



# How to be an EU QPPV... What You Need to Know and what's new

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## Is A QPPV Needed?



- Anyone marketing a medicinal product in any of the 27 Member States of the European Union (EU) or the 3 EEA Member States (Iceland, Liechtenstein and Norway) must have a QPPV.
- Also anyone applying to market a product in the above countries must prove they have the services of a QPPV in their MAA.
- Applies to all MAA procedures (centralised, decentralised, MR, national).
- Clinical trial Sponsors don't need a QPPV. 

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## Can there only be 1 QPPV?



- There can be only one for each PV system
  - Volume 9A, Part I, Section 1.2: "Each company (i.e. Applicant/Marketing Authorisation Holder or group of Marketing Authorisation Holders using a common pharmacovigilance system) should appoint **one** QPPV responsible for overall pharmacovigilance for all medicinal products for which the company holds marketing authorisations within the EU".
- Can be one QPPV for separate PV systems (e.g. one each for OTC, pharmaceuticals and vaccine divisions)
- National responsible people can still be appointed if required by national law (e.g. in Germany and France). In new EU PV legislation these people must report to QPPV.



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## Location of the QPPV



- Current EU legislation requires that the QPPV "shall reside in the Community"
- New legislation requires the QPPV to "reside and operate in the Union"
- Deputy/back-up for QPPV must also reside in EU (Volume 9A, Part I, Section 1.2.1)
- EEA as well as EU Member States are acceptable



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## Obligations of MAH and QPPV



- MAH and QPPV have overlapping and interdependent obligations as regards pharmacovigilance.
- Both need to be involved in establishing and managing the pharmacovigilance system.



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## Who is liable for Compliance?



- MAH or QPPV?
- BOTH...need mutual oversight of each other
- QPPV is a function of MAH and has specific personal responsibilities and liabilities (similar to GMP QPs)
- MAH has overall responsibility for its MAs, is legally liable both under pharmaceutical and consumer protection laws, and is ultimately responsible for the quality of the QPPV.



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## MAH's Responsibilities to the QPPV



- Described in Volume 9A, Part I, Section 1.2.2
  - "The Marketing Authorisation Holder should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the fulfilment of the QPPV's responsibilities and tasks."
- MAH should provide the following for QPPV:
  - Documented responsibilities (job description)
  - Procedures concerning QPPV
  - Supply of risk/benefit information to QPPV, including information from clinical and pre-clinical studies and from contractual partners (e.g. marketing partners and distributors)



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## MAH Support for the QPPV



- The MAH should ensure that the QPPV has sufficient authority
  - to implement changes to the PV system in order to promote, maintain and improve compliance
  - to provide input into Risk Management Plans and the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals).
- Responsibility without power is mere liability



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## QPPV's Responsibilities



- Described in Volume 9A, Part I, Section 1.2.1
  - Establishing and maintaining/managing the MAH's PV system;
  - having an overview of the safety profiles and any emerging safety concerns related to MAH's authorised products;
  - act as a single contact point for the Competent/Regulatory Authorities on a 24-hour basis;
  - have oversight of the PV system in terms of structure and performance.
  - Maintain and approve the Detailed Description of the Pharmacovigilance System (DDPS)



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## Responsibility for Reports



- The QPPV is also responsible for the following reports to Competent Authorities:
  - ICSRs
  - PSURs (for centralised products QPPV must sign, or have formal delegate sign)
  - Company sponsored post-authorisation safety studies (PASS)



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## Inspections



- Volume 9A, Part I, Section 1.2.1:
  - "The QPPV should also act as the Marketing Authorisation Holder's contact point for pharmacovigilance inspections or should be made aware by the Marketing Authorisation Holder of any inspection, in order to be available as necessary."
- The QPPV is also almost certain to be interviewed during a PV inspection.



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## Delegation of Responsibilities



- The QPPV may delegate specific tasks to appropriately qualified and trained individuals.
- Essential in large organisations.
- However, QPPV must maintain oversight of the system and the safety profiles of all products.
- Delegation should be documented. Can be described as part of the system, e.g. in SOPs, but QPPV should signoff relevant SOPs.



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## Back-Up For QPPVs



- Volume 9A, Part I, Section 1.2 requires MAHs to notify;
  - Their QPPV's contact details and
  - The back-up procedure for the QPPV
- Although the role of a deputy-QPPV is not defined in Volume 9A, Part I, Section 1.2.1 alludes to it:
  - "In case of absence, the QPPV should ensure that all responsibilities are undertaken by an adequately qualified person."
- Volume 9A refers to delegation but not to deputisation.
- Some CAs request a designated deputy-QPPV
- QPPV should exercise due diligence in who they delegate to.



