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Building on belief

Pharmacovigilance system master file and inspection readiness

Abstract

The Pharmacovigilance System Master File (PSMF) is a document, designed to summarize the pharmacovigilance (PV) system of the marketing authorization holder (MAH). This document is named differently in many countries, namely, PvMF in India and in the EU, it is known as PSMF. In the EU, this term was first introduced in the 2010 revision of the 2001/83/EC European Union Directive identified as 2010/84/EU as well as Regulation 1235/2010 [1][2][3], which jointly govern PV activities in the EU. In the European Economic Area (EEA), MAHs who hold market authorizations (MAs) for one or more medicinal products, are required to have a PSMF. Several countries have diverse PSMF requirements, while few others including the other ICH regions, do not mandate having a PSMF, details of which, have been discussed later in this paper.

Additionally, the requirements for PSMF maintenance, its various components, and how to have an inspection-ready PSMF have been discussed in detail in this paper.

Why do companies need PSMF?

The legal requirement for MAHs, to maintain and make the PSMF available upon request, is to strengthen and rationalize the monitoring of the safety of medicinal products, and for PV activities harmonization. The content of any PSMF should clearly display global availability of the safety information for medicinal products authorized in the region[4].

How should PSMF be maintained?

In the EU, the PSMF needs to be located, either at the site where the main PV activities are performed, or at the site where the Qualified Person for PV (QPPV) operates from. Following EEA agreements, the PSMF can also be located in Norway, Iceland, or Liechtenstein. The required location information for the PSMF is a physical office address of the MAH, or a contracted third party. The MAH is responsible for establishing the PSMF in an EU country, and for registering the master file location with the competent authorities in the Article 57 database. This document should be written in English, unless the MAH holds approvals in only one Member State, wherein, it can be written in the EU official language for that territory. Post Brexit transition, effective January 1, 2021, MAHs need to ensure that the UK PSMF is located at the same point in the UK, from where the reports of suspected adverse reactions are referred to[5].

The PSMF could be stored either in paper or in electronic form. It could be a virtual document, existing on different servers in the company, or at suppliers of data services, but a clearly arranged printed copy needs to be made available for inspections. Due to the COVID-19 pandemic, companies are maintaining the PSMF electronically, as a live document and inspections are being handled with remote assistance from the QPPV office.

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[1] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
[2] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
[3] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF
[4] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf
[5] https://www.gov.uk/guidance/guidance-on-qualified-person-responsible-for-pharmacovigilance-qppv-including-pharmacovigilance-system-master-files-psmf-if-the-uk-leaves-the-eu-w

What should PSMF contain?

The minimum requirement for contents of the EU-PSMF, and its maintenance are set out in the Commission Implementing Regulation (IR) (EU) No 520/2012, along with guidance of Good Pharmacovigilance Practices (GVP), Module II4.

The core sections need to contain details of the QPPV, structure of the MAH, information on the computer systems and databases, sources of safety data, data handling processes (ICSRs, PBRERs, REMs, studies, communication of safety issues, mechanisms for changes to the SmPC and patient leaflet), and Quality System for PV (subcontracted, and outsourced activities).

In the annexes, the below-mentioned items need to be detailed in a comprehensive way:

- The CV of the QPPV
- List of:
  - Contracts and agreements including subcontractors with copies of the signed agreements
  - Sources of safety data including affiliates and third parties
  - Computerized systems and databases
  - SOPs and procedures
  - Performance indicators
  - Scheduled and completed audits and those with significant findings and unresolved issues
  - Products and EU countries wherever approved
  - Audit trail of changes to the PSMF over the last five years

Inspectorate insights

i. Why Is PSMF Critical for Inspections?

PSMF embodies the complete PV system of the MAH, thereby providing an accurate reflection of all information that has an impact or is linked with PV. If the MAH, partner, or vendor, handles adverse events and other safety data from EU, it is critical to have the PV data in the PSMF, thereby becoming liable to inspections by the EU. Thus, the premises, records, documents, and PSMF are subject to inspection, whether in the EU or not, and non-EU companies should ensure that their EU partners' PSMF is up to date. Upon request by the National Competent Authority (NCA) or the European Medicine Agency (EMA), the MAH needs to provide a copy of the PSMF within a seven-day timeframe.

ii. How Can PSMFs Be Inspection-Ready?

PSMF maintenance can be a complex task, especially for companies where the PV system is distributed globally, or subcontractors are used. Companies need to have a mechanism to prepare and keep the PSMF up to date, as high-risk situations are likely to trigger an inspection. These high-risk situations include:

- Drugs with an RMP or post-authorization safety studies (PASS)
- Products with high sales volumes
- Products with limited alternatives in the market
- A company that has never been inspected
- A company with many products on the market or no previous drugs on the market

- Problems in other inspectable GxP areas
- A recent merger or acquisition
- A company that outsources some or all PV activities
- A new or changed PV database
- New PV service providers or changes at the service providers, PSMF delegation, etc.

