Federal Agency for Medicines and Health Products
(FAMHP)

Pharmacovigilance System Master File (PSMF), QPPV and audits

Matthijs Nele,
PhV Inspector, DG Inspection

BRAS - 15.05.2012

Content

- Introduction
- Old – New situation : - DDPS – PSMF
  - Local contact person requirements
  - Transition from DDPS → PSMF
- PSMF : - Specifications
  - Content (different sections and annexes)
- QPPV responsibilities
- Audits en inspections
- Conclusion

Introduction

The request a pharmacovigilance system master file (PSMF) was introduced by

Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (Recitals (22) and (25), Article 16(4), to harmonise and strengthen the conduct of pharmacovigilance activities in the EU.

➔ In force 2nd of July 2012

➔ Applicable on centralized procedures

And

Directive 2010/84/EU amending Directive 2001/83/EC (Recitals (7) and (35), Article 23(4), Article 104(3)(b))

➔ In force 21th of July 2012

➔ Applicable on MRP/DCP procedures (incl. NP)

GVP : Guideline

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annex: Draft list of GVP Modules[2]

GUIDANCE ON GOOD PHARMACOVIGILANCE PRACTICES (GVP)

INTRODUCTION	Legal Basis and Structure of Pharmacovigilance Guidance
MODULE I	**Pharmacovigilance Systems and their Quality Systems**
MODULE II	**Pharmacovigilance System Master File**
MODULE III	Pharmacovigilance Inspections
MODULE IV	Audits
MODULE V	**Risk Management Systems**
MODULE VI	**Management and Reporting of Adverse Reactions to Medicinal Products**
MODULE VII	**Periodic Safety Update Reports**
MODULE VIII	**Post-Authorisation Safety Studies**
MODULE IX	**Signal Management**

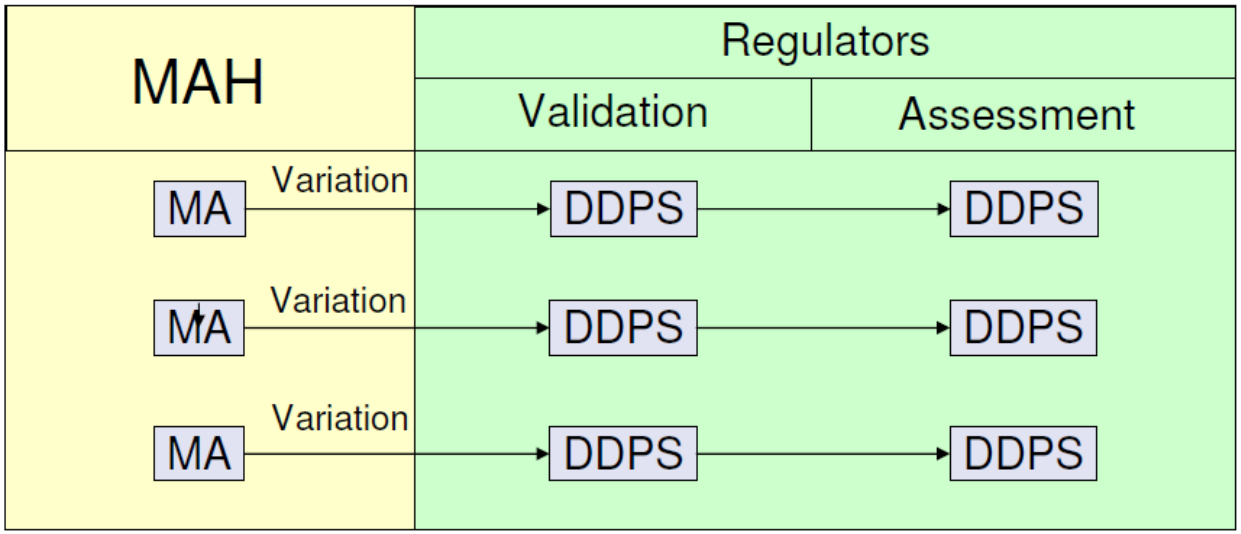
Draft version available during PC

Draft July 2012 ?

