Signal Analysis of Pre- and Post- Market Adverse Event Databases: An Overview

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Executive Overview
An objective and reiterative benefit-risk assessment approach is required to adequately balance the benefit of using a product and its associated and acceptable risks. Acceptable risks should ideally be preventable risks where possible, or at least minimal or manageable risks. Defining the safety profile of a drug or biologics product is based on current and new emerging patterns or on changes in old patterns usually deciphered from adverse event (AE) databases or other sources. Adverse drug reaction (ADR)/AE signal detection and evaluation, a process we refer to in this paper as “Signal analysis” is an important process that includes the traditional medical review approach used to identify and evaluate signals and define the initial safety profile of a drug or biologics product and its continued reassessment.

During pre- and post-market stages of drug development, AEs/ADRs are collected and stored in databases, and medical/safety expertise is routinely applied to detect and investigate potential and true signals and other events of interest (EOI). Standardized and customized descriptive, exploratory algorithms and appropriate statistical analysis are signal analysis tools that can be applied in a guided analysis manner to generate descriptive signal patterns and display statistical signal scores, respectively. During the pre- and post-approval stages of product development, the results of a standardized methodical signal analysis process, once adequately assessed by a medical/safety expert, should feed into the benefit-risk assessment process and risk management plan for the product.

This is a simple White Paper which attempts to demystify and simplify the process of signal detection and evaluation of pre- and post-market AE databases, and to present strategies and approaches to achieving this successfully.

Introduction/Background
The Food and Drug Administration (FDA), European Medicines Agency (EMEA), the Medicines and Healthcare Products Regulatory Agency (MHRA) and other regulatory bodies provide regulatory guidance and guidelines to ensure that drug and biologics manufacturers adhere to applicable regulations. In 2005, FDA released three guidance documents on risk management activities\(^1\), which focus on pre-marketing risk assessment, post-approval risk assessment, and minimization of identified or potential risks, respectively. In 2008, FDA started requiring Risk Evaluation and Mitigation Strategies (REMS) for specific drug products as deemed necessary by the agency, and the need for REMS is determined on a case-by-case basis. Essentially, based on FDA Amendments Act of 2007 (Title IX of FDAAA), FDA can require Marketing Authorization Holders (MAHs) to: submit REMS to ensure that the benefits of a drug outweigh risks; conduct post-marketing studies to assess risks and/or signals of serious risks, and identify unexpected serious risks; and add new safety information to labeling as deemed necessary by the agency.

Risk assessment and risk minimization constitute FDA’s definition of risk management. The pre- and post-market signal detection and evaluation process is a critical component of risk identification and assessment. A well-designed and well-executed data mining signal analysis process can generate statistical signals that can be further evaluated to decipher true or potential signals, or EOIs. In December 2008, EMEA released the Guidance on the Use of Statistical Signal Detection Methods in the Eudravigilance Data Analysis System,\(^4\) specifically for statistical data mining of post market spontaneous data. This EMEA guidance focuses on how to apply a quantitative data mining algorithm, Proportional Reporting Ratios, in a spontaneous database, to generate “Signals of Disproportionate Reporting (SDR)”, that is “statistical signals or scores”, and how to interpret SDRs and potential limitations in signal detection and analysis within the framework of such a pharmacovigilance database. Although statistically-generated signals are merely pointers to possible potential or true signals, they can help
medical and safety experts prioritize their detailed drill-down review of individual or aggregated reports, determine the most appropriate case series analysis to perform, and as such expedite their signal (potential or true) evaluation and risk assessment process. The results of evaluation and further investigation of a signal analysis feeds into a risk management process as illustrated in Figure 1 below.

**Figure 1:**

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**Definitions of Signals**

A safety signal for a drug implies that a specific drug-event association is reported more frequently relative to that drug and other events, or other drugs and the specific event of interest. However, whether the safety signal (e.g., ADR) is due to a specific drug or drug-drug interaction can only be deciphered based on detailed medical review of relevant and appropriate Individual Case Safety Reports (ICSRs), case series analysis, and other available information, including clinical and pre-clinical toxicology data.

