

Responding to concerns over the PSMF: Inspectors offer key insights

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Abstract

The pharmacovigilance system master file (PSMF) is a detailed description of the pharmacovigilance system used by the marketing authorisation holder for their authorised medicinal products. The PSMF is intended to be a live, custom-made document that accurately reflects the pharmacovigilance system put in place for a given product. It is expected to contain meticulous detail so that the marketing authorisation holder's compliance with current good pharmacovigilance practices guidelines can be assessed. This article focuses on the feedback provided by the inspectors during their assessment of the PSMF with an emphasis on areas for improvement.

Keywords: PSMF, Inspection findings, Metrics

In July 2012, the Pharmacovigilance System Master File (PSMF) became a requirement for companies filing new marketing authorisation applications. The PSMF is a detailed description of the pharmacovigilance system used by the Marketing Authorisation Holder (MAH) for their authorised medicinal products.¹ It is intended to be a live, custom-made document that accurately reflects the pharmacovigilance system put in place for a given product. Since its introduction, many questions have arisen about its scope, purpose, and implementation.

Much needs to go into the PSMF to ensure that it meets the goals established by the EMA to improve oversight and accountability of pharmacovigilance data. When requested as part of the inspection documentation, the PSMF should be made available within 7 days. Competent authorities can also request immediate access to the document at any time during a product's life cycle.

The PSMF improves oversight of the existing pharmacovigilance system, identifies deficiencies in the system, and provides insights into risks in the conduct of specific aspects of pharmacovigilance.

However, its implementation has posed several challenges: the PSMF includes extensive requirements that affect many functions and procedures; its maintenance is resource intensive; and adopting it has resulted in a steep learning curve for companies.

Today, with a growing number of companies implementing the PSMF, the issue is less about how to get started and more about how to overcome the problems that inspectors are pinpointing. Many companies are finding that they have to overhaul their PSMF because it lacks the details sought by the inspectors. Even though the PSMF guideline provides some details as to what is required, it is fairly open-ended, leaving a lot of room for interpretation.

Regulatory authorities at the Federal Institute for Drugs and Medical Devices in Germany and the Medicines and Healthcare Products Regulatory Agency in the UK have pointed out a number of gaps in the way the PSMF is being implemented. Their feedback has given MAHs certain insights into the regulators' perspectives on the guidelines and their expectations of the PSMF in practice. This article provides a practical guide on where and how the PSMF can be improved and what's been lacking – based on findings from inspectors.

Role of the qualified person for pharmacovigilance

Companies recognise that the PSMF is a valuable tool that enables oversight by the Qualified Person for Pharmacovigilance (QPPV), but the QPPV's involvement in dealing with major changes to the PSMF is not clearly understood. The QPPV must be informed of any content changes that fulfil the criteria for oversight of the pharmacovigilance system regarding capacity, function, and compliance. In addition, changes in the safety database,

major contractual changes, and organisational changes should be communicated to the QPPV.

The addition of corrective and/or preventive actions to the PSMF – for example, following audits and inspections – must be reported to the QPPV, who should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance. When an existing product requires a change or an increased workload with respect to any pharmacovigilance activity – for example, new indications, ongoing studies, or the addition of territories – the QPPV must be notified. Other areas that companies need to ensure the QPPV gets advised about are:

- Changes in arrangements for provision of the PSMF to competent authorities.
- Transfer of significant pharmacovigilance services to a third party – for example, the outsourcing of Periodic Safety Update Report (PSUR) production.
- Inclusion of products into the system for which the PSMF is responsible.
- Additions to or changes in the pharmacovigilance contact person nominated at the national level.

The QPPV must accept any such changes in writing.

Other findings involve proof of registration of the QPPV with the EudraVigilance database, the absence of details pertaining to the QPPV's backup arrangements, and contact information for the local QPPV nominated at the national level.

How much data?

One of the issues with the PSMF is that the guideline does not define boundaries covering data that should be submitted, which made it difficult for companies to determine upper and lower limits. If the PSMF lacked data, it raised flags, which often led to further document requests during inspection. The fact is that companies are reluctant to provide more data than required because they don't want to invest too much time or too many resources in including data that might not be needed. As a result, inspectors often found that the document lacked sufficient details.

