

Good Pharmacovigilance Practice – Challenges of Implementation

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The new legislation has been in place for almost 3 years now and there has been a lot of experience and discussion regarding some of the practicalities of implementation. If you are responsible for enacting its requirements, this can be quite daunting as you fight your way through all the legislation, guidelines and documents. As a consultant working with a number of companies, I have been able to see a number of approaches to do this. What follows is hopefully a pragmatic view of how best to approach this, which may also be of use when re assessing the PV system as a whole.

One Size Does Not Fit All

Primarily you need to understand your business, the type of products and disease areas as this will drive a number of aspects of the PV system that are needed. For example, if you have generic or well established products as per article 10 in directive 2001/83^[1] there may not be a requirement for periodic reports or they may be required with less frequency than newer higher risk medicinal products. If your company has more products in development, there will be a greater need to focus on the risk management plan, risk minimisation activities and all the unknown risks associated with a developmental product. Whilst case processing may remain relatively unaffected, signal detection, risk management activities and periodic reporting may change for the same product portfolio. How you resource your department will also be affected by the size of your company. Large organisations may have more resource but with linear experience compared with smaller organisations which of necessity have to use their workforce more flexibly. The possibility of out sourcing may come into the equation dependent on the type of products within the organisation. Global reach of an organisation also needs to be considered as there will be a need to comply with the appropriate regulations in other territories, and communication of changes in practice in the EU will be necessary for those with parent companies elsewhere. Whilst we are familiar with the EU and US requirements there may be other global requirements that need to be taken into account when assessing the PV system.

Assessing Requirements

The Pharmacovigilance System Master File (PSMF) sits at the heart of pharmacovigilance systems under the new legislation. It describes all the components of the PV system such as the QPPV responsibilities, department set up, sites of main activity, processes, quality management system, along with a list of all products and their authorisation status, and incorporates a log detailing changes to it. If you are new to a company, this should be a good overview. If you are updating an existing system to bring it up to date with the new legislation, this is both a useful framework as well as a required output.

Next it is useful to define the specific PV areas and your requirements for those areas as this will help in understanding the outputs, processes and skill set needed to meet objectives.

Benefit-Risk – Walking the Talk Through Product Development

If the new legislation had to be summarised in two words, they would be “Benefit-Risk”, and the new legislation seeks to proceduralise a

framework to ensure that “benefit-risk” is more than an abstract concept. Whilst using the language of existing activities such as risk-management planning and post authorisation studies, these are no longer at the periphery of pharmacovigilance systems, but firmly at the centre.

Thus pharmacovigilance input into product development is becoming ever more important. With the introduction in the EU of an ASR and then transition to the development safety update report (DSUR), along with the requirement of the risk management plan (RMP), pharmacovigilance activities in clinical development have been strengthened and will need to be resourced. PV should be a part of the development project team and along with the clinical physician should be aware of the evolving benefit:risk of the product. Section 3.19 – Summary of Important Risks in the DSUR^[2] should be used as the basis for the potential, identified risks in the RMP. It is now critical to ensure that benefit:risk aspects are addressed and documented adequately throughout the development programme as this will assist in preparing the RMP and minimise the requirements for post approval commitments in the shape of post authorisation safety and efficacy studies to answer any deficiencies which might have been addressed earlier in research. Close links with the clinical team are therefore essential in ensuring appropriate PV support is provided. The number of products in development, their stage of development and the number of ongoing studies will enable you to assess the resource needs of the department, bearing in mind that post marketing authorisation, these products will require additional reporting against their risk management plans.

The RMP is a detailed description of the risk management system^[3] and is required for every new marketing authorisation in the EU. The new EU PV legislation has focussed on risk, but in the context of the benefit and requires multi-functional input to address the different modules in the template. With the requirements of the new EU PV legislation it is clear that there needs to be the appropriate skill set within your PV department to manage this. Although the analytical and writing skills required to prepare an RMP may not change significantly, you may need to review the resource levels within the department and the ability to meet the additional RMP needs such as expertise in pharmacoepidemiology and post-marketing studies.

Moving into Postmarketing Pharmacovigilance

Whilst this might seem to be the familiar territory for drug safety professionals, the focus on benefit-risk has prompted changes even in familiar activities which need review in this context.

Alongside the RMP runs the CCDS. Whilst often considered a document for marketed products, a draft CCDS should be prepared during the development of a medicinal product so it is very clear what the label will look like for the marketed product. The skills required here will again be more analytical. You should ensure that there is a CCDS or a nominated SmPC for every active ingredient to ensure appropriate signal management.

