Regulatory Matters

The growing need for drug safety documents

SECTION EDITOR

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When I first started in regulatory writing (over a decade ago now, how time flies when you're a medical writer), the types of document that I would be involved in were typically clinical study reports, investigator brochures, maybe protocols, and then later clinical summaries and overviews. Posts advertising for regulatory writers would usually mention these documents, which were also the focus of the EMWA training programme. My impression was that the pharmaceutical companies did not give as much importance to drug safety documents as to other types of document. These documents seemed more like compilations of notifications of adverse drug reactions rather than documents that attempted to synthesise and analyse information.

Increasing prominence of drug safety documents

A greater focus on drug safety, both during drug development and post approval, has however led to a change in how these documents are perceived and increased documentation requirements. Drug safety documents are now becoming increasingly important to companies and regulators, and a quick glance at the current EMWA Professional Development Programme Brochure shows that workshops are available for the three main types: Periodic Benefit Risk Assessment Reports (PBRERs), Development Safety Update Reports (DSURs), and Risk Management Plans (RMPs).

Differences between drug safety documents and other regulatory documents

In terms of general processes, there are differences between these drug safety documents and other regulatory documents (which, from my perspective, I will call traditional regulatory document types, for want of a better term). One obvious difference is that in the case of PBRERs and DSURs, these are documents that are updated periodically, whereas other traditional regulatory documents are usually written on an as needed basis (except for investigator brochures and protocols I suppose). This periodic nature means that resource planning is more predictable although the timetables for submitting drug safety documents can be quite complex (see later discussion). RMPs are not needed according to

a periodic schedule, but they are still living documents that are frequently updated. To assist with the updating process, drug safety documents generally have a very modular structure.

Another difference is that drug safety documents will often attempt to integrate information from multiple sources within 'the real world' (e.g. spontaneous reports of adverse drug reactions from health care providers and literature reports) to a greater extent than traditional regulatory documents, which generally use clean data collected with well controlled procedures (for example, a case report form). The large number of sources coupled with their greater heterogeneity can be a challenge when writing and compiling drug safety documents.

Development Safety Update Reports

On submission of the marketing authorisation application, the safety of a drug will be exhaustively assessed by the reviewers. If safety issues are detected, this will be too late to prevent exposure of patients to the risk. The health authorities therefore continually monitor the safety of drugs in development. In the past, each International Conference on Harmonisation (ICH) region had its own requirements for providing updated safety information. As part of the drive towards common standard documents, the DSUR was introduced. (Note that a DSUR needs to be submitted for drugs that have already been approved if clinical development for a different indication, for example, is still ongoing). ICH Topic E2F provides detailed guidance on the structure and content of a DSUR (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Step4/E2F_Step_4.pdf).

Periodic Benefit-Risk Evaluation Reports

The number of patients exposed to a given drug during drug development may be too small to reliably detect small (but important) safety signals and patient populations are often limited to 'ideal populations'. Once on the market, not only are many more patients exposed, but patients are also treated who would not have been included in clinical trials. This 'real world data' provides important additional information on the use of the drug in clinical practice.

The main purpose of the PBRER, according to the ICH guideline E2C (R2) (available from https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf), is therefore to

"present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.."

The PBRER replaced the Periodic Safety Update Report (PSUR), itself an attempt by ICH to harmonise the format for safety reporting. The PSUR focussed, as the name implies, on drug safety. There was increasing recognition, though, that the safety of a product should be interpreted in the context of its benefit. Clearly, the threshold for acceptable safety risks is higher in an oncology product than in cough mixture. The PBRER, as its name (Periodic Benefit-Risk Evaluation Report) implies and as reflected by the mission statement above, attempts to put safety issues into context. In many ways, the benefit-risk section of the PBRER bears many similarities to the benefit-risk sections of a clinical overview.

Overlap between DSUR and PBRER and submission schedule

There will be a period in which a drug has been approved for a given indication but is still under development for another indication or, for example, while studies included in the Paediatric Investigation Plan are being conducted. Often, this period will extend for many years. During this time, both DSURs and PBRERs will be required. As there will be much overlap between the two documents (in fact, the modular nature of the two types of report means that some sections may be identical), it makes sense to develop and submit the two documents in parallel. This also eases the burden on the health authority reviewers. Working out the schedule to make this work is not always easy. The submission dates for PBRERs are generally gated on the first approval of the drug (International Birth Date or IBD) whereas DSURs are gated on first authorisation for the conduct of a clinical trial (Development International Birth Date or DIBD). Furthermore different regions may have different requirements regarding the frequency with which a document needs to be submitted.

Risk Management Plans

Unlike PBRERs and DSURs, RMPs do not follow a periodic schedule. An RMP must be submitted with an initial Marketing Authorisation Application and it is then updated following certain triggers, for example, the availability of new information that may have an impact on the benefit-risk profile. They may also be updated when an important pharmacovigilance milestone is reached (for example, when the results of a Post-Authorisation Safety Study [PASS] become available). In addition, the European Medicines Agency or a national health authority can request an update if these bodies consider it necessary. The upshot is that the timing of RMP updates is unpredictable, and there may be situations when an update needs to be submitted at short notice.

Typically, an RMP includes information on the safety profile, approach to risk minimization, plans for studies to generate further safety and efficacy information, risk factors for adverse events, and measurement of effectiveness of risk-minimization measures. The exact format and content is variable from one region to another, in part because, unlike PBRERs and DSURs, RMPs are not explicitly covered by ICH guidance. Companies will usually have an internal core global document that can then be adapted as necessary to the local requirements (the European Medicines Agency for example has detailed guidance on the structure of EU RMPs, see http://www.ema.europa.eu/docs en_GB/document_library/Regulatory_and_procedural_guideline/2012/11/WC500134650.pdf).

Potential opportunities ...

The increasing focus on pharmacovigilance and drug safety is generating a greater need for drug safety documentation. The documents discussed above need to be updated regularly (periodically in the case of PBRERs and DSURs) or in the case of an RMP, an update may be needed at short notice. As drug safety is not something that stops as soon as approval is obtained, PBRERs are still required even when clinical development of a product has finished. In some cases, the documents may be complex, and the interrelationship between these documents may need careful management. The result is a high documentation burden for pharmaceutical companies and potentially a good source of work for regulatory writers.