There are currently many definitions of a “signal” that for the most part are synonymous. For post-market risk assessment, the FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005), defines a “safety signal” as a “concern about an excess of adverse events compared to what would be expected to be associated with a product’s use. Even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive re-challenge or if the event is extremely rare in the absence of drug use.” The EMEA Guideline (December 2008) defines a “signal” generated by statistical methods as an SDR. As defined by the World Health Organization, a “signal” is “Reported information on a possible causal relationship between adverse event and a drug, of which the relationship is unknown or incompletely documented previously.” ([http://www.who-umc.org](http://www.who-umc.org))
Signal Analysis Methods

Signal analysis procedures should be implemented during the pre- and post-approval phases of product development as shown in Figure 2 below. Standardized, methodical descriptive algorithms and appropriate statistical methods should be applied in screening of data, both pre and post market data, and also should feed into an iterative benefit-risk assessment.

Statistical signal analysis methods applied in spontaneous databases are considered exploratory and not confirmatory. Exploratory signal analyses of adverse event databases for hypothesis generation can be integrated into traditional medical review and the risk assessment process. It is important to emphasize that statistical signal analysis scores, or SDRs, are primarily used for generating plausible hypotheses regarding a potential safety issue or concern. As such, statistical signal scores generated should not be directly used to define or compare the safety profile of any product without careful medical review and evaluation in the appropriate clinical context.

Figure 2:
Critical Questions about a Signal
The results of a signal analysis from a dataset that is riddled with data errors and which is not validated is not valid. Prior to starting and when performing signal analysis and evaluating safety data, a signal analyst or medical/safety reviewer should seek to answer critical questions that include the following: Is the dataset validated and appropriate? Are there major data errors or data violations within the dataset? Are the events and medications in the dataset appropriately coded using standardized and validated dictionaries such as the Medical Dictionary for Regulatory Activities (MedDRA) and WHO-Drug Dictionary (WHO-DD), respectively? Is the analysis dataset comprehensive, and/or cumulative or non-cumulative? Which statistically significant signals translate to true clinical significance based on available clinical data? Does the strength of a signal remain the same or does it change with time progression; that is, does it weaken or get stronger? Are there any confounding factors? Are there other possible contributing factors? Is a signal due to a specific drug or drug-drug interaction? Is a signal a new signal or known signal that is showing a new pattern?

Signal Analysis in Pre-Market Databases
A standardized approach to analysis of clinical trial data for potential safety signals is important to ensure that all signal analysts apply a reproducible and documented approach. Also, detailed review of the signal results should be performed by medical/safety experts. From the perspective of the FDA Good Review Practices (GRP) Guidance, there are two main aspects of clinical safety review: “a) to identify and assess medical significance of the AEs/ADRs reported in clinical trials, both placebo-controlled and uncontrolled studies; and b) to evaluate the sufficiency of safety evaluation conducted.” Therefore, when performing pre-market signal analysis it is essential to also analyze and evaluate safety data from the perspective of the expert regulatory reviewer. The FDA GRP Guidance document describes approaches that integrate safety findings across all studies and other clinical experience. It emphasizes the critical importance of considering safety findings in individual studies, with appropriate integration of the overall safety experience, that is, pooled studies safety data analysis. Furthermore, it is of critical importance to identify and translate statistically significant AE/ADR signals into true potential or identified risks based on expert clinical reviewer interpretation of safety analysis data, pre-clinical and toxicology data, and other available documented corroborative medical literature evidence.

The Benefits of a Pre-Market Signal Analysis Tool
Assessment of the safety of a product and development of the initial safety profile of a product is essential for its regulatory approval, and continued post-approval commercialization. It is also an ethical and legal issue to ensure that a drug product is safe and that the benefit of using such a product for the most part continues to outweigh its known and associated risks. Systematic efforts should then be put in place to try to continue to identify new risks or any changes in the known safety profile of the product. Careful evaluation of signal analysis results feeds into the development and update of the safety section of the Investigator’s Brochure, creation of the Development Core Safety Information document, initial Regional or Global Safety Surveillance Plan, Company Core Safety Information document, pre-approval Risk Management Plan (Development Risk Management Plan), Early Post-marketing Surveillance Plan, or Early Passive or Active Pharmacovigilance Plan, and other routine assessment and reevaluation of safety data.

