



Strategic and operational transition between pre- and post-authorisation safety in the EU

When an organization's first product is introduced to the market, the most challenging period is during the transition. This article focuses on what to expect from a pharmacovigilance perspective, and provides a guideline for getting organized at the time the first product is introduced to the market. The topics cover the main challenges rather than an exhaustive itinerary of all activities performed during this period of time.

Key points:

- ✓ Plan your system (structurally, and timing)
- ✓ Involve the right people
- ✓ Acknowledge the links between the different documents
- ✓ Get support when unsure

The process of organising pre and post marketing safety activities and transition time for a small organization's first product triggers many changes. To begin, one must set up standards and procedures and liaise with a number of different business units to ensure the process runs smoothly.

Basics: an integrated PV system

The first step is to ensure the management of an integrated PV system. This includes the safety profile of the product (medical), the processes in place for ensuring that the information is received, analysed and reported appropriately (regulatory, quality), and the validated tools to ensure appropriate recording of the information (technology). This system is valid for all products. The Detailed Description of Pharmacovigilance System (DDPS), and the Qualified Person For Pharmacovigilance (QPPV) apply for all products, whereas the Risk Management Program (RMP) and Company Core Data Sheet (CCDS) are product specific.

At the time of preparation of the application, in the worst case scenario, the internal regulatory department requests two key documents from the safety department- the DDPS and the RMP. The preparation of these documents is much more than just the document themselves, and the underlying efforts are enormous. In order to compile the RMP, you must have a good overview of the risk analysis of the product and for the DDPS, you need to have a good picture of your safety system structure, SOPs, and identify a QPPV.

The number of SOPs necessary will reach at least 10 or 12, if you follow the list clearly mentioned in the volume 9A.

So, in order to have an efficient transition period, one must move from being reactive to being proactive. Plan in advance to have a system in place so that you only need to include the components into your documents, thus leading to efficient document delivery and faster submission.

The RMP

The RMP is one of the first safety documents that you will need at application time and that you'll need to tackle in the development of the product. The ideal time to start the preparation of this living document is around phase II. At this time, it will be internal only, many sections will be incomplete and remain empty but these should get populated with time, possibly after the completion of each key study, or in synchronisation with the update of the IB. The preparation of a good RMP necessitates the participation of all relevant departments, and external experts if necessary. This multi-disciplinary team is important to ensure that all appropriate information is collected for the risk benefit assessment, but also that all departments are aware of the safety profile, of the identified and potential risks, as these will be presented in other documents, including the CCDS and SPC. Risks related to the pharmacological class will be at least included as potential risks.



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The multidisciplinary team needs to include preclinical, clinical development /pharmacology, medical safety, epidemiology, safety writing and be sure to seek experts opinion regarding sensitive therapeutic areas, unclear risk benefit ratio, NCE, etc. Consider the RMP as a living document and identify important identified risks, important potential risks, and unknown risks. Experience has shown that regulatory bodies accept the creation of subcategories but remember the three categories (important identified risks, important potential risks, and missing information) are mandatory and cannot be customised.

In addition to identifying the product's risks, it's important to have a plan for risk minimization activities. This plan will need to include the timing, budget and organisational aspects for your company. You may potentially discuss this with the authorities, or get help from ad hoc experts. Making the right assumptions and decision at this time may save you a lot of time, money and energy later in the process. Of note, the RMP needs to contain a section on routine PV practices, which of course will need to be in line with the DDPS. This also includes the QPPV contact details.

DDPS, the system before the document
The second necessary safety document to complete the application dossier is the DDPS. In order to structure the DDPS you will need to know about some key structural points:

- ✓ How is the internal/external organisation structured (safety, quality, territory)?
- ✓ In which countries will your product be launched, and what will be the distribution/licensing system, partnerships?
- ✓ What is the existing system?
- ✓ Who is your QPPV? Is it someone internal? Do you have an appropriate backup available?