The Database & Case Processing

The safety database continues to be instrumental in management of safety data within the department. Validation status is key and the

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database needs to be fully validated and updated with formal change control implemented to ensure the validity is maintained throughout its lifespan. You should think about how you want to use the database i.e. for expedited reporting for tracking regulatory authority submissions, performing data mining, reporting to ethics committees and investigators, managing workflow within the department as this will define your user requirements. It will be useful to consider compatibility with other software such as registration databases and medical information databases which could assist in ensuring compliance as it removes the need for multiple duplicate datasets. For most companies the new legislation does not have a major impact on the database. It should be noted though that the expedited requirements are strengthened with the need to submit both HCP and consumer serious cases and in some countries non-serious cases too. The non-serious cases need to be submitted within 90 days so they are on a different timeline to the serious cases. Databases where automated expediting occurs have been amended to take this into consideration. The reporting to Eudravigilance as a central database will likely start in a couple of years time as there is still a lot of clean up to do on the current database. With the implementation of this requirement, Eudravigilance will be the ONLY place to report to for ICSRs, hopefully alleviating some of the resource burden. There is a need to track invalid cases and this does need to be managed wither within the database or through an external system. Likewise whilst there isn't a need to report off label use without an AE there is a need to capture these events either within or through another mechanism so they can be used for summarising within the PBRER/PSUR.

Aggregate and Periodic Reporting – Swings and Roundabouts

Aggregate reporting is an area where there has been a shift with the implementation of the new EU legislation. Generic or well established products may no longer require periodic safety update reports (PSURs), lightening the burden of production. In order to determine the requirements of your products, you need to check against the EU reference date list⁽⁴⁾ which came into effect in April 2013. This list identifies those products that will go through the single PRAC assessment and covers both central and even some national authorisations now. The company PSUR schedule should be reviewed as this may show inefficiencies in report production and where harmonisation would be possible. If your generic active ingredient is on the list then you will need to abide by the frequency and birth date stated, by means of a Variation if the current frequency is part of the product licence. Harmonisation of periodic report due dates is needed to ensure efficient and effective resource use within the department. Unless the medicinal product is a generic, you will usually know the IBD (international birth date) and this should be used to drive the production and submission of aggregate reports that are required globally. The report format has changed significantly and most territories are accepting the new format. The development of different skills has been essential as the objective of the PSUR is now firmly in the benefit:risk arena; more analytical skills will be required to perform this activity than previously. Together with implementation of new templates, this needs to be considered when assessing resource needs.

Tracking Signal Management

Whilst a robust signal management system has always been essential to a fully operational PV department, there is a now a new requirement to track signal management⁽⁵⁾ and decisions made with their timeframes. The actual signal management system to be used will depend very much on the amount of data you have. Qualitative analysis will be appropriate for small datasets and data mining will be more appropriate for larger datasets. Importantly, clinical judgement should not be ignored no matter what the base method of analysis was. This further adds to the analytical skills needed within the department. Once a signal has been identified and validated, product label changes may be required. This will usually

be implemented through close collaboration with the regulatory labelling group and should be tracked to show there are no unnecessary delays. Occasionally there will be the need to communicate emerging or urgent safety issues to the regulatory authority (RA). It should be clear as to how this should be done and who is responsible for managing the safety issue communication to the RA. Governance framework is essential and there should be a global safety committee for high level decisions related to the above.

Post authorisation safety studies, optional until now, can now be a requirement at the time of the grant of marketing authorisation, as can post authorisation efficacy studies. The management of post authorisation safety studies (PASS) often falls between clinical, medical affairs and PV and it needs to be clear where various responsibilities lie, particularly where a company may not have been particularly active in this area previously. The stakes for well designed studies in this area are high and cross functional management may be the most efficient and effective mechanism for drawing on relevant expertise from the different areas. However it should be clear as to who has overall responsibility for the different activities such as protocol development, study management, final report production to name a few. There needs to be a clear method for tracking commitments that are part of the MA to ensure that these are addressed appropriately and within the correct timeframe. Access to pharmacoepidemiology expertise will also be essential here.

The legislation has a provision for post-authorisation efficacy studies, particularly in areas where there has been a change in the clinical endpoints for the disease the product is licensed for, thus making the original historical studies out of date.

Back at the PSMF

For any system, documented procedures are central to the efficient operation and GVP Module II – PV System Master File provides a list of critical processes that should be in place⁽⁶⁾. These are listed below and should be used to make sure you have processes to cover these areas.

- Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments, etc.
- Risk management system(s) and monitoring of the outcome of risk minimisation measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
- PSUR scheduling, production and submission, if applicable;
- Communication of safety concerns to consumers, healthcare professionals and the competent authorities;
- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications. [IR Art 2(4)].

A fully functional quality management system ensures that PV objectives can be met and quality objectives should be defined upfront to ensure compliance with PV legal requirements and also to ensure the protection of patients' and public health⁽⁷⁾. This will include specific Key Performance Indicators (KPIs) and metrics for the individual areas relating to PV as well as the overall infrastructure for the system. This includes

training and competency frameworks and assessments to ensure that everyone in the company knows how to report safety information and that those dealing with safety information daily are trained and competent enough to make the right decisions for patient and public safety.

Demonstrate Your System is Fit For Purpose

It is unlikely that you will make these changes without updating almost all of your existing processes. Once you have completed this exercise, it is a good idea to check that your updated processes work.

Audits are useful in providing evidence for the appropriate quality of the PV system and should be performed once the PV system is operational as this will provide confidence that the PV system is meeting the required needs. A series of process audits may be the most effective way of achieving this.

Overall, there are many considerations when setting up or taking over a PV system, type and number of development and marketed products, global reach, company organisation, skills and resources available. These

all need to be assessed systematically and process and infrastructure amended/introduced to ensure the company can meet its legal and ethical PV requirements.

References

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