Getting Ready for the PSMF

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There are less than 18 months to go before the pharmacovigilance system master file (PSMF) becomes a requirement for all medicinal products authorised in the European Union (EU). But waiting until the deadline approaches is risky. Implementation is far from straightforward, and taking a hurried approach is unrealistic.

The PSMF is a detailed description of the pharmacovigilance system used by marketing authorisation holders (MAHs) with respect to their authorised medicinal products. It was introduced by the European Medicines Agency as a means to improve oversight and accountability and is a requirement, according to the agency's good pharmacovigilance practice (GVP) guidelines. Regulators can request a copy of a company's PSMF during evaluation of the company's marketing authorisation application (MAA), and the document must be made available to the assessors within seven days of the request. If the document lacks sufficient details regarding the applicant's existing pharmacovigilance system as defined in GVP Module I, it could trigger a safety inspection.

For companies that filed new MAAs since July 2012, the PSMF is already a requirement, which also applies in retrospect to products that undergo renewal.

Purpose of the PSMF

The PSMF replaces two documents: the Detailed Description of the Pharmacovigilance System (DDPS) and the Summary of Pharmacovigilance System (SPS). The DDPS would be submitted with the license, and the SPS would be requested by inspectors before inspection. Neither document, though, provided (1) the oversight or amount of detail—about pharmacovigilance activities—that the PSMF includes or (2) the detailed compliance metrics that make up a main part of the new document. Moreover, producing two documents was a duplication of effort.

The PSMF has some great benefits: (1) it is a resource that provides the MAH, the qualified person for pharmacovigilance (QPPV), auditors, and inspectors with oversight of both a company's existing pharmacovigilance system and the targets set for compliance; (2) it makes it easier to identify deficiencies in the system or instances of noncompliance with the requirements; and (3) it provides insight into risks—or actual failures—in the conduct of specific aspects of pharmacovigilance as well as into timelines; roles and responsibilities; interfaces between the various pharmacovigilance departments; review frequency of the process documents; the validation status of the safety database; descriptions of online data management tools; responsible parties for the various pharmacovigilance processes; and key performance indicators.

Having the PSMF in place not only improves overall pharmacovigilance systems but also reduces the burden in terms of documentation submitted as part of the MAA, as well as version control and storage. The PSMF also stands as a

useful tool to inform the QPPV and third parties about significant changes to the pharmacovigilance system—for example, validation status of the safety database, major contractual agreements covering pharmacovigilance, mergers and acquisitions, or initiation of or changes to pharmacovigilance sites.

The document is also expected to provide insight into audit findings, including open corrective actions and preventive actions (CAPAs) related to the pharmacovigilance processes of a product. It is envisaged that the PSMF will be used for assessment of whether MAHs are compliant with current GVP guidelines. The document will also offer insight into how soon MAHs could disseminate important patient safety information to relevant audiences—for example, Direct Healthcare Professional Communication letters or summary-of-product-characteristics variation submissions that inform the competent authorities and the European Medicines Agency.

More broadly, the fact that regulations are constantly changing and becoming more complex means higher levels of interdisciplinary expertise are needed, which in turn increases the need for good tools that can detect and respond to safety concerns.

Introducing the PSMF

Companies that have implemented the PSMF have generally been ones applying via MAAs; however, many small and medium-size enterprises have also voluntarily introduced the PSMF. The general response is that once the tedious job of listing the details of pharmacovigilance processes is done, the result becomes a great tool for QPPV oversight and for detecting deficiencies in the planned or existing system. It's also a great tool for maintaining compliance with GVP Module I on pharmacovigilance and quality systems.

For MAHs that are preparing PSMFs at the time of market authorisation:

Things to consider
Clear overview of companies involved and of relationships between the **pharmacovigilance** department, organisations, operational units, third parties (outsourced activities), and contractual agreements
Proof of registration of the QPPV and deputy QPPV with EudraVigilance
Description of methods applied for the monitoring of pharmacovigilance system performance
Clearly defined targets for performance indicators
Matrix for pharmacovigilance activities versus name of standard operating procedure

For MAHs that are introducing PSMFs into their dossiers postauthorisation:

