

Improving Transparency and Benefit/Risk Assessments with the New Risk Management Plan



There is no doubt that the future of drug development lies in personalised healthcare – making sure the right medicine is given to the right patient at the correct time and dose. The rapidly expanding fields of pharmacogenomics and, more recently, metabolomics are testament to this trend. However, for personalised healthcare to be effective, patients also have to be engaged and involved in the process. So called ‘shared decision making’ is an ideal strived for in medicine but is a utopia that we have failed to realise effectively, because if patients are to be involved in the decision-making process, they must be empowered to do so. This means that they must be able to understand not only the benefits and potential harms of a treatment, but also be able to weigh this against the consequences of not having the treatment at all. To do this, patients need information about the medicines and their risks and benefits in a format that they can understand and evaluate.

Both the regulatory authorities and the industry as a whole have recognised this, and the process of drug development and treatment paradigms are changing as a result. Recent changes in European pharmacovigilance (PV) legislation are affecting the way the assessment of medicinal products is carried out in both pre- and post-authorisation phases, including new obligations to marketing authorisation holders for continuous benefit/risk assessment throughout the drug life cycle, and the need to make this information available to the general public. Coupled with this is a general industry movement towards greater transparency and patient engagement and involvement in healthcare decision making.

The ongoing assessment of a medicinal product’s safety and efficacy is not a new requirement, but these assessments were traditionally made in documents written specifically for regulatory assessors. The language used was that of specialists, which is no longer sufficient to fulfil the need for transparency and broader stakeholder (e.g. patient) involvement. Similarly, although benefit/risk assessments of medicinal products were made in the context of applying for drug approval, risk management focussed almost exclusively on safety in the post-marketing arena. Again, this does not address the need for the benefits of the medicine to be considered alongside the risks, nor how those translate into what may be a changing benefit/risk ratio over the long term.

Hence the recent raft of changes in PV legislation. These are the greatest changes in this legislation for almost 20 years, and although the changes affect many areas,

broadly speaking they all aim to increase transparency and emphasise the benefit of a medicine relative to its risk (both of which may change over time). The changes introduced to the risk management plan (RMP) exemplify this shift in thinking, both for increased transparency and a more holistic benefit/risk assessment. The purpose of an RMP is to provide a description of the risk management system that a company plans to implement to identify, characterise, and prevent or minimise risks associated with the use of its product. It must be written and submitted with most applications for marketing authorisation and must consider how the safety profile of the product may change once the product is being used in settings different from those in clinical trials. European legislation requiring submission of an RMP was first made in 2004¹, followed by the issuing of guidelines² and a template³. Those guidelines were updated this year in light of the general overhaul of the PV legislation and a new RMP template was issued⁴. The original RMP template consisted of two main parts: Part I addressed risk assessment and Part II addressed risk minimisation. The RMP was a means to make companies identify any important risks that may not otherwise have been recognised, as well as to consider in advance how they would watch for safety signals and react swiftly should a signal arise. The focus was solely on the adverse effects of the product.

The new template now divides the document into six main parts. Part I of the old template has been split into a section that describes what we already know and do not know about the safety of a product (the safety specification), and a section that lays out what we can do to increase our knowledge about the safety of a product (the pharmacovigilance plan). This highlights the desire to delve more comprehensively into the understanding of the safety profile for a product, teasing apart available knowledge from information that remains to be gained.



Outside of greater structural granularity, however, there are two main changes that bring the template up to date with the current PV mindset. The **first** is the need to address how increased knowledge on the efficacy of the product will impact on the risk assessment as a whole. Whereas in the past, companies were only expected to consider and perform studies that would further the understanding of the drug’s safety profile, now the same is expected for efficacy. Post-authorisation efficacy studies need to be considered that can close the gaps in knowledge about the efficacy of a product in the target population. The purpose is not to explore other areas of use for a product but to continue to expand on the knowledge base for the approved indication by gaining data on parameters such as the efficacy in notable subgroups and long-term efficacy. The inclusion of this new section (Section IV) makes clear just how serious the regulators are about making sure companies are assessing the ongoing benefits as well as the risks. The **second**, even more astounding addition to the new RMP, is a section whose sole purpose is to summarise all the salient points of the RMP in lay language (Section VI). This includes an overview of the disease epidemiology and a summary of the treatment benefits, including any possible unknowns about those benefits, a summary of any safety concerns and what risk minimisation measures are being implemented, a description of what post-authorisation studies are planned and a summary of any changes that have been made to the RMP over time. It is not really clear how exactly this new public summary will be used by the public, but it is a huge step forward in transparency and ensuring communication with stakeholders. By translating this kind of information from regulatory jargon into lay language and making it publically accessible, this will open whole new avenues for patient advocacy organisations, self-help groups, and patients themselves to better understand the products available to them. This will certainly aid in bringing these stakeholders closer to true empowerment in the decision-making process.

