Risk management plans – New challenges for a new era

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Abstract

The risk management plan (RMP) is currently a hot topic and the focus of much discussion in industry due to the recent overhaul of the RMP guidance template. The complexity of the new RMP has introduced many challenges in preparing a high quality document compliant with all requirements – not least in the production of the newly legislated Part VI.2 (summary for the lay reader). This article discusses different aspects of the challenges posed by the new RMP, from an industry perspective of applying the new legislation and template, through to the importance of, and difficulties posed by, writing for the general public, and a comparison of the EU RMP with its US equivalent, the risk evaluation and mitigation strategy or "REMS".

The new RMP

The new EU risk management plan (RMP) has seen many changes; for example, the introduction of an evaluation of the medication benefit, thereby emphasising that risk management is a balance between risk(s) and benefit(s). Other changes include new sections on the potential for off-label use and on misuse and medication error, and the requirement for a lay language summary for the general public. These new sections aim to present a more all-encompassing discussion so that the medication can be seen in the proper benefit–risk context.

The most striking change in the template is the new modular format. Obvious advantages of this are facilitated RMP updates and submission to regulatory authorities: the modular format makes it possible to "lock" a part that ceases to change, which means that review times are decreased, as is the risk of human error or making changes to sections that should not be changed. Additionally, the modular format enables consistency, as it is possible to re-use parts of the RMP content in other documents, such as the development safety update report (DSUR), periodic safety update report (PSUR) or other regulatory documents, albeit that those parts always need to be reviewed to make them fit for their specific purpose.

A complete RMP contains 14 separate sections and modules, plus 12 annexes,[1] which poses one of the major challenges of how to handle these separate sections. Apart from the large number of sections, due to the "locking" process, all of these sections may also have a different version number. This could obviously lead to confusion during submission, which is why the European Medicines Agency (EMA) has mandated in a "Questions and answers on presubmission guidance" that companies must submit all sections and modules in one complete RMP as a single pdf file.[2] These instructions also state that the RMP Word-version must contain the same submission version number but with a suffix "W". However, it is currently unclear how to recognise the RMP version that is agreed at the time of the opinion but that requires some amendments, *versus* the version that already contains these amendments, as the EMA's example shows the same number for two such versions. Thus, the changes have brought some useful advantages, but there are clearly a few "bugs" to resolve.

Increasingly, non-EEA countries request a RMP, as this is a detailed description of the currently available benefit–risk balance and the risk management system for any medication. It might, however, pose a logistical challenge if these countries request changes to an RMP, which might even contradict the EMA-requested changes. One possible solution would be to have a core RMP in which the company decisions are captured, plus country- or region-specific annexes, describing the specific exceptions or additions for that country or region (including the EU). Submission of the core RMP plus a country-specific annex seems to be the most elegant solution.

Another challenging situation involves "old" or legacy products. If requested, an RMP must be written, but the creation of an RMP might be difficult for old medications, since often the required information for these established products is not available. A pragmatic approach to dealing with this might be to use the core summary of product characteristics (SmPC) as the source of information. All events included in Section 4.8 ("Undesirable Effects") are by definition "identified risks"; all events included in Section 4.4 ("Warnings & Precautions") describe class effects and effects for which the relationship

is less clear, so these are "potential risks". However, as the RMP requires a description of only the important identified and potential risks, an assessment of relevance is necessary. Evidence of missing information can be found throughout the SmPC, and the benefits of using the medication can be derived from the pharmacodynamics section of the SmPC, or alternatively from the approved product indications.

In addition to the challenges brought about by the updated RMP guideline, the process is further complicated by ongoing updates to the RMP requirements. Development of a risk management system is an ongoing process, and more recent changes need to be taken into account,[3,4] There is no longer an automatic requirement to update RMPs on a fixed time (yearly) basis, but rather whenever there is a significant modification to the product's benefit–risk profile. Another recent change has come with the release of Module XVI: where in the past it was sufficient to evaluate only the *outcome* of the risk minimisation, now it is also required to describe process indicators, which give an insight into what extent the programme itself has been executed as planned.

Section VI of the RMP

Another key RMP change has been to Section VI, which is split into two parts. The first (Section VI.1) comprises several of the summary tables used in the earlier RMP sections. These tables are also used as part of the European public assessment report (EPAR), which is fully accessible to the public via the EMA website. The second (Section VI.2) is the newly titled "Elements for a Public Summary" and is intended to be a summary of the salient points of the RMP written in "lay language" for the general public. This section has several sub-headings covering:

- The epidemiology of the disease being treated
- The clinical benefits of the drug
- A summary of the risks involved in taking the drug
- A more in-depth discussion of the important identified risks and the important potential risks
- An explanation of any information missing from the RMP (eg, because studies were not or could not be undertaken in certain sub-groups of the population)
- The actions that have been taken to reduce or minimise the risks presented by taking the drug
- Information on how to prevent/minimise these risks
- The intended post-authorisation development plan
- The lists of studies involving the drug
- A summary of changes made to the RMP over time.

