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COMMENTARY

Benefit Risk Management Plans?

Stella C. F. Blackburn · Peter R. Arlett

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A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the benefit–risk balance is positive for the target population. However, it is accepted that, for many reasons, not all risks will have been identified at the time the medicine is authorized and many will only be discovered or fully characterized post-authorization. It was on this basis that the regulatory requirement for risk management plans (RMPs) was originally introduced. The safety specification of the RMP describes what is known, and not known (including missing information), about the safety profile of the medicine and summarizes the safety concerns with the product. The pharmacovigilance plan details how these safety concerns will be further identified and characterized, whilst the risk minimization plan describes measures to minimize and mitigate the risks where possible.

RMPs came into regulatory use in Europe in November 2005 following the revision of the pharmaceutical legislation and the adoption of the International Conference on Harmonisation (ICH) guideline on pharmacovigilance planning—ICH E2E [1]. Although many companies had had some form of risk management in place for some years, this was the first time that companies were required to formally submit the plans for certain products to the regulatory authorities for evaluation as part of the marketing application. Whereas ICH E2E included the safety specification and the planning of post-authorization pharmacovigilance activities, the EU RMP also included risk minimization measures. The introduction of RMPs in the EU was tempered so they were required only "where appropriate" [2]. In practice, "where appropriate" approximated to all new active substances, biological medicines and significant changes to a marketing authorization. In 2010, a major revision to the EU pharmacovigilance legislation led to the requirement for all new marketing applications to include "the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof" [3, 4].

The new legislation is supported by an update to guidance on the conduct of pharmacovigilance in the EU. The European Medicines Agency, in cooperation with the national competent authorities, is publishing Good Pharmacovigilance Practices (GVP) in a series of modules addressing different facets of pharmacovigilance [5]. The module on risk management systems is already published and provides for the RMP also to have a modular structure consisting of seven parts [6]. Directive 2001/83 states in its recital (which explains the legally binding parts of the legislation) that "the concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance …" [2]. This concept of assessing the balance between benefit and risk is the cornerstone of regulatory science and practice, and underpins the workings of the European Medicines Agency, its committees and its partners in the national competent authorities.

However, in the same way that the safety profile does not remain static post-authorization, it is likely that, for some medicines, the effectiveness of the medicine in normal clinical practice may not equal the efficacy shown in the controlled environment of the clinical trial. There may be sections of the target population where the benefit may be greater or less than that shown in the clinical trials. Although clinical trials are powered to demonstrate

S. C. F. Blackburn · P. R. Arlett (✉)
European Medicines Agency, 7 Westferry Circus,
Canary Wharf, London E14 4HB, UK
e-mail: Peter.Arlett@ema.europa.eu

efficacy, the numbers studied in clinical trials will not usually allow the identification of 'efficacy factors' or stratification of the target population for efficacy. In normal circumstances, it is unrealistic to expect that every subpopulation within the indicated users of the medicine will have been studied or that efficacy will be homogeneous across a heterogeneous population. For many medicines this heterogeneity may not be clinically important but it is a factor that should be considered in the planning of post-authorization development.

The recent pharmacovigilance legislation amending Directive 2001/83 and Regulation 726/2004 introduced the possibility for competent authorities to require efficacy studies post-authorization under certain circumstances [2–4, 7]. In the recital to the legislation, reference is made to requiring studies post-authorization "to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice." The grounds for requiring post-authorization efficacy studies are (i) where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed; or (ii) when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.

In these circumstances, if the regulatory authority has placed an obligation on the marketing authorization holder to conduct an efficacy study, the legislation specifically says that "Where the [national competent authority—Directive; Commission—Regulation] confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly" [3, 4]. Therefore, since the risk management system is updated as a result of an efficacy study becoming a condition of the marketing authorization, it is implicit that the RMP contains elements relating to benefit as well as risk. This also reflects the general move in the legislation towards integration of the review of benefit and risk post-authorization including the shift of periodic safety update reports to be benefit risk evaluation reports based on all available data.

To enable any efficacy studies to be included in the RMP and also put into context, a new section, part IV of the RMP entitled 'Plans for post-authorization efficacy studies', has been developed. In it, companies are requested to provide a brief overview of the applicability of efficacy data to all patients in the target population; factors that might affect the efficacy of the product in everyday medical practice and variability in benefits of treatment for subpopulations. This allows for discussion of the need for further efficacy studies in the current indication.