Old / New situation : DDPS → PSMF

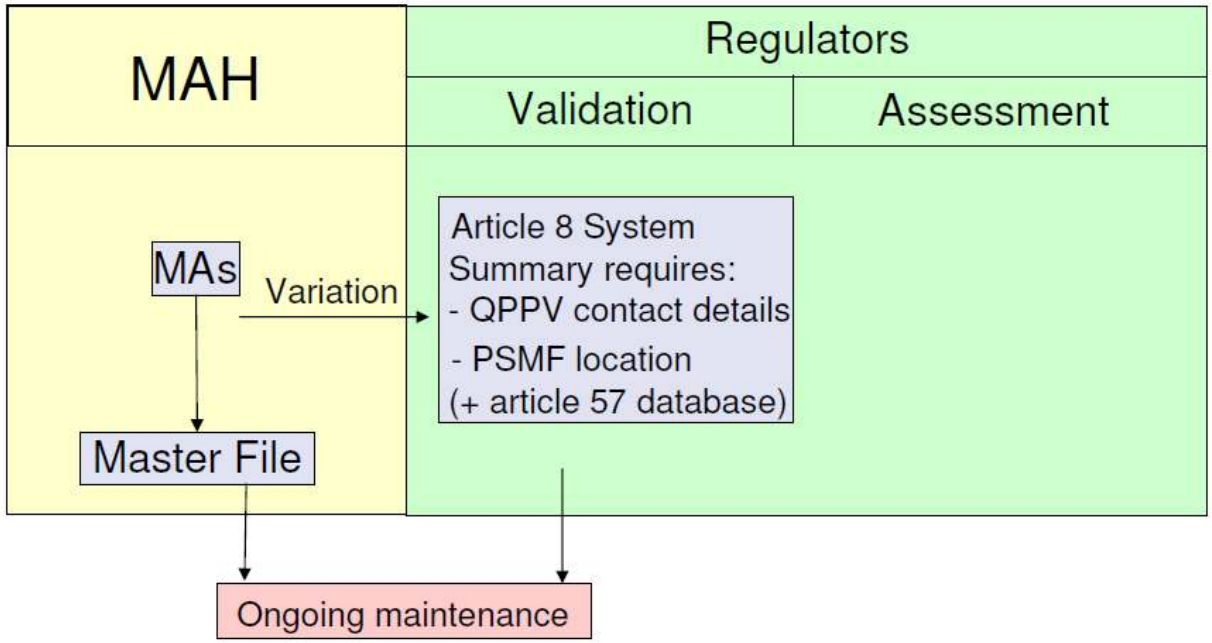
DDPS	→	**Master file**
Part of applicati	→	No part of application, accessible at the Master file site location
detail cription of PhV s ucture In 9A)	→	detailed (new content – defined) in GPV, module II
pdated with variations	→	limited variations, available on demand within 7 days

Simplification - the concept (past)



Variations required for DDPS updates include: QPPV change, QPPV contact details change, back up of QPPV, change in the safety database, change in contractual arrangements, topics covered by written procedures, PV sites, (other) (*CI.9 of variations classification guideline*

Simplification - the concept (Future)



The PSMF will be kept up to date without variations. Variations will be required only for changes to the pharmacovigilance system summary (Article 8)

Old / New situation : local QPPC → contact person

before 21/07: Local QPPV

-P-nu (cir 4)
(pharma /veterinary)

-1attest y perience

-24h/24h – 7/7 days

- certificate of MAH (circ 545) stating who was the local responsible QPPV

-When changes apply : update by annex of circular 520,to be sent to PhVinsp@fagg.be

after 21/07: local contact person

-No P number required
-No attest on experiences

24h/24h – 7/7 days

-Should operate in Belgium
-MAH should state that local CP has the appropriate qualifications to perform his PhV activities
-Linguistic requirements
-Should report to the EU-QPPV

When changes apply : update by adapted annex of circular 520 (new circular),to be sent to PhVinsp@fagg.be