The following aspects are expected to be included in the document:

- Description of the methods applied for monitoring pharmacovigilance system performance.
- List of performance indicators, including both performance measurements and targets.
- Matrix with pharmacovigilance activity versus Standard Operating Procedure (SOP) name.

- Description of risk-based approach to audit planning and/or audit frequency.
- Audit notes.
- Logbook to show individual changes to the body of the PSMF.

Clarifying metrics

Metrics or key performance indicators are central to the PSMF and must be included in the annexes together with the results of those measurements. The indicators used to monitor the pharmacovigilance system performance should, at a minimum, include timeliness of individual case safety report and PSUR reporting, quality of submissions, timeliness of safety variations, and overview of adherence to risk management plan commitments or other obligations or conditions for marketing authorisations.

Feedback from inspectors has defined the extent of some of the metrics. For example, compliance data for safety variations should include the following:

- Date on which the company decided that a safety variation was necessary – and the rationale for choosing that date.
- *Targeted* submission date and *actual* submission date (against internal timeline as per SOP).
- Date of approval by the Committee for Medicinal Products for Human Use at the EU level and at the national level, as applicable.
- Date of revision of the text of the summary of product characteristics, including questions around the 10-day timeline to update the electronic Medicines Compendium website.
- Date the patient information leaflet was introduced to product packs.

Annexes and logbook

The content of the annexes can undergo frequent changes; however, the changes do not have to be recorded in the logbook. Annex information can be managed outside the PSMF (independently versioned) but should be available on demand. Annex-related inspection findings include lack of details about worldwide agreements applicable to an EU-authorized product, including affiliate agreements (Annex B); incomplete list of countries in which the product is being marketed; and insufficient details surrounding the nature of the activity and site contact details (Annex C).

The logbook should reflect descriptive changes made to the main body of the PSMF. Changes to the PSMF annexes do not need to be recorded in the logbook; however, change control should be in

place. A frequent finding concerning the logbook is that it contains only generalised descriptions of the changes made to the main body of the document, for example, a major update to the section about the QPPV; the logbook should provide specific details regarding individual changes made to the body of the PSMF.

Recording deviations and corrective and/or preventive actions

Deviations from the quality system should be documented in the main body of the PSMF until they have been resolved. Although it is not expected that every unplanned SOP deviation will be recorded, the MAH is expected to demonstrate that assessments of the impact of such deviations were carried out. In addition, the logbook should contain information regarding the addition, amendment, and removal of notes concerning significant audit findings or quality system deviations.

Notes associated with significant audit findings are to be recorded in the main body of the PSMF. Cross-references to the associated audit report are to be avoided. The note should include a brief summary of the finding, a summary of the corrective and/or preventive actions, the date on which the finding was identified, and the anticipated resolution date. Only audits conducted or commissioned by the MAH are to be included in the PSMF.

Corrective and preventive actions associated with unresolved notes in the PSMF should be identified in the corresponding annex. Notes can be removed from the PSMF only when the proposed corrective and preventive actions have been fully implemented. Recording removal of the audit notes verifies that sufficient improvement has been demonstrated or independently verified.

Responding to the EMA's findings

Information from inspectors and assessors represents a useful guide to help companies improve

the PSMF. Regulators have made it clear that it is not acceptable to simply list the MAH's documented procedures. Rather, the PSMF should contain a description of the processes of:

- Continuous monitoring of risk-benefit profiles
- Risk management systems
- Individual case safety report collection, collation, follow-up, and reporting
- PSUR scheduling, production, and submission
- Communication of safety concerns
- Implementation of safety variations.

Besides the safety database, any other systems or databases that are used to receive, collate, record, and report safety information must be described. These include medical information systems, product quality databases, clinical trial systems, and any other system important for the collection of safety data.

The MAH also has to provide proof that any delegated activities are performed in compliance with legal requirements. The PSMF should document deviations from pharmacovigilance procedures (including impact) until they have been resolved.

Implementation of the PSMF remains an immense and complex task, but the level of details that inspectors have started to provide in their feedback goes a long way to assist companies and their outsourcing partners in the preparation of a comprehensive document – one that will limit exposure to problematic inspections.

Reference

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