CONFERENCE PAPER

Drug Safety 2007; 30 (7): 615-616
0114-5916/07/0007-0615/$44.95/0

You've Found a Safety Signal – Now What?

Regulatory Implications of Industry Signal Detection Activities

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Abstract

Signals detected by measuring disproportionality of drug-event combinations are only statistical indicators of possible real safety issues, and are not *per se* necessarily medically important. Nevertheless, once a signal is observed, sponsors are obligated by regulations and ethical considerations to determine whether it represents a new product-associated risk by additional analysis, validation and evaluation of its clinical relevance. Signal strength does not necessarily correlate with medical significance. Strong signals most often represent known, expected and/or medically trivial adverse reactions or confounding by treatment indication, common co-morbidities or other common concomitant treatments. Conversely, any product with reasonably extensive clinical use and reporting of suspected adverse reactions is likely to manifest many weak but clinically unimportant signals, creating significant background 'noise'. Since relatively rare, medically important adverse drug reactions are often likely to manifest as weak signals, sponsors face a potentially onerous burden of evaluating multiple signals in order to distinguish true, clinically important events of concern from spurious signals.

This paper discusses the regulatory, clinical and potential legal liability issues that confront industry as a consequence of signal identification activities, including: current and anticipated regulatory requirements for detection, assessment and reporting; the reliability of the data used for signal generation; assessment of clinical relevance; organisational approaches and responses to observed signals; targeted clinical and scientific responses to observed signals; and potential regulatory, legal and commercial impact.

"*The idea is not to generate signals; the purpose is to create actionable information.*"

Once a drug safety signal is observed, companies are obligated, by regulations and ethical considerations, to determine whether it represents a new product-associated risk. Sophisticated analysis and evaluations of clinical relevance are often hampered by poor quality of data; much of the information that is needed to make good clinical judgements is missing in spontaneously reported data.

Pharmaceutical and regulatory agency personnel have to accept that the quality of data collected is crucial for information retrieval and understanding signals.

When evaluating a signal it is important to prioritise the cases that contain enough data. Using a broader definition of the medical condition, one needs to create a case series, assembling data from all available sources.

The output of the complete process is not to generate and transmit signals; the purpose is to

create useful information that can be conveyed to the users of the product and thus improve the benefit-risk balance of the drug.

Signal detection activities are especially useful for regulators because they have primary responsibility for protecting public health. They are also in an advantageous position having access to current data on all marketed products. Additionally, regulators can also request additional information from various companies.

In contrast, the pharmaceutical industry has limited ability to use comparators in signalling, it can be done internally but only using their own 'subset' of data. They are obliged to report signals to regulatory agencies and are legally liable from the moment the signal is detected, possibly long before it is confirmed, if in fact it ever is.

Therefore, the most important thing pharmaceutical companies should do is to establish signal management procedures integrated with the signal detection process, that is, planning what to do after a signal is found *before* finding one.

Signal management is resource intensive. The purpose of planning is to anticipate what data would be required to evaluate signals and identify which data sources can be brought to bear within the relevant time frame.

In March 2005, the US FDA published its final guidance on pharmacovigilance.[1] Although the document is not a regulation and therefore not legally binding, it is the FDA's intent for every potential risk to be reported to it together with all available additional information. Although there are no predefined timelines, this involves a substantial amount of work for every signal. 'Potential risk' is not adequately defined; establishing a transparent triage process to discern issues involving 'potential risks' from 'non-potential risks' may assist in consistency and regulatory compliance.

The FDA draft guidance 'Drug Watch' for emerging drug safety information,[2] published in May 2005, proposes the use of the Internet to communicate all evolving safety issues to the public. This implies that every signal detected, after some preliminary analysis, will be communicated publicly regardless of whether they will ever reach the threshold for inclusion in the product label. **1**

In Europe, the guideline on risk management systems for medicinal products for human use[3] refers to an "important safety concern" instead of "potential risk". As in the FDA guideline, no exact definition of this ambiguous term has been given.

To conclude, no one can argue with the necessity of signal detection. This is a public health activity that should be carried out by product manufacturers and regulators. However, it is essential to remember that signals do not necessarily represent actual risks. For signal evaluation to be effective, it must focus on important clinical safety issues, but at present regulators and the industry still expend far too much effort and attention on minor issues with no public health impact. Ultimately, it is up to product manufacturers to improve their signal detection and evaluation procedures.

Acknowledgements

No sources of funding were used to assist in the preparation of this paper. The author has no conflicts of interest that are directly relevant to the content of this paper.

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1 Post-conference note: the US FDA subsequently substantially modified this proposal in its final guidance (Drug Safety Information – FDA's Communication to the Public) of March 2007.