A pre-market approval signal analysis process adds to the traditional review process for:

- Standardized routine signal detection and evaluation approach that is reproducible.
Identification of potential or true signals, or EOIs based on probable or possible association of an AE/ADR and the index product.

Assessment of the medical significance of a signal and a signal strength (where quantified) and unexpectedness, along with review of reporter and company causality assessment.

Evaluation of alternative explanations for causal association of a potential or true signal, or EOI.

Prioritization of potential or true signals, or EOIs, for review by medical/safety experts for further assessment, where warranted, to determine those of any or significant safety concerns.

Increasing Efficiency

A well-defined signal process is supposed to add scientific efficiency to the work of traditional safety and medical experts and data analysis reviewers. As such a signal analysis process should be comprehensive and at the same time streamlined for easy execution. The process should not be burdensome, but rather a facilitative process added to routine traditional medical expert safety assessment work. As illustrated in the schema (Figure 3) below, the use of appropriate signal analysis tools supported by the right technological platforms greatly enhances and facilitates the work of medical and safety experts. The efficiency of routine signal analysis by those who assess and evaluate safety data can be significantly increased. For example, to manually assess and evaluate in detail 1000 patient cases (containing thousands of AEs/ADRs) containing about 3,000 events (MedDRA Preferred Terms) by one individual can take some time. To facilitate this effort, the use of an appropriate signal analysis application can significantly reduce data review and assessment time.

Figure 3:

A Schematic Representation of Increasing Efficiency Using a Signal Analysis Application and Decreasing Efficiency with Only Manual Input Process

Detection of Signals from Pre-Market Safety Data

In the pre-market setting, a true denominator exists: the total subject number (N) exposed to a drug. In addition, the placebo controlled group is used as the background threshold. Signal analysis in this setting involves calculation of incidence based on either individual studies or pooled studies data. In addition, safety patterns are deciphered in demographic subgroups or subpopulations by indication, possible confounding effect of concomitant medications, comorbid factors or medical history burden are also evaluated. Statistical analysis should be appropriately applied. When extensive subgroup analysis is being performed, the impact of the data multiplicity effect should be carefully weighted to minimize the possibility of generating false
positives. In the signal analysis triaging process of pre-market data, expert safety and medical skills are required to understand and interpret the potential or true signal patterns that may be embedded in the data. Although the focus of this White Paper is not on data management, there are also essential data preparations (as shown in Figure 4 below) that need to be implemented to ensure that signal analyses are being performed on standardized and validated datasets. Below is a schematic representation of pertinent pre-signal analysis data management activities.

**Figure 4:**

A High Level Overview of Pre-Signal Analysis Data Preparation

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**Pre-Signal Analysis Clinical Data Collection and Standardization**

Clinical trial protocol data from various sources should be collected based on GCP guidelines. Such data collected either via an electronic data capture procedure or manual case report form entry, should be processed via a validated, comprehensive data management process which includes: validation of all entries or data capture and scheduled edit checks (also ad hoc checks as deemed necessary), adverse event and drug coding using standardized dictionaries such as the MedDRA and WHO-DD, respectively, and data discrepancy reconciliation performed against original data sources and databases (where applicable). Once all data are clean, it is essential to ensure that all data fields and data structure are standardized prior to application of a signal analysis process or procedure.

**Developing Signal Analysis Algorithms**

The FDA's Premarketing Guidance, which deals with pre-approval risk assessment, very nicely discusses safety assessment that should be performed at a minimum in order to evaluate pre-market risk of a drug or biologics product. When developing the signal analysis algorithms to be included in a pre-approval signal analysis process, it is essential to ensure that such algorithms can be applied to individual studies, as well as pooled studies (where appropriate). Pooled studies signal analysis should be done based on acceptable study design similarities and statistical principles. In addition, designing and developing pre-market algorithmic signal analysis procedures should consider background data, which may be placebo or another background comparator. If a signal analysis application is being developed, this should include a comprehensive and robust graphical capability that allows the signal analyst to view data in different graphical format. Color-coded graphics are very powerful visualization tools for uncovering hidden or subtle data patterns that may be embedded within the dataset.
Signal analysis algorithms should include at a minimum analyses that allow the analyst/reviewer to evaluate all relevant safety data. Hence, a comprehensive signal analysis of pre-clinical data allows a series of exploratory analyses and calculation of incidence based on individual studies and pooled data (where appropriate). The role of a Signal Analyst or Safety Data Reviewer\(^5\) should include at a minimum the review and assessment of:

- Serious adverse events
- Discontinuation/dropout events (in clinical trials)
- Frequency or incidence of the events that are, or may be, causally related to the use of the drug or biologics product
- Dosage Analysis: Evaluation of the extent of exposure at relevant doses
- Other Dosage Analysis: Dose, plasma level, duration of exposure, etc.
- Adverse event profile of vulnerable populations such as: pediatric, elderly, pregnant women, etc.
- Adverse event profile of high-risk populations: for example, patients with impaired liver or kidney functions, consistent, spurious or intermittent spikes or abnormalities of hepatic or renal function tests, comorbid illnesses, metabolic status and genetic characteristics, such as, genetic predispositions, etc.
- Cardiac events and related events
- Drug-drug interactions or potential interactions, other drug-related factors
- Demographic analyses, e.g., age, gender, ethnicity, race, etc.
- Concomitant medications burden
- Comorbidity burden
- Rare/sentinel events
- Events whose causality are associated with the mechanism of action or pharmacology of the index drug (Type A events)
- Events not associated with the mechanism of action or pharmacology of the index drug (Idiosyncratic Type B events, Type C events, etc.)
- All other relevant safety data

Figure 5 below presents a high level signal analysis process that incorporates descriptive algorithms in a signal application guided analysis.

**Figure 5:**
As shown in Figure 5 above, the pre-approval signal analysis algorithms should provide a comprehensive risk evaluation methodology that allows the signal analyst and/or review to perform a thorough and detailed signal detection and evaluation of all available safety data. The signal analysis process should also support the overall risk-benefit assessment of a product, and feed into the regional/global safety surveillance strategies and initial risk management plan.

**Pre-Market Data Constraints**
When performing signal analysis it is important that a signal analyst/reviewer also factors in the specific quality of the clinical trial dataset, limited data size, and the exploratory nature of signal analysis. Signal analysts and reviewers need to be adequately trained to understand the signal process and tools being applied. It is important that processes are standardized and documented and governed by well-implemented standard operating procedures.

**Screening of Standardized Databases and Generating Signals**
Post data cleaning and standardization appropriate signal analysis algorithms are developed, tested and validated. Application of pre-market signal analysis algorithms in standardized signal analysis databases is done to look for and decipher potential or true signals, or EOIs. Figure 6 below shows an integrated data management and signal analysis process. The size of a dataset determines the events that are detected, ranging from very common, frequent, infrequent, rare to very rare. In many cases due to dataset size limitations of clinical trial data, rare to very rare events may not be detected.

A signal analysis process also involves generating the incidence or frequency of adverse events generated in treatment groups relative to the background rates. Based on the frequency of occurrence determined for AEs/ADRs, they should be categorized into frequency groups. The CIOMS III working group\textsuperscript{10} has recommended the following standard format for estimating adverse event frequency to allow categorization under the following groups:

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency Range</th>
<th>Percentage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>&gt; 1/10</td>
<td>(&gt; 10%)</td>
</tr>
<tr>
<td>Common (frequent)</td>
<td>&gt; 1/100 and &lt; 1/10</td>
<td>(&gt; 1% and &lt; 10%)</td>
</tr>
<tr>
<td>Uncommon (infrequent)</td>
<td>&gt; 1/1,000 and &lt; 1/100</td>
<td>(&gt; 0.1% and &lt; 1%)</td>
</tr>
<tr>
<td>Rare</td>
<td>&gt; 1/10,000 and &lt; 1,000</td>
<td>(&gt; 0.01% and &lt; 0.1%)</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000</td>
<td>(&lt; 0.01%)</td>
</tr>
</tbody>
</table>