The Section VI.2 information is drawn from the preceding RMP sections, but since it is aimed at the general public, the language and "tone of voice" used is very different from that within the rest of the document. Although medicines information aimed at, and written specifically for, patients is not new, this is the first time that a section specifically written for the lay reader has been mandated for RMP inclusion. This poses a unique challenge for the authoring team, because not only must the action and use of a drug be explained, but also the benefit–risk equation must be described in such a way that the reader can understand and appreciate why the drug has been prescribed, rather than simply being given information focused on potential side effects.

Health literary and the importance of Section VI

The growing fields of pharmacogenomics and pharmacogenetics, with the ultimate aim of "personalised medicine", require and enable patients to have more input into the choice of their treatment. However, in order to make a choice, patients must be properly informed. This is not as simple as sending out lengthier package leaflets, or handing patients an SmPC and expecting them to decipher it. This would be a challenge for even the most interested patient, not because of a lack of intelligence, but because of the generally low levels of health literacy.

Health literacy can be defined as the ability to obtain, process, and understand the basic health information and services needed to make appropriate health decisions and follow instructions for treatment.[5] There are many factors that contribute to an individual's level of health literacy, including general literacy, personal experience in the healthcare system, the complexity of the information being presented, cultural factors, and how the material is communicated. It is notable that in the UK, more than half of the adult population has a reading age of 14 or below.[6] Health literacy is important because low levels have been shown to correlate with poorer health and higher mortality[7,8,9] and the ability to understand the information presented is obviously of importance when trying to explain very complex risk *versus* benefit information to patients as part of the RMP.

RMP authoring

As already outlined, the new RMP contains some very complex information and concepts. To properly address all of the various topics and sections now required in the RMP, a team of authors is needed. It is important to recognise that an RMP is much more than just a collection of safety data. It is a strategic plan of how and what the company will monitor over the product lifecycle to understand and manage the benefit–risk profile. This means that colleagues from various departments within a company must discuss and develop the RMP content and strategy as a team. The document depends on contributors with the appropriate experience not only from pharmacovigilance, but also from the clinical and regulatory departments. Due to the Section VI summary in lay language, people specialised in communication to non-healthcare professionals should also be involved.

This is particularly important, considering the challenges of low health literacy. Writing for patients is often harder than writing for professionals, and the information should be presented in a way that comes naturally. The text should avoid clichés and wordy phrases, and use simple, plain language. It should avoid "over-detailing" and, considering the reading age of the general population, should be aimed at or below the level of 11–12 years. This means the language should use one or two-syllable words, grouped into short sentences and short paragraphs, containing one idea per paragraph. Difficult words slow reading speed and this decreases understanding, but using the active voice can help enormously as the reader feels they are being addressed directly. With that in mind, the choice of vocabulary is very important – some informality in the language can be very helpful (eg, "help" instead of "assistance"; "medicine" rather than "medicinal product"), along with using very specific wording (eg, "house" instead of "domestic dwelling", or "car" instead of "vehicle").

The importance of user testing

Once the text is written, a key part of producing a high quality, compliant Section VI.2 is testing. Although readability scoring (such as the Flesch-Kincaid scoring system)[10] can be helpful, this only measures the text complexity and is based on the physical characteristics of the letters, not the content of the sentences, the grammar, or the complexity of the vocabulary used.

User testing, ie, asking individuals from the expected target audience to read the document, is far more useful than readability scoring because it is "real-world" testing of the text and enables the writer to check that what they *believe* they have written is the same as the message that is understood by the reader.

Overall, Section VI should be considered in its own right and needs to be written by someone with the expertise to translate the science into lay-friendly text. This is the "public face" of the RMP and the drug, and if written correctly can be an incredibly useful resource for patients and physicians alike.

The US REMS plan

So how does the new RMP compare with its US counterpart, the REMS? According to the FDA, "REMS is a risk management plan that goes beyond requirements in the drug prescribing information to manage serious risks associated with a drug. Under the Food and Drug Administration Amendments Act of 2007, the FDA has the authority to require a manufacturer to develop a REMS when further measures are needed to ensure that the drug's benefits outweigh its risks".[11] By comparison, at its core, the EU RMP documents the measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions.[12]

In contrast to the RMP, the REMS is not a routinely required document and, as of 20 September 2013, only 64 individual and six shared REMS were identified on the FDA website. REMS may be prepared for individual drugs or may be "shared", extending beyond just one drug as part of a programme to manage risks for a products class. For example, in 2012, extended release/long-acting opioid analgesic REMS were approved encompassing 20 companies and more than 30 products (new drug applications (NDAs) and abbreviated new drug applications (ANDAs)).[13] This is very different to RMPs, which are routinely required for a product as part of EU marketing authorisation applications.