Things to consider
Clearly defined list of tasks delegated by the QPPV to the deputy QPPV
Contact information for the local contact or local QPPV at the national level (local contact for pharmacovigilance)
Inclusion of all sources of safety data (e.g., patient support programmes, market research programmes, non-EU sources, noninterventional studies, registries, postapproval named-patient-use programmes, other patient support and disease management programmes, surveys of patients or health-care providers, compassionate use or named-patient use, and information gathering on efficacy or patient compliance)
Flow charts clearly describing the ICSR processing from collection to reporting,

including details regarding main steps, parties involved, and time frames
Description of electronic repositories
Details of compliance data for PSUR and **risk management plan** submissions, for expedited reporting, and for other performance indicators as applicable, including clearly defined targets
Audit notes, including open CAPAs and resolution dates

Metrics or key performance indicators are central to the PSMF and must be included in the annex together with results of those measurements. The GVP guidance lists minimum metrics for inclusion, but it also says companies should develop their own, company-specific metrics appropriate to their unique situations and scenarios. Inclusion of metrics is a useful tool not just for regulators but also for the company and its QPPV so as to ensure compliance and identify deficiencies in the preexisting pharmacovigilance system.

Areas that companies must monitor are:

- Timeliness of Individual Case Study Report (ICSR) and Periodic Safety Update Report (PSUR) reporting
- The quality of submissions, which would encompass completeness of information contained in ICSRs, adequacy of follow-up, and results of internal quality control checks on the ICSR and PSUR
- An audit finding by the pharmacovigilance system
- Timeliness of safety variations
- Adherence to risk management plan commitments

It is up to companies to determine the most-useful and best metrics that would provide them with an effective overview of the functioning of their pharmacovigilance systems.

Potential Problems

Despite the fact that the PSMF will ultimately become mandatory, many companies remain reluctant to introduce it, partly because they believe they still have a long time before the July 2015 deadline and partly because the new GVP guidelines require the training of relevant staff, which can be costly.

The problem with putting off implementation is that the PSMF is a complicated document that takes time and significant thought to prepare and construct. Companies also have to spend time considering whether they'll prepare the PSMF themselves or outsource the task. And if they decide to have a third party manage it for them, they have to ensure a mechanism of oversight is in place.

As with any major new development, problems can and will arise. For example, the German regulatory agency—the Federal Institute for Drugs and Medical Devices—provided an assessment of PSMFs it had received as of May 2013, noting that throughout the documents there were deficiencies in the information pertaining to pharmacovigilance systems. For example, in many of them, the section about the QPPV lacked proof of registration of the QPPV with the EudraVigilance database, lacked details about backup arrangements in the absence of the QPPV, and lacked information on the pharmacovigilance contact person nominated at the national level.

Being Prepared

The move to outsource all noncore functions means many companies are turning to service providers to manage either their entire

pharmacovigilance function or aspects of it. It is companies, however, that retain overall responsibility for the safety of their products and for making sure that the third parties they choose (1) can provide the necessary support, (2) have a thorough understanding of the regulatory guidelines, and (3) demonstrate the necessary compliance with the regulations.

Given the importance of the PSMF in the preapproval and postmarketing phases of a product life cycle, companies must ensure strong communication between members of the cross-functional team of subject-matter experts, who will be integral to the development of all of the annexes covering the information for all products. Companies must ensure transparency and communication with third-party vendors also, when dealing with process updates such as standard operating procedures, validation updates to their safety databases, and compliance information. All such updates have to be documented in the PSMF, which will be the first aspect that auditors scrutinise.

The PSMF requires a significant commitment, but early adoption can help companies avoid higher costs and greater complexities later, once it becomes mandatory.

About the author

Dakshayini (Daks) Kulkarni is Senior Pharmacovigilance Officer at ProductLife Group. In this role, she provides support to a variety of companywide pharmacovigilance (PVG) systems initiatives to facilitate process improvements that better align ProductLife's activities with the goals of its clients.

Daks serves as the senior contact for all PVG issues, liaising with clients and other cross-functional teams to help meet new pharmacovigilance needs across the lifecycle of the product, from clinical through the post-approval phase. Daks specialises in post-marketing safety management and reporting and European safety regulations and also helps clients prepare for meetings with regulatory authorities.

Daks has a Ph.D. specialising in cancer immunology from the Advanced Centre for Treatment, Research & Education in Cancer (ACTREC) at the Tata Memorial Centre, through affiliation with the University of Mumbai.

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