!!Local representative should be notified before submission of an application, at latest on End of Procedure

Transition DDPS → PSMF

Common Rules

• Centralized procedures : before 2 July 2012
→Old regulation

• National (incl MRP/DCP) procedures : before 21 July 2012
→Old regulation

Europese Commission published Q and A's for the transition period :
http://ec.europa.eu/health/files/pharmacovigilance/2012_02_qa_phv.pdf

Transition DDPS → PSMF

Type of medicinal products	Requirement for a PhV system	Requirement for the location of the PSMF in the application	Requirement for a risk management system	Requirement to submit a risk management plan
TU herbal simplified registration	**APPLIES**	*DOES NOT APPLY*	**APPLIES**	*DOES NOT APPLY*
Herbal medicinal product other than TU simplified registration	**APPLIES**	**APPLIES**	**APPLIES**	**APPLIES**
Homeopathic simplified registration	*DOES NOT APPLY*	*DOES NOT APPLY*	*DOES NOT APPLY*	*DOES NOT APPLY*
Homeopathic medicinal product other than simplified registration	**APPLIES**	**APPLIES**	**APPLIES**	**APPLIES**

➔although applicants for THMP registrations will not have to include a PV system summary in the application, article 104 still applies in that a PSMF will need to be made available and maintained

Transition DDPS → PSMF

- **What :**

All existing authorisations (except HSR) must be considered in the PSMF, whether they have currently a DDPS or not.

When?

- By renewal or by ultimate 2 July 2015 (central procedures or 21 July 2015 (NP , MRP, DCP)
- No grace period foreseen

How?

DDPS → PSMF = Variation Ia,
Submission of the summary of the PSMF
Every variation to the content of the summary of the PSMF = variation Ia, according to guidline (if the Guideline is not ready by 21 Juli, CMDh considers a proposal via Art 5 procedure for Unforeseen variation).

To clarify if non-DDPS products need a variation : different interpretations

Transition from DDPS → PSMF

-Submission of information about the location of the pharmacovigilance system master file that occurs at times other than a marketing authorisation application or a renewal application must be submitted as a variation .

-In order to facilitate the submission of master file location information for more than one product covered by a single pharmacovigilance system (and therefore with a common pharmacovigilance system master file), the variations can be grouped as per the Commission Regulation (EC) No 1234/2008 and the associated Guideline).

Substantial number of PC comment regarding the need for a single 'one-off' change to PSMF rather than country by country grouped variations - for transitional QnA to cover. It is not anticipated that this is possible within the legal framework (EMA reg/legal to comment if different).

Content Summary of the PSMF

1.8.1 Summary of Pharmacovigilance Master file

-Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance

-A statement signed by the applicant to the effect that he has the necessary means to fulfill the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

-The contact details of the QPPV

-Curriculum Vitae of the QPPV (?)

- PSMF location and PSMF number

Master File : specifications

-Provides an overview of the pharmacovigilance system

-may be requested and assessed by national competent authorities during marketing authorisation application(s) or post-authorisation. 7 days to deliver PSMF.

-The pharmacovigilance system master file shall be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site where the qualified person responsible for pharmacovigilance operates [IM Art 3(1)], irrespective of the format (paper-based or electronic format file

- The supervising authority for inspections is that country where the PSMF is located.

Master File : specifications

• When determining the main site → consider the most relevant EU site for the pharmacovigilance system as a whole and have an appropriate rationale for the location decision.

• In the situation where the main activities take place outside the EU, or where a main site cannot be determined, the location should default be the site where the QPPV operates.

• MAH may apply for separate PhV systems (and thus more than 1 PSMF per MAH is possible) f.e. different categories of medicinal products.

•To clarify : 1QPPV/ 1 PSMF / PhV system/

1 Local contact person / PSMF

• A QPPV may be employed by more than one MAH, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one system of the same MAH, provided that the QPPV is able to fulfil all obligations.

