PSURS and PBRERS: One Year On

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INTRODUCTION

Since July 2012 we have officially been operating under EU legislation Directive 2010/84/EU amending directive 2001/83/EC for National and Mutual Recognition processes and Regulation (EU) No 1235/2010 amending regulation (EC) No 726/2004 for Centralised processes. The legislation is accompanied by the Commission implementing regulation No 520/2012.

In this brave new world, Volume 9A guidelines have been replaced by 16 Good Pharmacovigilance Practices (GVP) modules enshrined in law. GVP Module VII covers Periodic Safety Update Reports (PSURs) and is the subject of this paper.

KEY CHANGES AND CHALLENGES TO PBRERS

The PSUR now has an alternative name - the periodic benefit-risk evaluation report or PBRER and while it doesn't exactly roll off the tongue, it does give an indication of what is expected from these 'new look' PSURs. Compared to ICH E2C (R 1)[1] document and Volume 9A PSUR guidelines, there are twice as many sections to the new PSUR; particularly important additional sections include non-clinical data, signal and risk evaluation, benefit evaluation and an integrated benefit risk analysis.

The PSUR now requires timely and precise input from many functions (eg non-clinical, clinical, medical affairs) previously blissfully unaware that such a document existed. Hence, the resource requirements reach far beyond the traditional safety department. While it is hoped that this will ensure a much more balanced document allowing for the conduct of a full and cumulative benefit-risk analysis, coordination of the collection of the requisite information in a timely way from various disparate parts of the company is a major challenge. The involvement of any non EU partners offers a unique aspect for consideration in this respect.

The new PBRERs require more evaluation and interpretation and are less of a 'data dump'. Thus the traditional data review by System Organ Class, which had more emphasis on individual case review, has been replaced by a more holistic active signal detection and evaluation process necessitating a completely different approach by the MAH. By way of recognising this (at least in part), the timelines between data lock point and submission have been slightly increased (from 60 to 70 calendar days for PSURs covering intervals of up to and including 12 months, and from 60 to 90 calendar for PSURs covering intervals in excess of 12 months). Clearly these are still challenging timelines especially since the documents are more resource intensive, certainly in the short term.

Based on current experience, an additional hurdle that may be encountered is that Pharmacovigilance Risk Assessment Committee (PRAC) questions may arrive during the PSUR/PBRER authoring phase with the requirements to provide answers within that PSUR period.

Somewhat paradoxically, the additional resource and workload required for legislative compliance is particularly onerous for the first PBRER for a mature product. This is because, as previously indicated, the PBRER includes an evaluation of benefit. For many mature products, a formal evaluation of benefit information will not have taken place since the initial Marketing Authorisation (MA) was granted or additional indications were approved. Moreover, in sharp contrast to new products which have well-defined indications that are common throughout the EU, mature products, especially those that have been available for 30 years or more, often have very broad indications and this along with divergent decision making by regulatory authorities, and regional differences in prescribing practices over the subsequent years, often leads to considerable variation in the authorised indications of these products throughout the EU. As the authorised indications form the basis of the benefit evaluation, the consequence is that the benefit evaluation for the first PBRER may require drafting pretty much from scratch.

The amount of information to be assessed for a PBRER may be extensive and the changes in clinical trial design and medical management that have taken place in most therapy areas over the decades can make data presentation complicated. It is not uncommon to find that a product introduced many years ago as a first-line treatment option has, in the subsequent years, been superseded by alternative treatments. Although the benefit-risk profile of the reference product itself may not have changed over time, the emergence of safer or more effective alternative treatments may negatively impact the relative benefit-risk ratio of the product in everyday medical practice. It is anticipated that compliance with the new pharmacovigilance legislation could restrict the authorised indications of some mature products and the impact on resources for life-cycle management of these products may therefore extend beyond the production of PBRERs.

Other potential issues include the fact that the use of addendum reports and summary bridging reports to account for differences in scheduling and periodicity (previously available ICH E2C (R1)) are no longer acceptable making it difficult to address differences in scheduling in non-EU countries.

Additionally, Japan has not yet implemented ICH E2C R2 and as such the consideration and translation of the worldwide PBRER for submission together with the Japanese PSUR at day 90 presents a challenge. As the ICH E2C R2 PBRER is submitted at day 70 or 90, depending on the interval under review, as explained above, the timeline to comply with the requirements is very short.

A new assessment procedure involving the Pharmacovigilance Risk Assessment Committee (PRAC) is now in place for centrally authorised products, the final conclusion of adopted assessment reports and the recommendations of the relevant regulatory committee are published on the European medicines web portal. For nationally authorised products, in a move towards rationalisation, a single EU PSUR assessment has been put in place.

The new procedure allows the PRAC to address any queries to the Marketing Authorisation Holders (MAH) who has to respond before the procedure is complete. In theory the MAH should have up to 30 days to address any queries but in practice these sometimes arrive very late making it difficult for the MAH to pull together a response within the specified timelines (bearing in mind the response may require input from a wide variety of functions). If the response is not submitted within the narrow time window, the PRAC decision is made on the basis of the original information received, ironically potentially impacting negatively on patient care.

An additional point to consider is the fact that there have now been several instances where the PRACs guidance and or expectations are not always completely harmonised with that of The Committee for Medicinal Products for Human Use (CHMP) rapporteurs which puts the MAH in an unenviable position.

OTHER CHANGES TO THE PBRER PROCESS

On the plus side, PSURs will not be required for ALL products in the EU as the new legislation waives the obligation to submit PSURs routinely for generic products, well-established use products, homoeopathic products, and traditional herbal products.

Also documents including the PSUR, Risk Management Plans, Development Safety Update Reports etc are now modular in structure with some modules overlapping one or more documents, allowing for an easier flow of information as well as a more structured evaluation within each document.

CONCLUSION

There are always inevitable teething problems the first time a new process is implemented and the PBRER is no exception. However the basic premise of assessing any risk in the context of any benefit is sound, and ultimately it is hoped this will benefit both patients and prescribers. ●

References/citations from this article are available upon request.