A REMS is needed when the FDA determines that additional safety measures *beyond* product labelling are required to ensure the benefits exceed the risks. There are several factors that can indicate the need for a REMS. These include:

- Teratogenicity: this could mandate a negative pregnancy test prior to each dispensed prescription
- Hepatotoxicity: this could mandate monitoring of liver function tests
- Neutropenia (and therefore infection): this could mandate patient education regarding signs of infection.

The request may also be triggered at various time points, before or after marketing, reflecting an emerging safety profile. Points to be considered when evaluating the need for a REMS include: the anticipated exposure to the drug – both the population exposed and their duration of treatment; clinical need (seriousness of the condition); anticipated benefits; the nature and seriousness of anticipated adverse events; and if the drug is new.

By comparison, the topics which must be considered for the EU RMP are implicit in the RMP sections, together with any drug- or class-specific concerns.

What REMS content is required?

While the EU RMP clearly defines the content required, including a long list of required annexes, the REMS content guidance is less concrete. The only element all REMS must have is a timetable. Beyond that, there are various elements that can be included depending on the purpose of the particular REMS. They may require a medication guide/package insert, a communication plan, "Elements to Assure Safe Use" (ETASU), and/or an implementation system. If the drug is a generic (ie, requires an ANDA) then the REMS may only need a medication guide/package insert, a communication plan, ETASU, and/or an implementation system.

It is possible to view approved REMS on the FDA website. An example of a REMS with a communication plan (chosen at random from the website) includes Bydureon (exenatide), indicated for type II diabetes. The stated goal of this REMS is to inform healthcare practitioners (HCPs) about the risk of acute pancreatitis and potential risk of medullary carcinoma of the thyroid.[13]

Adusave (loxapine), an acute agitation therapy, provides an example of a REMS with ETASU, which is the most extensive part of a REMS programme.[13] The goal of this REMS is to mitigate the negative outcomes associated with Adusave-induced bronchospasm. Hence prescribers must be trained and certified in approved clinics; the drug is administered in-clinic only, with supply from approved distributors/wholesalers. The REMS implementation system describes how the sponsor will monitor and evaluate those participants in the healthcare system who are implementing the ETASU measures where required.

Those submitting dossiers in Europe will recognise that the approach to risk management can be widely variable but is commonly "routine pharmacovigilance". In that case, one may ask, is an RMP truly necessary for all products?

REMS: Timetable and types of assessment

All NDA/biologics license application (BLA) REMS must have a timetable for assessing the effectiveness of the risk minimisation measures. Assessments must be reported at least at 18 months, three years, and seven years after REMS approval. The outcomes drive further actions. However, the need to continue these assessments may be eliminated after year three, as described on the FDA website. The EU RMP requires applicants to specify the measurements and milestones to be used to assess the effectiveness of the interventions, if any, and/or for the assessment of, for example, safety studies conducted under the remit of the RMP.

The methods of assessment are broad and should be selected on the basis of fitness for purpose. Examples may include: HCP surveys to test understanding of REMS; analysis of adverse events that triggered the REMS; prescriber compliance with their

REMS-driven certification, eg, training and enrolment procedures; patient data capture quality; real-life usage data and correlation with numbers being monitored.

Modifying REMS

REMS can be modified in light of emerging safety data. Review of the FDA website provides an example in the form of Promacta (eltrombopag) which is indicated for thrombocytopenia. After a period of monitoring, the requirements for prescriber, patient and pharmacy enrolment were removed.[13]

In summary, the goals of the REMS are the protection and enhancement of public health. It seems that the overall philosophy is aligned between Europe and the US, although the vehicles may look different and there is no US requirement to formally document what is effectively "routine pharmacovigilance". However, despite the challenges of implementing both the RMP and the REMS, it is most definitely a worthwhile endeavour.

Conclusion

The RMP has undergone a major overhaul. There is no doubt that the current, updated RMP is more robust and more transparent than before, and will certainly increase the much needed transparency surrounding medicines. It is hoped that the new modular system will also speed the process of RMP (and possibly other regulatory document) production, and enable consistency between the various documents. The introduction of the new Section VI should, if approached and written correctly, improve not only healthcare professionals' knowledge, but also that of the wider general public, and is a medium for companies to explain some of the results and rationale involved in the clinical development process for that particular drug.

Although there are still remarkable differences between the US and Europe, it is hoped and anticipated that with time, these will become more aligned in their requirements. In the meantime, although there are the inevitable teething problems to be resolved, the update to the EU RMP has the potential to transform it into a much more user-friendly document than previously.

The RMP has changed dramatically, and these changes have brought some unique challenges for industry. However, the overall result should be a more robust risk management system and an increase in transparency, leading ultimately to better health protection.

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