Additionally, to have an inspection-ready PSMF, organizations must have ways for receiving all PV-related information from cross-functional stakeholders and service providers. Some of the common oversights are:

- Outsourced activities
- The security and availability of data and records
- QPPV oversight
- Third-party and vendor activities
- Inclusion of risk assessments of third parties in the audit schedules
- The functioning of the Quality Management System
- Enlisting all sources of safety data
- Having a list of validated databases with required validation documents
- Updated organizational structure mentioning the QPPV's role
- Proper governance and escalation matrix
- Complete and accurate company-wide information relayed to the PSMF author

iii. Inspection Metrics

Most inspection findings are related to deficiencies in the data provision of the PSMF[6], some of which are:

- Data provision for supervision by NCAs including via inspection
- Non-comprehensive PSMF data content
- Supervision and oversight in PSMF maintenance

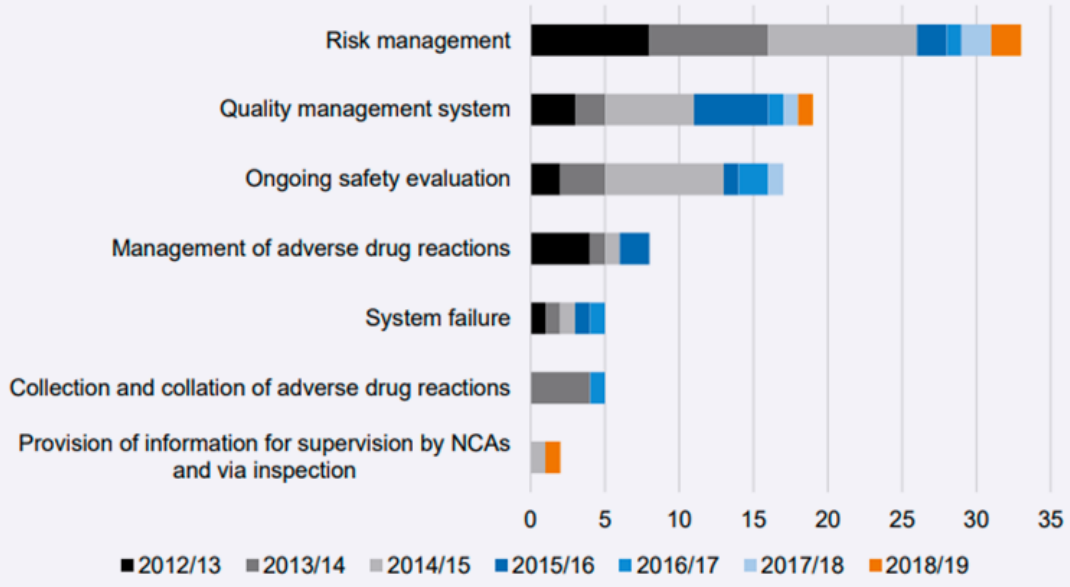

Figure 1: Number and distribution of critical findings across topics

[6] https://www.gov.uk/government/statistics/pharmacovigilance-inspection-metrics-2009-to-present

For a total of 89 critical findings across different topics between 01 April 2012 and 31 March 2019, the distribution is as below:

PSMF requirements in other countries

Recently estimated figures suggested that over 30 countries across the globe, now have requirements for a PSMF. Countries governed by the League of Arab States accept the EU-PSMF, but require additional document names, such as the PV System Sub-File[7]. Meanwhile, India requires MAH to maintain a PSMF, where the main PV activities take place[8]. TGA Australia accepts a global PSMF with a description of the Australian PV system[9], whereas other ICH regions, namely, Japan PMDA, as well as Health Canada or USFDA do not mandate a PSMF. However, all the Health Authorities can request for an EU PSMF, if the MAH has products registered in the EU.

Summary

In summary, the PSMF should provide a clear overview of all critical PV processes and procedures in managing compliance with the legal requirements. The PSMF must always be kept up to date and there must be a process for ad hoc revisions as well as periodical updates. The future strategies of data inclusion in PSMF would be more advanced, owing to Artificial Intelligence (AI) techniques. AI tools can be used to automate almost every aspect of data inclusion, thereby reducing the cycle time and ensuring better quality and accuracy in PSMFs.

[7] http://www.panaceapharmaprojects.com/panaceainsights/global-pharmacovigilance-what-are-the-challenges/

[8] https://pink.pharmaintelligence.informa.com/PS122184/India-Specifies-Requirements-For-Pharmacovigilance-System-Master-File-Qualified-Person

[9] https://www.tga.gov.au/sites/default/files/pharmacovigilance-inspection-program-guidance-medicine-sponsors.pdf

About the author

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Prantika Khetarpal is a Pharmacovigilance professional with over 18 years of work experience in Core Pharma organizations, Outsourcing vendors, and Academia. With an over 14 years of experience in Pharmacovigilance Operations and Management, she brings forth a vast knowledge and exposure in expanding PV footprint globally and leading PV in multiple geographies. She has an experience of leading and participating in successful Health Authority Inspections, of US-FDA, MHRA, EMA, BfArM and TGA inspections also being a Pharmacovigilance System Master File (PSMF) author herself, in her previous work experience. She is experienced in Global PV transitions & presently within TCS, she is working as a PV Domain Consultant.

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