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## QPPV Qualifications



- Volume 9A has no specific requirements:
  - "The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfil the responsibilities and tasks of the post. If the QPPV is not medically qualified, access to a medically qualified person should be available."



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## What is "Appropriately Qualified"?



- A QPPV's qualifications, knowledge and experience should be appropriate to the nature of their MAH's activities.
- For example, there's no need for them to have in depth knowledge of clinical trials if their MAH does not sponsor any clinical trials.



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## DDPS



- There is an expectation that the QPPV approves their MAH's Detailed Description of the Pharmacovigilance System (DDPS).
- Provided in Module 1.8.1 of MAA
- Post-authorisation changes to DDPS must also be notified.



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## Variations Regulation



- Variations Regulation (EC) 1234/2008 came into force on 01 January 2010.
- Applies to MAs granted through centralised, decentralised, and MR procedures.
- Applied to MAs granted through national procedures via Directive 2009/53/EC.



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## Updating the DDPS



- Variations Regulation requires changes to the DDPS to be notified as variations
- A new PV system is a Type II variation
  - Can be Type IB if system has already assessed for another product.
- Other Changes to an existing DDPS are mostly Type IA<sub>IN</sub> (IN = immediate notification, 14 days)
- Only non-operational changes are Type IA
- Requirements given in Sections C.I.8 and C.I.9 of classification guideline  
[http://ec.europa.eu/health/files/betterreg/pharmacos/classification\\_guideline\\_adopted.pdf](http://ec.europa.eu/health/files/betterreg/pharmacos/classification_guideline_adopted.pdf)

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## PV System Master File (PVSMF)



- Required by new EU PV legislation to replace DDPS:
  - Required for new MAAs by July 2012 and for all remaining products from 21 July 2015
  - MAH required to perform regular audits of their PV system and prepare and implement appropriate corrective action plans
  - Unlike DDPS is not part of MAA. Only a brief description of PV system and location of PVSMF will be required in MAA.
  - Will be produced and maintained by MAHs as a stand-alone living document that contains an up-to-date description of their PV system and the quality system that supports it
  - Must be readily available and provided to the CAs within 7 days and be permanently available for inspection at one or more specified sites within the EU/EEA.
  - Repository for unresolved inspection/audit findings

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## Information Flow



- The PV System should ensure that the QPPV receives timely and accurate information concerning:
  - Changes in product risk/benefit
  - Feedback on how well the system is performing (i.e. is it compliant?)



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## Monitoring Compliance



- Two main methods used:
  - Metrics: e.g. are ICSRs and PSURs being submitted on time.
  - Audits: Audits of PV function against legislation and guidelines (e.g. Volume 9A) as well as against company procedures.
- QPPV should have access to audit reports and be made aware of non-compliance.



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## Interfaces



- A compliant PV system requires effective interfaces with multiple stakeholders. For example:
  - Medical Information
    - Spontaneous reports, HCP safety related enquiries
  - Regulatory Affairs
    - Product labelling, Reg Authority enquiries, PSURs
  - Product Quality
    - Product technical complaints involving AEs
  - Clinical Development
    - SAE from studies, Study results concerning safety and efficacy
  - Sales and Marketing
    - Spontaneous reports, providing safety information to HCPs
  - Quality Assurance
    - Audits, SOPs, Quality Systems



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## Issues facing QPPVs



- 'Scope creep' - Regulators increasingly expect QPPVs to have oversight of all activities which impact on PV and not just core PV activities.
  - Quality
    - Product quality reviews
    - PV Inspection finding related to out of date PIL in product pack
  - Regulatory
    - Update of SPCs/PILs
    - Submission of variations (e.g. DDPS)
  - Marketing
    - Market research programmes
    - Patient support programmes
    - Applies to global and local programmes



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## Issues facing QPPVs



- Information overload
  - 'Main point of contact', so all documents sent to the QPPV
  - Multiple e-mails on the same topic
- Oversight of local Responsible Persons (RPs)
- Managing your company's expectations
  - 'Font of all knowledge' for PV!
  - Senior executives outside the EU who don't understand the role and responsibilities

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## QPPVs in practice



- "Oversight should cover the functioning of the MAH's pharmacovigilance system in all relevant aspects."
- Regardless of company size
- Same legal accountability
- Working to the same standards
- How to show compliance in systems of differing complexities without micromanaging?

