The changing face of (benefit-)risk management

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Abstract

Over the last 20 years the focus of post-approval management of medicines has changed from risk management to the assessment and management of benefit-risk. In the EU this has been reinforced by changes in the legislation underpinning pharmacovigilance and the introduction of Good Pharmacovigilance Practice (GVP) modules. The documents used by companies to present and manage the benefits and risks of a product to regulators changed in 2012, requiring a change in focus for companies and regulators which needs to be reflected in increased cross-functional working and continued benefit-risk assessments.

Keywords: Benefit-risk, Signal, PSUR/PBRER, Risk management, Risk Management Plan (RMP), Lifecycle

Background

In the late 1950s and early 1960s thalidomide was used as a hypnotic and anti-emetic. It seemed to have a low level of obvious side effects in patients, although some side effects were noted by Dr Florence and reported in the British Medical Journal in 1960.[1] Then as the use of the drug spread, some obstetricians started to notice congenital abnormalities in babies born to mothers who had taken thalidomide during pregnancy.[2] This was the start of the unfolding of what is described as the thalidomide disaster, which was responsible for the initiation of systems to monitor the safety of marketed medicines in many countries of the world.[3] These systems encourage health care professionals to report suspected side effects of medicines to national regulatory authorities and have been very successful in detecting safety concerns in marketed medicines over the years.[4,5]

However, by the late 1990s there was a move to be more proactive about drug safety management. In 2001 a concept paper was agreed by the International Conference on Harmonisation to define a risk management guideline (ICHE2E), which was finalised in 2004.[6] The aim of this guidance was to better define what was known about the safety profile of a medicine when it was licensed, in terms of the number of patients studied and the types of risks identified, as well as plans for obtaining further data and managing the known risks. It was anticipated that such an approach would help to ensure that the safety profile of a product early in the post-marketing phase would be closely monitored to detect any new safety concerns early, and also to ensure that the safety profile as seen in the clinical studies was reflected in clinical use.[7]

The European Medicines Agency (EMA) adopted this guideline in 2005 as part of Volume 9A of the Rules Governing Medicinal Products in the European Union.[8] The EMA Risk Management guidance was mainly aimed at new products and those with an emerging safety signal that might require management beyond labelling. All products submitted for a marketing authorisation were required to have a risk management plan as part of the submission. To improve consistency across products, the EMA introduced a risk management plan template in 2006. Whilst the guidance was clear and the template was relatively easily managed, there was no attempt to combine information on benefits and risks and no information for the lay reader. As familiarity with the template and guidance grew, it was also clear that there was a lot of duplication in the document and concern that the risk management plans may not be achieving all they had set out to do.

There have been a number of reviews of the impact of the guidance on the risk management of medicines, both internal[9] and external[10] to the EMA, and some of the perspectives from these were taken into account for the new guidance and template which came into effect in 2012 as part of the implementation of the European pharmacovigilance legislation.

DOI: 10.1179/2047480615Z.000000000286

2012 PV legislation

The European pharmacovigilance legislation introduced in 2012 through Regulation (EU) No 1235/2010 and Directive 2010/84/EU was a major revision of medicines legislation in European countries which also took into account emerging trends in the healthcare sector such as increased transparency, provision of patient accessible information, and a focus on consideration of both benefits and risks. The outworking of the legislation for the companies, the individual European regulatory authorities, and the EMA is guided by a number of modules on Good Pharmacovigilance Practice (GVP)[11] which replace Volume 9A of the Rules Governing Medicinal Products in the European Union. The GVP modules of key interest in this article are GVP modules V and VII, which cover risk management planning and the periodic benefit-risk evaluation report (PBRER) as defined in ICH E2C(R2). Please note: This is described in the EU as the Periodic Safety Update Report (PSUR), but this article will retain the ICH document naming convention.