Content PSMF: focus on new points compared to DDPS

No obliged template in the GVP – however, detailed guidance will be given and can be used

- QPPV details :additional requirements
  - A description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;
  - A list of tasks that have been delegated by the qualified person for pharmacovigilance (in Annexes)

- Product list : with details about authorisation/MS, commercialisation, etc…)

- Delegating activities / third parties : Description of the delegated activities, MAH ultimate responsibility

Content PSMF: focus on new points compared to DDPS

- Computerised systems and databases : The validation status

- Sources of safety data :

▪Medical information sites, affiliate offices, third parties (license partners or local distribution/marketing arrangements, describing contracts and agreements

- PV system performance : evidence of the ongoing monitoring of performance of the PhV system including compliance of the main outputs of pharmacovigilance [IM Art 4(1), Art 11]:

▪An explanation how the correct reporting of ICSRs is assessed.
▪Figures/graphs showing compliance of 15-day and 90-day reporting;
▪Description of quality of submissions and performance. E.g. compliance PSUR reporting; overview timeliness of safety variation submissions;
▪Where applicable, an overview of adherence to risk management plan commitments, or other relevant obligations or conditions of MA

Content PSMF: focus on new points compared to DDPS

- Quality System :
  - List of Processes (annex) :

    -Reference number, title, effective date (for all standard operating procedures, work instructions, manuals etc.), and a description of where the documents can be accessed.
    - SOPs from to service providers and other third parties should be clearly identified.
    - Documents relating to specific local/country procedures need not be listed, but a list may be may be requested on a per country basis

  - Training : - Description of the resources
    - the number of people involved in PhV activities and a reference to the location of their qualification records;
    - Listing of sites where the personnel are located;
    - summary description of the training concept, including a reference to the location training files;

Content PSMF: focus on new points compared to DDPS

- Auditing :
  - Proces description (timeframe, approach)
  - List of the scheduled and completed audits in the annex
  - This list should describe the date(s), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites
  - CAPAs and their impact included (removed when resolved), deadlines for completion and date of theCAPA plan

- Annexes (lists)

Content PSMF annexes

The Qualified Person responsible for pharmacovigilance, Annex A

- The list of tasks that have been delegated by the QPPV,
- The curriculum vitae of the QPPV and associated documents
- Contact details supplementary to those contained in EVMPD if appropriate

The Organisational Structure of the MAH, Annex B

- The lists of contracts and agreements
- Copies of signed agreements

Sources of safety data, Annex C

- List of studies, registries, surveillance or support programmes
- Lists associated with the description of sources of safety data

Content PSMF annexes

Computerised systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E
- Lists of procedural documents

Pharmacovigilance System Performance, Annex F
- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

Quality System, Annex G
- Audits schedules
- List of audits conducted and completed
- CAPA : resolved? (still under discussion to be included or not

Products, Annex H
- List(s) of products covered by the pharmacovigilance system
- Notes concerning the MAH per product

Content PSMF annexes

Change control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed

Documentation to support notifications and signatures concerning the pharmacovigilance system master file, as required

EU-QPPV

The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the pharmacovigilance activities and the quality system [IM Art 13(1)].

The MAH should therefore ensure that :

- the QPPV has access to the PSMF as well as authority over it and is notified of an changes to it.

- the QPPV has the authority over the pharmacovigilance system and the PSMF

- should allow the QPPV to implement changes to the system and to provide input into risk management plans (see Module V) as well as into the preparation of regulatory action in response to emerging safety concerns (see Module XII).

EU-QPPV

The types of changes that should be routinely and promptly notified to the QPPV are:

•updates to the PSMF or its location that are notified to the competent authorities;
•the addition of corrective and/or preventative actions to the PSMF(e.g. following audits and inspections) and deviations
•changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
•changes in arrangements for the provision of the pharmacovigilance system master file to competent authorities.
The recipient QPPV should explicitly accept the following changes in writing:
•inclusion of products into the pharmacovigilance system for which the QPPV is responsible
•transfer of responsibility for a pharmacovigilance system to a QPPV.

Audits : Module IV

➔IV.C.1.1.1 Requirement to perform an audit

The marketing authorisation holder in the EU is required to perform a regular audit of their pharmacovigilance system. [DIR Art 104 (2)].

