Detection and Management of Safety Signals

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What defines a signal? Why do we need to do signal detection and what steps are involved? Although signal detection can take many forms, there are basics to the process no matter where you market your products.

The FDA Guidance for Industry entitled Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (from March 2005) is the reference most commonly used by companies marketing pharmaceutical products in the U.S. This guidance evolved from one of three papers delivered by the FDA as part of PDUFA III which resulted from public comment on risk management for regulated drugs. As stated, the guidance is not intended for all products but focuses on products which may pose a clinically important and / or unusual type or level of risk. The guidance is also geared towards the post-approval period of a product. The FDA 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. The FDA is clear that the topics presented in the guidance are in-line with international discussions as well.

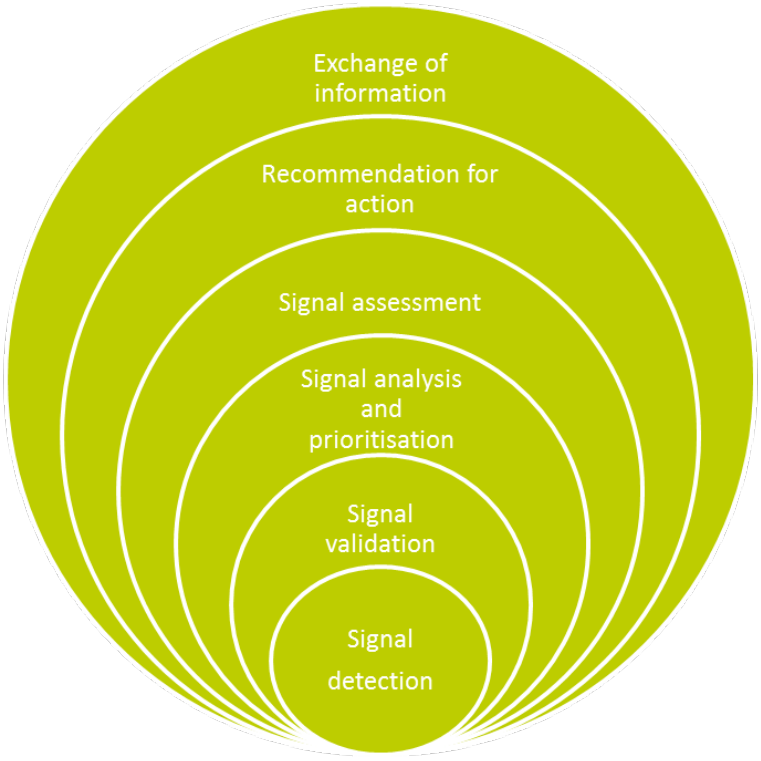
European Medicines Agency (EMA) has released the Good Pharmacovigilance Practice (GPV) Modules. Module IX is the Signal Management module (June 2012). This module employs the CIOMS Working Group VIII, *Practical Aspects of Signal Detection in Pharmacovigilance*. This GVP Module IX defines a signal as information that arises from one or more sources 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, as it is judged to be of sufficient likelihood to justify verification.

SIGNALS—WHERE DO THEY COME FROM?

Signals can arise from postmarketing data presented in Individual Case Safety Reports (ICSRs). Postmarketing data will be found in aggregate as well, for example submitted in periodic reports (PSURs, PBRERs, and PADERs). Signals can derive from pre-clinical or clinical data; periodic screening

of published literature, and even from social media. Events can be associated with other products in the same class – this may take additional comparison studies or can be a quick determinant of a potential signal if there is a similar class risk already known. Signals indicate the need for further investigation.

A schematic outline of the processes described in the GVP Module IX Signal Management looks as follows:



SIGNAL DETECTION

Signal detection is a continuous process in safety surveillance. This can be carried out by more than one method depending on what is most appropriate for the given data set. Complicated tools may not be needed for a small data set. These methods include review of ICSRs, statistical analyses in large databases, or a combination of these two methods.

A review of the ICSRs found in proprietary safety database is one method for single detection. The ICSRs can originate not only from spontaneous and clinical reporting, but from Post-authorization Safety Studies or other means of active surveillance. ICSRs can also originate from a review of published literature.

Causality assessment is a major factor for any signal identification process. Causality should consider the number of cases, demographics (including age and gender), the specifics of the primary suspect product, (dose, formulation and route of administration), the reaction (including signs and symptoms if available), the temporal association, and the dechallenge and rechallenge response. The causality link between the drug and potential signal should also consider any confounding factors, concomitant medications, underlying disease, the reporter's assessment (typically seen from a Healthcare Professional, not consumer reporters) and lastly the plausibility of a biological and pharmacological relationship.

Based on the need, advanced complex software can be utilized to calculate a variety of statistical algorithms and assess disproportionate reporting. This is especially useful when analyzing a large amount of data. In addition to these more advanced software programs, analyses can be made

by using Excel data and computations.

Signal detection should always involve the appropriate parties providing clinical oversight and judgement, not just a statistical score.

SIGNAL VALIDATION

The signal validation process is described in GVP Module IX. This process takes clinical relevance into account, along with any previous awareness of the events or like events. This is the step where an expansion of the investigation should occur by reviewing similar reports found from literature searches; pre-clinical or clinical findings; and screening the larger databases (FDA AERS, Eudravigilance, etc.).