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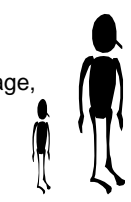
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## Different size companies



- Differences
  - QPPV activities
  - Back-up / Deputy arrangements
  - Systems required to comply with regulations
  - Size of the PV department
  - Size of the PV budget
  - Other resources – legal, audit
  - Product Portfolio - number, type, age, territories, type of MA
  - Number and type of studies

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## Different QPPV Modalities



- Full time QPPV with corporate governance role outside routine PV activities – sometimes with a QPPV office
- QPPV working within the PV team, responsible for global or European PV activities and staff management
- QPPV responsible for PV activities and other department(s) (e.g. Reg Affairs, Med Info, clinical trials)
- Contract QPPV working remotely.



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## Deputies/Backup Modalities



- Full time Deputy working with the QPPV
- Permanent Deputy working within the PV team, possibly a local RP.
- Permanent Deputy working in a related department (e.g. Reg Affairs, Med Info)
- Permanent contract Deputy working remotely but in close contact with QPPV
- Ad hoc Deputy appointed as required.



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## Large company QPPVs



- The QPPV office
  - Small team to support the QPPV/Deputy
  - Usually consists of admin and PV staff with access to product experts, and specialist support staff (e.g. legal, stats)
  - Receives, co-ordinates, collates documentation
- QPPV needs a strategic overview and cannot be too involved
  - Has to have good staff and very robust systems
  - Communication is vital
  - Needs to be able to identify where to focus attention



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## Small Company QPPVs



- Minimal support network
- May be contractor, may have more than one role
- Deputy may be ad hoc or in another department, so delegation is difficult
- QP needs to be able to see the big picture but will also be very hands on and involved in routine activities
- But infrequent need to carry out some activities can result in de-skilling, so may need to rely on outside specialists for some activities

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## Small & Large Comparison



Activity	Small Company QPPV	Large Company QPPV
SOPs	Writes/ approves PV SOPs	Overview/ approves key SOPs only
ICSRs	May do case processing/ expediting	Monitor metrics data
PSURs	Closely involved in writing and QC/QA, approves	May review, comment, approve. Monitor submission compliance data
Safety review/signal detection	Prepares data, key member of safety review team	Informed of all assessments, may review summary data or become involved depending on issues.
Updates to reference safety information	May drive update. May prepare revised labelling and supporting docs.	Aware, informed of labelling committee discussion and may attend meeting
Responses to CA request for information	Co-ordinate, may prepare response. Approves response	Will be informed. Involvement dependant on nature of request
Risk Management Plans	Write, implement, monitor	Input into, may approve, review compliance data.
PV training	Prepare, carry out	Confirm programme in place

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## Changing Environment



- Newer regulatory requirements require even more interaction between PV/QPPV and other MAH departments. For example:
  - Risk Management Plans (RMPs)
  - Paediatric Implementation Plans (PIPs)
  - Development Safety Update Reports (DSURs)
  - Product Quality
  - Quality Assurance
  - In-licensing, out-licensing and divestment



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## Risk Management Plans (RMPs)



- Is PV sufficiently involved in the design of RMPs?:
  - Do they meet requirements?
  - Are they achievable?
  - What is their impact on the PV system?
  - How are they implemented/disseminated throughout the MAH and to partners?
  - Mechanisms for reporting the results and measuring the effectiveness of RMP activities
  - Synchronisation between PSUR and RMP



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## Paediatric Implementation Plans



- The collection and analysis of safety information in the paediatric population is a major focus of PIPs.
- PIPs are compulsory for all new MAAs (and new indications for older products)
- Volume 9A requires the reporting of paediatric safety data in PSURs



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## PIP Commitments



- Initial PIPs are submitted during early stage clinical development (end of Phase I).
- PV is less likely to be involved at this stage of development.
- However, many PIP commitments are deferred until adult indication is approved.
- PIPs therefore become post-marketing commitments for which QPPV may have some responsibilities.
- Also safety is critical part of all PIPs.



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## Clinical Development



- In addition to standard SAE reporting PV must be informed of clinical trial results that alter marketed product risk/benefit profiles.
- QPPV has PASS responsibilities
  - Volume 9A, Part I, Sections 1.2.1 and 7.1
- For the same product consistency should be maintained between the safety information contained in IBs and SmPCs.
- DSURs – Pre-authorisation documents so do QPPVs have any responsibilities for these?