These questions may seem simple but are not easy to answer in small organisations. If this is your first product approval, there is a large chance that your company simply does not have a network of affiliates, that you don't know exactly at this time who will sell or distribute your product because a partner is expected, but not identified yet. There are chances that the company is not ready to invest large amounts of money in a safety system while waiting for a

partner, so this is where the preparation of the DDPS requires creativity.

While preparing the DDPS, it is important to cover as much as possible, and describe the system as you imagine it even if it still is virtual. If you have identified partners and consultants to support the system, the corresponding contacts need to be attached to the DDPS. In addition, you'll need a strong QA and SOP system. This system may have bridges to other organisations or service providers but it will need to be completely thought through. Although not everything needs to be in place at the time of submission, the plan needs to be clear or at least clear on what is unclear. On top of the regular contents of a DDPS, here are some tips for submitting DDPS to authorities:

- ▶ Don't use the future tense in the document without clearly mentioning a calendar for process implementation
- ▶ Provide flowcharts for all processes including timelines
- ▶ Attach contracts with key providers, provide the list of your partners and delegated responsibilities
- ▶ Add a clear audit plan for your global organisation, including your providers
- ▶ Include the CV of the deputy QPPV, and the medically qualified support to QPPV if the QPPV is not a physician.
- ▶ Remember to detail the location of the data (electronic and paper, clinical and safety)

The QPPV

Many people believe that having a QPPV isn't necessary if the product isn't approved or launched, however, whereas the QPPV contact details will need to be included into the RMP and the DDPS, and the later responsibilities of the QPPV must be considered. It is therefore important to ensure that he or she is involved very early on in the preparation of these two documents.

The overall responsibilities of the QPPV include the contribution to the RMP, the system strategy which is described in the DDPS, review and approval of the DDPS, the SOPs and the quality assurance systems implemented prior to approval. In addition, the QPPV will be involved in answering the D120 questions.



The CCSI and its interdependence to other safety documents

In parallel with the preparation of the RMP, the QPPV will liaise with the regulatory and safety team to complete the contents of the CCSI.

Again, this information originating from clinical data, is linked to other documents.

Information originating from the RMP and all important identified and potential risks should be included in the section “warning and precautions” of the CCSI. All of these will also be presented as AEs of interest in the Periodic Safety Update Report (PSUR).

The adverse reactions presented in the undesirable effects section originate from statistical analysis and from individual case medical analysis. A focus on diagnosis versus symptoms is important for a meaningful medical analysis.

The post-marketing safety operations

A good time to start getting ready for daily post marketing activities (case reception and processing), is to start building your system in parallel with the preparation of the RMP and DDPS. The safety database used during the clinical trials period will be the same for the post marketing activities. However, there are significant differences between SAE originating from clinical trials and post marketing serious and non serious cases.

Pre-market cases are reports received via CRA or directly from the investigator. They are controlled data, in English and usually with only SAEs, whereas post-marketing cases originate from multiple sources. The safety system needs to be organised to ensure a complete data collection which includes literature (in the local language), affiliates/local contacts, competent authorities, etc.

A key point to remember is that the data collected during the first months after product launch is key, as this is when issues or signals may arise. These signals may of course be detected on a single case level, at signal detection, but also commented and analyzed at the time of aggregate report preparation.

Conclusion

It is important to plan a system with the appropriate structure and timing, involve the right people, acknowledge the links between the different documents and get support when unsure.

About the author

Véronique Basch first gained international research experience in California and later at the University Hospital of Zürich. She then embarked on a career in drug safety at Novartis: first at Novartis Ophthalmics as a Medical Safety Expert and then at Novartis Pharma as a Team Leader in the global safety operations group. In this position she was involved in all aspects of pharmacovigilance and drug safety, including data management, training, medical analysis, periodic safety update report (PSUR) writing, quality assurance, project management, and team management.

Véronique joined HPM Healthcare & Project Management (Geneva) SA in September 2004 as Head of Drug Safety where she developed the Drug Safety department activities. HPM was acquired by UBC in May 2009.

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