If all relevant documentation is suggestive of a new potentially causal association or a new aspect of a known association, further assessment is required and the potential signal is now referred to as validated. If a signal is not validated, documentation must be made on the method and rationale for this determination and the event should continue to be part of routine surveillance.

In the EU, all validated signals are tracked by European Pharmacovigilance Issues Tracking Tool (EPITT). Further analysis is needed and the confirmed signal will be added to the Pharmacovigilance Risk Assessment Committee (PRAC) agenda for further investigation.

SIGNAL ANALYSIS AND PRIORITIZATION – HOW DOES THIS NEWLY VALIDATED SIGNAL IMPACT PUBLIC SAFETY?

A few points to consider: Are there consequences if there needs to be treatment discontinuation—does the risk of the adverse event outweigh the benefit to continuing therapy? Is the event seen in special populations? Are there patterns of use available to analyze, perhaps misuse or abuse is playing a hand in this sudden change in the safety profile?

An additional point to consider is the novelty of the product. The greatest number of reports is made within 2 years following launch. This can affect the under-reporting of serious adverse events of a more established drug, which in turn will affect the reporting rates.

The signal should be noted and tracked as confirmed, unconfirmed or refuted. Track the flow of what is being done for each signal. The prioritization should also include a timeframe for the completed evaluation of the signal.

SIGNAL ASSESSMENT

Signal Assessment broadens the scope of the signal detection process and determines if there is need for additional data or if any actions are warranted for safety reasons. Standard MedDRA queries (or SMQs) are helpful and should be utilized to help broaden the search of terms in the databases. This broadened search of information can also extend to

other drugs in the same class. Data sources to consider at this stage include searching of pharmacological, non-clinical and clinical data, including application dossier, literature articles, spontaneous reports and other unpublished information.

RECOMMENDATION FOR ACTION – IS FURTHER ACTION NEEDED AT THIS TIME?

Actions can include immediate action – such as suspending the continued marketing of the product; increasing the frequency of reviewing the data in aggregate, Dear Doctor letters, the implementation or continuation of post-authorization safety studies, an update to the label or packaging, and adding to or developing Risk Minimization Plans. If a potential signal is detected there must be communication made to the competent authorities immediately. This communication should also include the proposed plan of action to be taken.

EXCHANGE OF INFORMATION

Outcomes are to be made public and shared with healthcare professionals, patients, stakeholders, etc.

The EMA requires the implementation and utilization of quality systems used to track all steps of this signal management process for each potential signal detected. Validity and data security are essential in this quality system and must also be documented. Per the EMA, monitoring shall be proportionate to the identified risk or potential risk; the FDA shares this sentiment.

Eudravigilance is monitored by the EMA and other local agencies monthly. Possibly, there could be an increased frequency in monitoring of products that meet certain criteria, including but not limited to known risk of misuse or drug abuse; use in special populations (children, geriatrics, pregnant women, renal-impaired patients, etc.) and if there are new therapeutic uses of an established active ingredient (new route of administration).There is involvement by the Member States and PRAC throughout these processes. The information is made available on the websites as well.

In sum, signal detection is a process which can be lengthy and involve numerous parties and expertise. Signaling should be reflective of what is appropriate for the product involved and should consider the size of the dataset. Documentation is essential! Track the actions taken with each potential signal investigated. Signal detection, as with any pharmacovigilance goal, is needed to ensure safety concerns are expedited to protect public health against potential threats.

NOTES

1 *FDA Guidance for Industry – Good Pharmacovigilance and Pharmacoepidemiologic Assessment March 2005*

2 *EMA Guidance on Good Pharmacovigilance Practices (GVP) Module IX Signal Management June 2012*

3 *Report of Council for International Organisations of Medical Science Working Group VIII. Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010)*

4 *Oracle Empirica Signal 8 Jumpstart*

ABOUT THE AUTHOR

Robin Williams, B.S., CMC has over 16 years of experience in the pharmaceutical industry where she has held positions in clinical reference laboratories, pre-clinical and clinical research, postmarketing call center management and pharmacovigilance (clinical and post-marketing). Robin is currently a Senior Safety Scientist with Ashfield Pharmacovigilance, authoring periodic reports and working closely with safety physicians on signal detection and management for numerous clients. Robin is trained in Signal Detection and Management through DIA and Oracle.

Robin has been a member of DIA and American Medical Writers' Association.

ABOUT US

Ashfield Pharmacovigilance, formerly known as Drug Safety Alliance, is a global leader in safety and risk management services supporting pharmaceutical, biotech, medical device, consumer health and animal health organizations. Uniquely focused on pharmacovigilance, we provide outsourced solutions and modified services to augment existing safety departments. Founded in 2000, we were acquired by UDG Healthcare in 2012 and are proud to be part of its Ashfield division.

Ashfield Pharmacovigilance is headquartered in Research Triangle Park, North Carolina. Learn more about us at www.ashfieldhealthcare.com and follow us on Twitter @Ashfield_USA and LinkedIn.

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