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## Development Safety Update Reports



- ICH DSUR guideline
  - Adopted by CHMP in September 2010
  - Accepted in EU now but compulsory after September 2011
- Not just about safety, more like Development Status Update Reports
- Example DSURs on ICH website for Commercial and Non-commercial Sponsors
  - <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>



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## Product Safety Information



- Changes to product information are one of the main outputs of a PV system.
- QPPVs therefore need to ensure:
  - A product's risk/benefit profile is accurately reflected in its labelling
  - Labelling updates are implemented in an efficient and timely manner
- PV involvement is essential



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## In-licensing and Out-licensing



- The in-licensing of a new product may have a significant impact on a PV system (i.e. increase workload)
- The QPPV is responsible for in-licensed products
- PV must be involved in due diligence and contract (safety data exchange agreement) negotiations
- For out-licensing partner PV systems must be adequate. Audits may be required.



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## Divestment & Local Products



- A QPPV is responsible for all of an MAHs products that are marketed in the EEA.
- Responsible for local products as well as global/regional products (POLOs = products of local opportunity)
- QPPV remains responsible until divestment is completed in all EEA MSs



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## Product Quality



- Some AE reports involve Product Technical Complaints (PTCs)
  - Quality of product, packaging, instructions for use etc.
- Lack of efficacy reports
- Analysis of returned product
- Drug/Device combinations
- Adverse reactions linked to manufacturing changes (e.g. erythropoietins and PRC) or indicative of possible counterfeits
- If HCPs and/or patients can't use a product correctly this adversely effects risk/benefit profile.



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## New Legislation

- Directive 2010/84/EU and Regulation (EU) 1235/2010
- Few changes to QPPV role but major impact on PV systems changing the way QPPVs work:
  - Pharmacovigilance System Master Files
  - Non-interventional post-authorisation safety studies
  - Direct reporting of local RPs to QPPV
  - Removal of PSUR requirements for low risk established (and harmonised?) products
  - PSUR work sharing and SmPC harmonisation (Core Safety Profiles). Already occurs on a "voluntary basis".

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## Required knowledge for QPPVs



<ul style="list-style-type: none"> <li>• QPPV Responsibilities</li> <li>• Case processing/expediting and safety databases</li> <li>• Literature review</li> <li>• PSUR writing</li> <li>• Signal Detection</li> <li>• Risk benefit analysis</li> <li>• Risk management planning</li> <li>• Audit and Inspection</li> <li>• SDEAs and partner interfaces</li> <li>• GCP/Clinical Trial regs (if relevant)</li> <li>• Quality Management</li> <li>• Product Labelling</li> <li>• Basic Epidemiology</li> <li>• Basic Marketing</li> <li>• Project Management</li> </ul>	<ul style="list-style-type: none"> <li>• Communication across hierarchies and professions</li> <li>• Team working</li> <li>• Leadership</li> <li>• Assertiveness skills</li> <li>• Delegation (what, when and to whom)</li> <li>• Influencing skills (up and down)</li> <li>• Negotiation skills (both technical contracts etc. and in day to day activities)</li> <li>• Presentation skills</li> <li>• Crisis/issue management</li> <li>• Time management</li> <li>• Stress management!</li> </ul>
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## QPPV Qualities



- Outstanding communicator
- Excellent at time management and prioritising
- Focused on quality and compliance
- Encyclopaedic knowledge of PV regulations and ability to apply them
- In depth knowledge of company processes – can turn their hand to just about everything
  - Able to process cases, write PSURs/ASRs/RMPs, review clinical data.
  - Needs to understand GMP, GCP and Regulatory processes
- Able to negotiate with and influence/motivate others
- Can see the big picture and knows how to pick battles
- Good team player able to work on their own
- Hard-working, enthusiastic, flexible, adaptable, detail orientated (mildly obsessive?), prepared to help out other departments, able to make a little go a long way, has several pairs of hands and maintains a sense of humour at all times!

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## QPPV Requirements - Summary



- MAHs share responsibility with their QPPV
- MAHs must support their QPPV
- MAHs have ultimate responsibility for the products they market
- QPPVs must have adequate experience and qualifications to carry out their duties
- QPPVs must have sufficient authority
- Authority is both earned as well as conferred



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