The RMP and PBRER are now orientated more towards the management of the benefit-risk profile of a product rather than just the risk profile and have ensured an increased and continuing focus on benefit-risk assessment and management.[12]

As a consequence of this increased focus on benefit-risk management, regulatory authorities, the pharmaceutical industry, and academia are now paying far more attention to benefit-risk assessments, and the quality and communication of those assessments. For example, a major work package within the EU-PROTECT research project addressed quantitative benefit-risk methods.[13] EU-PROTECT was a public–private partnership which was part of the Innovative Medicines Initiative (IMI). It aimed to assess the utility of various benefit-risk methodologies and particularly how the benefit-risk assessments can be visualised. Other approaches have been investigated by the Centre for Innovation in Regulatory Science (CIRS), most recently with the Unified Model for Benefit-Risk Assessment (UMBRA) initiative.[14] At the same time, regulators, pharmaceutical industry associations, and academic groups are working on guidance to improve standardisation of the assessments and to develop methods that will help in the display and review of the benefit-risk of products. This is also being taken forward by the recent ICH working group established to update section 2.5.6 of the CTD (ICH M4E(R2)).[15]

New requirements for the RMP

The new requirements for risk management plans introduced within GVP V[16] retained the principles of ICH E2E. The format of the risk management plan is now modular with the aim of increasing the ease of updates. Additionally there is now some guidance in GVP V on how to define important identified and potential risks, and what might constitute missing information relevant for inclusion in the risk management plan. The document now contains specific sections on the benefits of the treatment as well as a section designed for non-scientific readers which is publically available on the EMA website. This is all in line with the comments above on increased transparency, provision of patient accessible information, and a focus on consideration of both benefits and risks. There are also some sections common to both the RMP and the PBRER, as discussed in the PBRER section below.

In summary, the RMP is a document where information on the population studied (size, demographic distribution, duration of treatment, and clinical trial inclusion/exclusion criteria) is provided along with information on the important identified and potential risks and the missing information (e.g. relevant populations not studied, long-term safety). This information is accompanied by proposals for obtaining more safety information (the PV plan), information on benefits and proposed risk minimisation measures for the important identified and potential risks and for the missing information (Risk Minimisation measures). The effectiveness of these risk minimisation measures becomes an integral part of the benefit-risk assessment.

For companies an important point to note is that updating of the RMP has now been decoupled from the PBRER in terms of regulatory RMP submissions. However, given the sections common to both the RMP and the PBRER, companies may decide to maintain an internal updated RMP document for consistency reasons.

New requirements for the PBRER

The updates introduced to the PSUR as part of the GVP guidance were much more major than those for the RMP and reflect changes agreed at the ICH level in ICH E2C(R2).[17] The new PSUR document, renamed the PBRER, focuses on the review and discussion of the safety and efficacy data from the most recent time period, as well as the cumulative data and how the overall benefit-risk profile has changed during the current reporting period. It also introduces the concept of the difference

between benefits and clinical study endpoints, and encourages companies to clearly identify the benefits of treatment. EMA GVP module VII[18] implements ICH E2C(R2) and provides clear guidance on the need to understand the risks in the context of the benefits and the need to understand both the benefit and safety information in the context of the uncertainties in each of these. For example, a relatively small treatment-exposed population may imply uncertainty in both the benefit estimate as well as the risk estimate. The impact on the benefit estimate is that we will be less sure about the overall extent of the benefit and aware that it may be smaller than we have seen. The impact of a small population on our confidence in the safety data is that we may be concerned about risks that we have not yet had the opportunity to see (because either the safety population is too small or too refined or the studies were too short). The consequent impact on understanding of the benefit-risk profile of such a product is that there is more concern about the unknowns in the safety profile in the context of concern about the generalisability of the benefit information. Each PBRER requires a formal assessment of the benefit-risk of the product which takes into account all the data for the product and how effective the risk minimisation measures are in reducing either the risk of a side effect or the severity of the side effect if it occurs. This assessment will consider the importance and the magnitude of the benefit and will weigh against that the important risks in the context of their frequency and seriousness AND the context of the benefit.

