands of databases - a valuable time-saving option compared to the manual limitations of literature search.

- Direct data transfer option from relevant literature into case processing – Saves data entry time and deletes possibility of trivial errors that might delay data lock/submission deadlines.

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