PIPA Guidelines for Signal Management for Small and Medium Sized Pharmaceutical Companies

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This document provides practical points to consider when performing signal management for small and medium sized pharmaceutical companies. Signal management comprises signal detection, signal prioritisation, signal assessment and stakeholder communication.

Definitions are provided at the end of this guidance and in the PIPA Pharmacovigilance (PV) Glossary1. Further references are also available on the PIPA website.

However any definitions used in a signal detection process should be defined by the individual company in a signal detection and management SOP.

Introduction

Article 104(3) of Directive 2010/84/EU, which is due to be implemented in July 2012, states that marketing authorisation holders shall:

"(d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a;

(e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products".

It is a regulatory requirement[2] for all Marketing Authorisation Holders (MAHs) to demonstrate a systematic and documented approach to signal management, the output of which is appropriately reflected in the benefit-risk profile of the product under consideration.

The signal management[3] process can be defined as the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed.

The signal management process shall cover all steps from detecting signals (signal detection), through their validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made.

Signal Detection

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1.1 Sources of Data for Signal Detection

You should consider searching the following sources listed in Table 1 (not every source may be appropriate for every product or MAH). If you do not use a particular source of data, consider documenting your justification.

Table 1. Checklist of Potential Sources of Data for Signal Management

Individual Case Reports
● Regulatory Authority reports (e.g. Anonymised Single Patient Reports [ASPRs])
● Clinical Trials SAEs
● Post-marketing reports (to MAH)
● Serious adverse reaction reports from organised data collection systems (if applicable) e.g. clinical trials, post-authorisation studies, registries, post-authorisation named-patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers
● Medical and scientific literature
Information (including reports) from Sources including
● Non-interventional studies e.g. marketing projects
● Post-authorisation safety studies
● Medical and scientific literature
● In vitro and in vivo laboratory experiments
● The Media – the internet (including company-sponsored websites, internet forums, social media), journals and newspapers (as appropriate)
Other Department Data
● Regulatory data requests, e.g. regulatory agency requests for information, product referrals, reference safety information (e.g. SmPC) updates
● Product quality complaints associated with adverse events
● Medical enquiries
Aggregate Data
● Aggregate clinical trial data (include periodic reports e.g. Development Safety Update Reports [DSURs] / Adverse Events [AEs], laboratory data, pre-clinical data)
● Periodic Safety Update Reports (PSURs)
● Milestone data specified in the Risk Management Plan (RMP)
Other Data Sources
● Regulatory databases (e.g FDA AERS, MHRA drug analysis prints [DAPs] / product analysis prints [PAPs])
● Other databases (e.g WHO Vigibase)[4]
● Epidemiological data (e.g. General Practice Research Database [GPRD] / registries)
● Competitor product SmPCs (e.g. from the eMedicines Compendium [eMC])
● Competitor intelligence.

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Some of these may be useful for identification of signals, some of them are used primarily for validation of signals, while some would be used for both.

Although not all of these data sources will be found in the safety database, you should ensure the following cases are included in signal detection activities at defined intervals:

- Healthcare Professional (HCP) and consumer reports
- Serious and non-serious reports
- Non-valid cases (containing details of at least an adverse reaction and a medicinal product)
- Product quality complaints, if related to safety (e.g lack of efficacy reports)
- Special situation reports.

Determine how the reports are included in signal detection activities and justify your approach e.g. consider a tracker for non-valid cases and schedule periodic reviews.

As a MAH, you should have a rationale for periodic aggregate reviews based on defined risk factors. This is what inspectors will ask to see. In addition to monitoring the above data sources for ADRs, you should monitor reports for the following uses in special situations:

Special situations[5]

- Lack of efficacy (a change in benefit may be as important as an increase in risk)
- Medication errors
- Off-licence use
- Overdose/misuse/abuse
- Pregnancy/breastfeeding/lactation
- Suspected transmission of infectious agents
- Paediatric use
- Overdose/misuse/abuse
- Compassionate/named-patient use
- Reports received between submission and approval of Marketing Authorisation.

Good Practice dictates that all sources of safety information are considered together for a single active substance, e.g. clinical trials, post-marketing, registries etc for qualitative and simple quantitative signal detection methods.

1.2 Frequency of Data Review for Signal Detection

The appropriate frequency of data review is determined by, among other factors, the risk inherent in the product and may be specified in the PSUR and/or Risk Management Plan (RMP) (if applicable). It is important to document and justify the rationale for the frequency in a documented procedure.

Some common determinants of frequency of data review (e.g. monthly/quarterly/annually) to consider are:

- Number of AEs / Adverse Drug Reactions [ADRs] received per year
- Potential public health impact of an adverse event e.g. patient exposure data
- Maturity of the product e.g. number of years on the market
- The safety profile of the product and whether there are events/interactions that are being actively monitored e.g. as part of a RMP. Even if the product has been on the market for many years, new safety concerns may be identified.

It is advisable to review all safety information in a given review period, e.g. quarterly, six monthly, annually.

Prioritise products/actives/cases for review and justify and document your approach in an appropriate procedure.