Benefit-risk in the product lifecycle

As we move through the product lifecycle the key benefit-risk related product activities remain the same (signal detection, evaluation, management of potential and identified risks, evaluation of that management). What changes is the amount and type of data we have on which we can base our assessments. For example, there may be new studies in different indications, which change the types of benefits we consider and may also increase the amount of safety data available. Additionally, there will be reports of suspected adverse reactions from the safety monitoring systems mentioned in the Background section of this article. These reports can identify new safety signals that will need to be evaluated[19] and, if considered real, may need to be considered as part of the benefit-risk assessment. They may also help to provide new information on known risks. Figure 1 describes the overall benefit-risk lifecycle for a typical product.

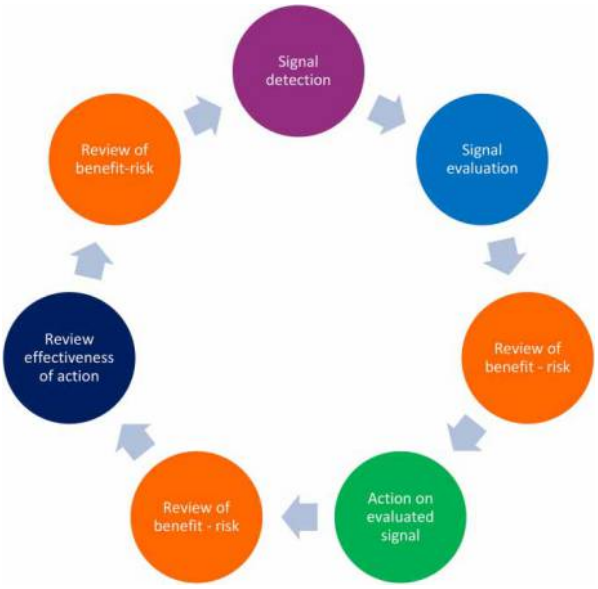

Figure 1: A life cycle approach to benefit-risk management.

As the product lifecycle continues, new safety risks will emerge from regular reviews of the data. These new risks will need to be evaluated and managed and the benefit-risk of the product will need to be re-evaluated. As more data accumulates, it may be possible to identify sub-groups of patients who respond better to the product (or less well), and subgroups who have a greater risk of more serious side effects. Trying to identify and characterise these subgroups is an important part of maximising patient benefit and minimising risk.

Conclusion

Over the last 20 years the focus of post-approval management of medicines has changed from risk management to the assessment and management of benefit-risk. The assessment of benefits and risks needs to consider the importance and the magnitude of the benefit and to weigh against that the important risks in the context of their frequency and seriousness AND the context of the benefit.

The overall benefit-risk assessment is described and reported periodically in the PBRER and should take into account all the data available on both the benefits and the risks of the product for a given indication. This assessment requires cross-functional working within global companies and also an understanding of the place of the product in the health care systems of different territories. It also requires a good understanding of how patients view both the benefits and the risks associated with the treatment, which often depends on the underlying condition being treated and the alternatives to the treatment.

Interestingly, thalidomide has been licensed once again, this time with stringent risk management measures in place to prevent the tragic consequences to the foetus if exposure occurs during pregnancy. The indications for treatment with thalidomide vary between different countries of the world but reflect the need for the benefit to outweigh the risks. Examples include leprosy and cancer. In the EU thalidomide is licensed to treat multiple myeloma, a disease with limited treatment options. Patients are educated about the benefits and the risks, and the effectiveness of the risk minimisation is monitored closely.[20] This illustrates the importance of managing risks in the context of the benefits and identifying those diseases or patients where the benefits of treatment outweigh the risks.

Conflicts of interest and disclaimers

Lesley Wise works as the Head of Global Risk Management and Pharmacoepidemiology for Takeda Development Centre Europe Ltd. The information and views set out in this article are those of the author and do not necessarily reflect the corporate opinion or position of Takeda.

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