Prioritization of Potential Signals for Evaluation

From clinical trial data, expert review of safety data and signal analysis results need to be prioritized, especially for life threatening, potentially fatal serious events, discontinuation events and events which have potential to cause serious clinical sequelae. To facilitate assessment of signals generated, a review prioritization scheme needs to be developed. For example, Type B and Type C events may be prioritized for further review over Type A events, since the latter are known to be events that are based on the mechanism of action or pharmacology of the drug. However, Type A events, especially serious cases, should still be carefully evaluated, and all identified and potential risks appropriately mitigated. Adverse liver, kidney or cardiac function events also need to be prioritized especially when assessed to have some causal association\textsuperscript{11} with the index drug or biologics product. In addition, events that may be infrequent or rare, if detected, and assessed not to have any other plausible causality\textsuperscript{11} other than the product under investigation, should be prioritized for further safety/medical expert review. There may also be other important events such as QT prolongation, Stevens-Johnson Syndrome, sudden death, Progressive multifocal leukoencephalopathy, etc., that if reported, even a single case, should be prioritized for detailed review and evaluation, along with other apparent causality, such as a concomitant medication(s), concurrent illness or medical or disease history, etc.
Assessment of Causal Association

When performing aggregate data analysis, the fact that an adverse event is occurring at a high incidence does not automatically mean that the index drug or biologics product is the responsible culprit. An unbiased assessment of causal association should be performed by safety and medical experts to ascertain the true causality. In clinical trials, incidence or frequency of adverse events generated for subjects exposed to the test/index drug should be compared to those computed as placebo or background rates. In addition, investigator causality assigned, and other possible causal factors such comorbidity effect, concomitant medications burden, genetic predisposition factors, etc. should be carefully considered. When assessing possible causal association(s) widely accepted criteria (e.g. the Austin Bradford-Hill Criteria\textsuperscript{11}), guidelines such as the CIOMS Working Group III recommendations\textsuperscript{10,12} and others are helpful.
While an adverse effect that is truly attributable to a drug or biologics product should not be missed, one that is not should not be erroneously credited to a product, hence skewing the safety profile. Signal analysis of pre-market data can significantly enhance the traditional process for developing the safety profile of a new drug, but clinical trial data size is largely limited. Once a new drug or biologics product has been approved by a regulatory authority and market launched, the drug exposure usually increases significantly, especially if the target treatment population is large. This reality makes post-marketing surveillance critical in addition to being a regulatory requirement.

**Signal Analysis in Post-Market Databases**

During the post marketing phase of a drug or biologics product, effective pharmacovigilance and risk-benefit assessment are critical regulatory requirements to ensure continued safe drug delivery to patients. Post-drug approval, there is no true denominator factor N (exposure factor), so calculating the true incidence of an event is not possible because N is usually estimated. Traditional signal analysis methods, primarily diligent medical/safety review and assessment of individual and aggregate case reports should be applied in review and evaluation of spontaneous events, and may be augmented with statistical algorithm-based data mining approaches such as statistical Frequentists’ approaches and/or Bayesian methods as shown in Figure 7 below.

**Application of Data Mining Algorithms**

More widely applied in spontaneous AE/ADR databases to generate statistical signal scores [PRR, Empirical Bayesian Geometric Mean (EBGM) and Information Component (IC), respectively] for drug-event combinations, are Proportional Reporting Rates (PRR $^{13,14}$) and other Empirical Bayesian methodology, such as Multi-item Gamma Poisson Shrinker (MGPS) $^{15-18}$ and Bayesian Confidence Propagating Neural Network (BCPNN) $^{19,20}$. Figure 7 below shows a high level signal analysis methodology applied in spontaneous databases. Examples of drug-event combinations that can be evaluated using the above statistical algorithms are as follows:

- Suspect/other drug-event [MedDRA preferred term (PT)] combinations
- Class-specific drug-to-event PT combinations
- Drug-to-multiple PT events (syndrome) combinations
- Concomitant medication-to-event PT combinations

To adjust for confounding factors such as sex, age, etc., statistical-based analyses can be stratified by sex or age group for example, when computing signal scores for drug-event combinations.
Post-Market Data Constraints
While performing signal analysis of post-market data, it is important to bear in mind known constraints and challenges that apply to spontaneous reports data which include absence of a true denominator, incomplete and/or inaccurate clinical information, inconclusive tests or diagnosis and incorrect and/or inappropriate clinical diagnosis and missing data, in addition to reporting biases due to a host of factors.