Categorise cases by specific attributes, e.g. seriousness, expectedness. For example, prioritise all fatal cases or medically confirmed, serious, unexpected and related events.

1.3 Signal Detection Methods

The common signal detection methods that can be used include:

1.3.1 Qualitative[6]

Case-by-case manual review of individual case reports (a single case, in some rare instances, may constitute a signal). A human assessor reviews line listings or individual CIOMS forms for a given period. No comparison is made with cumulative data.

1.3.2 Quantitative[6]

Quantitative signal detection utilises statistical methods to identify drug-event pairs (or frequent combinations of a drug and an event) that occur with disproportionately high frequency in large spontaneous report databases. Typical methodologies used include the Proportional Reporting Ratio (PRR) or the Empirical Bayesian Geometric Mean (EBGM).

It should be noted that this method may identify a signal of disproportionate reporting which does not necessarily indicate there is a signal to be further investigated or that a causal association is present[7].

Limitations regarding the use of quantitative methods for small and medium sized companies include:

- Cost
- Complexity
- Increased risk of false positive signals in small datasets
- Obtaining results not representative of general adverse drug reaction reporting (due to over representation of a particular therapeutic area in a smaller database)
- Lack of access to a large diverse reference data pool (representing the background noise).

1.4 Simple-Quantitative Signal Detection

This method may include review of CIOMS II line listings and frequency tabulations. It is important to not only use periodic line listings for signal detection, but to also include cumulative tabulations to assess changes in frequencies of events from a period as compared to your overall safety database background.

As a minimum, a medical review of these listings should be considered. It is also suggested that the QPPV reviews these listings. These persons do not have to produce the listings.

To review data from the safety database for each active substance you may wish to run a minimum of three listings:

- Period frequency summary tabulation
- Cumulative summary tabulation[8]
- Period CIOMS II line listing.

Summary tabulations may include the absolute number and relative proportions of events. For each active substance, review summary tabulations to identify clusters of events. This should be at the most appropriate MedDRA level decided by your company e.g. Preferred Term (PT) or System Organ Class (SOC) level.

If your period line listing has identified no cases, ensure this is documented e.g. in your signal detection review meeting minutes. Remember to review data captured outside the database when available e.g. review MS-Excel® tracker for non-valid cases.

Now that signal detection has been completed you will need to consider prioritising how to review the signals you have detected.

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Signal Prioritisation

Given the number of signals produced, smaller companies may not need to prioritise signals for a particular product, choosing instead to assess all detected signals. However, for most companies a process for prioritisation of these signals is required. Signal prioritisation is a critical part of the signal management process.

For small and medium sized companies, assessing all signals in detail is resource intensive because of the high number of false positive signals. Prioritising allows action to be taken more expeditiously for higher priority signals than for other signals.

Larger companies may consider adopting an approach similar to the MHRA Impact Analysis for signal prioritisation, where the impact of a signal is summarised through two scores[9]:

- Quality of the evidence (strength of evidence for causality e.g. Bradford-Hill Criteria)[10]
- Public health impact of the signal.

The MHRA impact analysis produces a four-level categorisation which leads to a proposal for further action from high priority signals which need further assessment to the lowest priority signals which require no immediate action (e.g. may either be closed or require further monitoring only).

For small and medium companies a more informal approach using the factors above can be used (CIOMS VIII[11]) as long as this is justified and documented. You may also want to consider prioritising using one or more of the "always serious" lists below:

- "Always Serious" ADRs and Designated Medical Events (see definitions).
- Other examples:
  - CIOMS V[12]
  - EMA Important Medical Events list[13]

Finally, consider using expectedness as part of your prioritisation.

Signal Assessment

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3.1 Signal Assessment Strategies

After a signal is prioritised, other sources of data should be systematically assessed to determine whether sufficient evidence of causality exists, and what further action, if any, may be required.

Sources of evidence include:

- The individual case safety report(s) (ICSR(s)) that triggered the signal
- Other ICSRs with similar event terms identified e.g. by using Standardized MedDRA Queries (SMQs)[14]
- Scientific literature
- Clinical trial and pre-clinical data
- Epidemiological data[15].

The use of SMQs is recommended in order to retrieve and review similar cases of interest when potential signals are identified within a database.

In practice many signals can be assessed on the strength of the ICSRs triggering the signal. Criteria to consider when reviewing a signal from a case series are provided in CIOMS VIII[16].

Depending on the case load (number / volume of cases), the data may be stratified according to age, gender, ethnicity, concomitant medication or disease. This may identify populations at highest risk for the event and also reduces confounding[2].

A judgement about whether a signal is validated depends on the number and quality of case reports, the nature of the reaction, type of drug and the population exposure[7].

3.2 Decision Making Following Assessment

There are three possible options following signal assessment:

- **Close signal**

  The signal was refuted based on the available evidence and no further action is required. The decision and rationale for closing a signal should be documented. However, if further evidence becomes available the signal can be re-assessed.

- **Continue monitoring**

  In some circumstances a decision cannot be made until the evidence supporting the signal is strengthened. Except for situations of extreme risk, these signals are monitored until sufficient evidence becomes available to either confirm or refute the signal. The decision and rationale to justify monitoring a signal should be documented.