➔Requirements for audit reporting in the EU

- The MAH shall place a note concerning the main findings of any audit relating to the PhV system in the PSMF
- Based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented.
- Once the corrective actions have been fully implemented, the note may be removed [DIR Art 104(2)] (see Module II).

Audits : Module IV (draft)

- The risk-based approach to pharmacovigilance audits
- The Audit Strategy and risk assessment for strategic audit planning
- The risk-based annual audit programme and risk assessment at the tactical level
- Planning and fieldwork
- Reporting and actions based on audit recommendations and FU
- Independence and objectivity of audit work and auditors
- Qualifications, skills and experience of auditors
- Audits undertaken by outsourced audit service providers

Audits

➔An **audit programme** should cover all parts of the pharmacovigilance system including:

- Critical pharmacovigilance processes (see Module I);
- The quality system, to assure that it complies with the established quality requirements and to determine its effectiveness.
- Interactions and interfaces with other departments (e.g. medical information, regulatory affairs, product quality, sales and marketing);
- PhV activities conducted by affiliates and pharmacovigilance activities delegated to an another organisation subject to contractual arrangements.
- The rationale for the timing, periodicity and scope of the individual audits should be based on documented risk assessment

Audits : list of examples of risk factors

➔<u>non-exhaustive list of risk factors</u> ➔ to be considered for a risk based assessment for audit planning.

•**risk to availability of adequately trained and experienced pharmacovigilance staff**, e.g. due to significant turn-over of staff, deficiencies in training processes, recent re-organisation, recent increase in volumes of work;

•**significant changes to the system** since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements;

Audits

- **Criticality of the process,** e.g.:
  How critical is the area/process to proper functioning of the system. When deciding when to audit an affiliate, to consider the nature and criticality of the PhV activities that are being performed by affiliate or third party

- **Outcome of previous audits**, e.g.
  Has the area/process ever been audited (if not, then this may need to be prioritised depending on criticality); if previously been audited, the audit findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;

- **Identified procedural gaps relating to specific areas/processes;**

- **Other intelligence** relating to compliance with legislation and guidance, for example : information from compliance metrics, from inspections, from complaints, from other external sources, e.g. audits

•previous information (e.g. inspection history and non-compliance notifications/information from other authorities) indicates that the applicant has poor history/culture of compliance.
mechanism to confirm that improvements have been made to the system before a new authorisation is granted;

Inspections

Pre autorisation inspections :

-Not mandatory, but may be performed in specific circumstances.

-Applicant has not previously operated a pharmacovigilance system within the EU

-Previous information (e.g. poor inspection history compliance and non-compliance notifications/information from other authorities);

-Mechanism to confirm that improvements have been made to the system before a new authorisation is granted where there is a history of serious and/or persistent PhV non-compliance

-Ability for risk minimisation activities or other safety concerns

Pre Authorisation Inspections : recommendations

If the outcome of the pre-authorisation inspection is that the applicant is unable or unlikely to comply

Following recommendations may be considered:

•non approval of the marketing authorisation;

•a re-inspection prior to approval to confirm critical findings/recommendations are addressed

•granting of the marketing authorisation with the recommendation to perform an early post-authorisation pharmacovigilance inspection.

Inspections

-Focus on communication within the EU :

-Planning and conduct of inspections

-Combined country inspections

-Share information on inspection deviations / CAPA which then may be used : -to plan national inspections
-to manage follow up of specific CAPA (coming from other-country inspections)

Conclusion

Simplification – operational

•A uniform information set describing the pharmacovigilance system is available to the QPPV and for the purposes of audit. Tool for QPPV to oversee and manage system.

• There is a reduced burden in terms of documentation submitted as part of the MAA, for MAHs and NCAs: version control, storage.

•Less routine assessment of the system description: a practical reference for inspection and audit

•There will be a harmonised and consistent PSMF for NCAs to use to plan Inspections

• Opportunity to use existing systems and to generate content for submission when requested

Thank You