Medical/Safety Expert Evaluation of Individual and Aggregate Reports
Emphasized in the EMEA Guidance, statistical signals must be evaluated in the context of clinical information by medical and safety experts in order to decipher which signals are potential or true signals and if and how they translate to potential or true risks, their clinical significance and health impact. Based on medical/safety expert causality assessment of the signal analysis results, events are prioritized for further evaluation, especially serious adverse events, adverse drug reactions and events that led to drug discontinuation or dosage adjustment, which are assessed to be possibly related to the study drug.
Escalation of Potential or Suspected True Signals for Further Evaluation

Signal analysis is for plausible hypothesis generation that is based on scientific/medically sound rationale. In-house procedures and processes should be developed on how to handle SDRs, potential signals, true signals or E0Is, once they are identified. Expert in-house teams should be convened to prioritize review of signal scores and escalate review of critical safety concern to the appropriate next level as deemed necessary. In some cases, as an added precaution to ensure objectivity in the assessment of the signal analysis results, the decision may be made to escalate for further expert review and evaluation. A team of external Key Opinion Leaders with distinguished expertise in relevant discipline may be convened. All pertinent signal analysis results data are then made available to this team for detailed review and expert judgment opinion.

Post-Market Signal Scores Interpretation

A statistically significant signal does not automatically imply a potential or true signal or risk nor does it imply causal relationship between a product and an adverse event (AE) or adverse drug reaction (ADR). In some cases, a statistically significant signal score may be a false positive when evaluated in clinical context. A reported single rare or sentinel event, particularly a potentially life-threatening or fatal event where probable causal association implicates an index drug as suspect, usually requires escalation for further evaluation. Caution should be exercised while interpreting statistical signal scores.

Conclusion

Full or partial automation of signal analysis is an additional pharmacovigilance tool that definitely adds critical value to risk assessment and risk management processes. A signal analysis process should be a logical, scientific, systematic and standardized approach to conducting iterative safety assessment or risk assessment. Routine signal analysis work needs to be performed by signal analysts for signal reviewers and other expert medical expert reviewers.

As the drug development process continues to be made more efficient, semi-automatic signal analysis process will also continue to evolve as an effective tool that is performed on a routine basis as part of safety assessment work.

About the Author

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Dr. Jacinta Aniagolu-Johnson is a trained biomedical and clinical research scientist, an AE/ADR signal analysis and pharmacovigilance, risk management and drug safety surveillance subject matter expert. She has over 18 years combined expertise and cross-functional knowledge in biomedical and clinical drug development research, Drug Safety Surveillance and Pharmacovigilance and risk management. In the last ten years, she has focused on signal detection and evaluation as an integral component of pharmacovigilance and risk management. Dr. Aniagolu-Johnson has published papers in peer-review journals and presented papers and posters at US DIA, Euro DIA, PharmaEd and ISPE conferences.

Currently, as the Director, Pharmacovigilance and Risk Management at Synowledge, Dr. Aniagolu-Johnson directs client Pharmacovigilance and Risk Management project activities. She provides leadership, guidance
and subject matter expertise in the areas of Drug Safety and Pharmacovigilance, and Medical/Scientific Affairs. Dr. Aniagolu-Johnson develops signal analysis descriptive algorithms and standardized methodology for pre- and post-market adverse event databases, including regulatory databases. She conducts and supervises data mining analysis performed by applying statistical algorithms such as PRR, MGPS, and BCPNN. Also, she performs signal detection and evaluation reviews, qualitative signal trend analyses using a graphical tool, writes signal analysis reports, and develops SOPs, REMS, RMPs, RiskMAPs and other Drug Safety or clinical drug development-related documents.

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