However, explaining risk ratios is challenging even when the audience is familiar with this type of information. Explaining the risks and benefits in a way that enables patients to make an informed decision about their treatment can be exceptionally difficult. This is partly because patients do not have a clear understanding of risk, which is often further muddled by their fear of the situation⁵. It is also because the way that risk and benefit information is presented is often confusing and difficult to understand, leading to misinterpretation at best.

The goal then of Section VI of the RMP is to simplify and explain the very complex information contained in the body of the RMP, so that patients can make an informed choice about their medicine. Starting with an explanation of the disease in question, it should explain why that disease should be treated and the medicines currently available for doing so. Such epidemiological data can be as difficult to understand as benefit/risk assessments, and so this also needs to be simplified as much as possible and any limitations of the data (e.g. if the information is only available for a certain area and estimates have been extrapolated) should be made clear.



The difficulty lies in really understanding what the general public truly knows. For example, when alternative treatments are being discussed, some context should be given – patients may not understand what terms such as ‘gold standard’ or ‘first line’ really mean, and so it is helpful to explain how and why particular medicines are used more often than other medicines. When considering particular sub-populations (e.g. the elderly), the language used needs to be clear enough to be sure people reading it understand if they belong to that group. There are many 70 year-olds who do not consider themselves to be ‘elderly’!

Another possible hurdle to effective communication to a lay audience is the use of several tables outlining the ‘important identified risks’, ‘important potential risks’ and ‘important missing information’, followed by tables summarising the risk minimisation measures etc. These tables are arguably the most important part of the section, but also the most difficult to write. The lay public is not used to scanning tables for messages the way people in the industry are. The tables presented in this section need careful designing to make sure the information is complete, unbiased, and intelligible by the patient.

As with all documentation, a well-structured, logical flow enhances the readability enormously. Plain language is also essential, and scientific, medical and statistical jargon should not be used, or at least explained in plain language in addition to the technical term. Relative risk information needs to be communicated in a way that anyone can grasp. For example, instead of stating that drug X can reduce hypertension by 50%, it is better to explain using a frequency as an absolute risk, saying the risk of developing hypertension is reduced from 4 people in 100 to 2 people in 100 by taking drug X. Although studies have been inconclusive about whether patients understand risk better if it is presented as frequencies rather than percentages⁶, it has been shown

that the perception of risk is lower when the information is presented as a percentage⁷, while changes in risk seem larger when presented as relative risk^{8, 9, 10, 11, 12}.

Beyond the discussion of risk, it's equally important that patients are fully informed about the benefits of treatment options. In addition to describing 'preventability' and 'risk minimisation measures', the existence of baseline risks, i.e. the risks that patients would face without any kind of treatment, need to be discussed as well. This is to avoid scaring people away from available treatments because they mistakenly believe that the only risks are those caused by the treatment and that they would not have any adverse outcomes if they refused the medicine. Getting this balance right is vital to truly empower patients to evaluate all of the treatment options available to them.

Personalised healthcare will soon be of age, and greater transparency in the communication of knowledge around the available treatments is a necessary step in the evolution of drug development and healthcare provision. The success of this hangs on our ability to provide information that enables everyone to understand and interpret complex data and concepts. Although challenging, this is not impossible, and is crucial not only for patients but for every audience - from regulators through to healthcare professionals, as their role grows from assessment of medicines to helping patients interpret their benefit/risk ratios.

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