- **Take further action**

  After a signal is validated further action is required. The decision and rationale to take further action for a signal should be documented. The actions may include the following[17]:

  - Notify the Qualified Person for Pharmacovigilance (QPPV)
  - Enhanced monitoring or follow-up techniques
  - Consult internal or external experts
  - Targeted clinical investigations
  - Comparative observational studies
  - Active surveillance schemes
  - Clinical trials.

4 Stakeholder Communication

If there is a change in the benefit-risk profile as a result of a validated signal the following actions should be considered:

Within your company (according to internal procedures):

- Notify your QPPV (if they have not been involved in the signal validation process)
- Escalate within the global safety function (or department) (if applicable)
- Discuss with other company departments, especially the regulatory department
- Collate a safety data package relating to the validated signal
- The QPPV (or appropriate delegate) will work with the regulatory department to communicate with the regulatory authorities, as appropriate
- Communicate with regulatory authorities
- If a signal is being monitored, but has not been validated, it may be useful to describe this in PSURs and RMP updates, where applicable.

After confirmation of a signal the following actions may be initiated:

- Variation of the Summary of medicinal Product Characteristics (SmPC) and Product Information Leaflet (PIL)
- Revision of the RMP (if applicable)
- Provision of safety information directly to HCPs (including clinical trial investigators, where appropriate) / patients or the public, for example through letters or the company's website.
- Product recall
- MA withdrawal.

Some of these actions may require notifying the competent authorities first, e.g. in the case of provision of safety information to HCPs/patients/ the public.

Other Issues

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5.1 SOPs / Documentation

In addition to the signal detection SOP, signal detection documentation, such as agendas and meeting minutes must adequately capture all decisions and subsequent actions. These may be reviewed at an audit or regulatory authority inspection.

5.2 Tracking of Signal and Meeting Actions

Actions and signals should be tracked over a period of time e.g. open signals, implementation of agreed actions for a validated signal and time to resolution of signal, to provide a visible audit trail[18].

This is particularly important where there may be a history with a signal over time (and over several signal detection meetings), involving multiple decisions.

5.3 Quality

Signal detection and signal management are part of the pharmacovigilance system and therefore should be included in any internal company pharmacovigilance systems audit.

6 Definitions

For ease of use of this document, selected definitions relating to signal detection are captured here.

However, for a more complete list of definitions relating to signal detection and other pharmacovigilance activities, please see the PV glossary on the PIPA website and the annex to the Good Pharmacovigilance Practice Guidelines.

Signal Management

The set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed.

The signal management process shall cover all steps from detecting signals (signal detection), through their validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made.

Signal Detection

The act of looking for and/or identifying signals using event data from any source.

Drug-event Pair

A combination of medicinal product and an adverse event which has appeared in at least one case report entered in a spontaneous report database.

Designated Medical Event (DME)

Adverse events considered rare, serious, and associated with a high drug-attributable risk and which constitutes an alarm with as few as 1 to 3 reports. Examples include Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, anaphylaxis, aplastic anaemia and torsade de pointes.

References

1. PIPA PV Glossary. http://www.pipaonline.org/membersarea/pv_glossary.jsp
2. Guideline on Good Pharmacovigilance Practice. Module IX – Signal Management. European Medicines Agency (2012).
3. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010). pg 116.
4. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010). Appendix III, pgs 121 – 135.
5. Guideline on Good Pharmacovigilance Practice. Module VI - Management and reporting of adverse reactions to medicinal products. European Medicines Agency (2012).
6. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010). pg 113-114.
7. Guideline on Good Pharmacovigilance Practice. Module IX – Signal Management. European Medicines Agency (2012). Section B.3.2.2.
8. ICH E2C(R2) Guideline on the Periodic Benefit-Risk Evaluation Report (PBRER).
9. Waller P, Heeley E, Moseley J. Impact Analysis of Signals Detected from Spontaneous Adverse Drug Reaction Reporting Data. Drug Safety. 28(10):843-850, 2005.
10. Bradford-Hill A. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine 58: 295–300, 1985.
11. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010). Pg 89 Table 9.
12. Current Challenges in Pharmacovigilance: Pragmatic Approaches (Report of CIOMS Working Group V). http://www.cioms.ch/publications/frame_available_publications.htm
13. Eudravigilance EMA Important Medical Event (IME) terms list http://eudravigilance.ema.europa.eu/human/textforIME.asp
14. Council for International Organisations of Medical Sciences (CIOMS). Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004. Available on CIOMS website http://www.cioms.ch/
15. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010).Pg 92.
16. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010). Pg 91 Table 11.
17. Council for International Organisations of Medical Sciences (CIOMS) WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (2010). Pg 93 Table 12.
18. Guideline on Good Pharmacovigilance Practice. Module IX – Signal Management. European Medicines Agency (2012). Section B.4.1.

These guidelines were developed by the
PIPA Signal Detection Working Party

www.pipaonline.org/membersarea/signaldetection.jsp

For the current version of this document, please consult the PIPA website (www.pipaonline.org)

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