It should be emphasized that the requirements for efficacy studies relate to gaps in knowledge around the authorized indication and not to developing new indications; nor is it intended, or likely, that many medicines will now need to have a post-authorization efficacy study. But, for the minority of medicines where there are important questions about some aspect of efficacy, the RMP provides an opportunity for planning post-authorization development for both efficacy and pharmacovigilance purposes in a structured and efficient way.

The risk management plan is also not intended as a document to discuss the overall benefit risk of the product—in the post-authorization phase that is the role of the periodic safety update reports. The RMP is a planning document stating the current knowledge about the safety profile of the product, the planned post-authorization development to investigate further any gaps in the knowledge and the measures to minimize or mitigate risks. The RMP also states how the effectiveness of risk minimization measures will be evaluated and details of any studies for this purpose.

There have been questions on whether the new EU legislation, by including a provision for efficacy studies, is increasing the hurdles that companies must jump to gain authorization and increasing the developmental costs of medicines by widening the field for post-authorization data-collection. However, it can be argued that the new legislation provides a double chance to maximize the benefit risk balance of a medicine. Not only can the risks be reduced but the benefit could also be increased. One principle risk minimization goal is to prevent patients most at risk of developing a particular adverse reaction from taking a medicine. With 'effectiveness management' the corollary is an opportunity to either limit patients with the least chance of benefit from taking a medicine that has important associated risks or by identifying patients who are most likely to get the most benefit thereby optimizing the benefit risk balance of the medicine.

The new pharmacovigilance legislation also requires the publication of a public summary of the RMP. This new requirement is an important change. The new legislation promotes transparency in that many documents previously considered as confidential are now published. The summary of the RMP, and the agenda and minutes of the Pharmacovigilance Risk Assessment Committee are examples of this and should enable greater understanding of the processes whereby risk management plans are evaluated.

The definitive format of the summary of the RMP, and how it will be published by the Agency and the national competent authorities, is still under discussion. However the basic content, like that of the RMP as a whole, is established in the European Commission Implementing

Regulation and in GVP [6, 8]. Whereas the RMP may cover several medicinal products that have the same active substance, the summary is product specific. Its content includes the following:

For each indication

- overview of disease epidemiology (extracted from the safety specification);
- summary of existing efficacy data (from part IV);

and for each medicinal product

- summary of safety concerns,
  - important identified risks,
  - important potential risks,
  - important missing information;
- summary of risk minimization activities by safety concern;
- planned post-authorization development plan (i.e. both pharmacovigilance and any efficacy activities);
- studies which are a condition of the marketing authorization;
- major changes to the RMP over time.

The inclusion of 'benefit' in the summary in the form of the disease epidemiology and how the medicine changes the natural course of the disease is a move towards providing a balanced picture to patients of the risks and benefits of a medicine. The public summary of the RMP along with the European Public Assessment Report (EPAR) and the summary of the EPAR forms part of the Agency's strategy of transparency in relation to the knowledge and evaluation of medicinal products.

The new EU pharmacovigilance legislation specifically recognizes that there may be questions about efficacy that can only be answered post-authorization. The legislation also specifically requires that the RMP includes information about these post-authorization studies. Why then do we not call it a benefit risk management plan? The legislation defined an RMP as "a detailed description of the risk management system," which is in itself further defined as "a set of pharmacovigilance activities designed to identify, characterise, prevent or minimise risks relating to medicinal products including the effectiveness of those activities and interventions" [3]. And there, lies the issue. The legal definition of an RMP makes no mention of benefit despite the specific requirement elsewhere in the legislation for details of post-authorization efficacy studies to be included within it.

So where does that leave risk management? It is clear that we have moved from the original concept of pure management of risk to a more holistic approach where both parts of the benefit risk equation are examined. Risk management, less than 10 years ago, the new kid on the regulatory block, is now established and regulators are taking steps towards post-authorization benefit management with the aim of optimizing the benefit risk balance of a medicine. What has arrived is the concept that research doesn't stop with the granting of a marketing authorization. The key question is where in the continuum of the knowledge of a medicine's profile should authorization occur? The answer is specific to the medicine in the context of the indication and population, and management of benefit and risks and post-authorization development planning are already part of the RMP. How we characterize benefit and seamlessly integrate the investigation of benefit and risk factors into an RMP is the direction to travel. By optimizing the target population in regard to both benefit and risk, the benefit risk profile of a medicine can be further enhanced.

The expansion of risk management in the new EU legislation to all new products, and to include efficacy as well as pharmacovigilance planning, provides patients, healthcare professionals, regulators and the pharmaceutical industry with an opportunity to optimize the benefits and risks of medicines.

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