European and US specific requirements for vaccine PV

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DCVMN training on PV,

May 2017

European and US specific requirements

- ICH
- US specific requirements
  - IND reporting
  - NDA/BLA reporting
  - REMs
- EU specific requirements
  - QPPV
  - PSMF
  - RMPs

European and US specific requirements

ICH

ICH-GCP

Clinical studies should be carried out according to International Conference on Harmonisation (ICH) / WHO Good Clinical Practice (GCP) standards. This provides a unified standard for the European Union (EU), Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organisation (WHO). Thus, any country that adopts this guideline technically follows this same standard. Most countries world-wide have adopted ICH-GCP guidelines

European and US specific requirements

US specific requirements

IND reporting - ICSRs

- Format: electronic or Medwatch form (FDA 3500 A) – Foreing cases may be submitted on CIOMS I Forms
- Report to CDER or CBER division for the specific IND
- Analysis of Similar Events (AOSE)
- Electronic reporting in eCTD possible if the IND is eCTD format
- For 7-day IND reports (fatal/life-threatening) not submitted in eCTD format, rapid communication (e.g phone, facsimile, email) may be used

European and US specific requirements

US specific requirements

- New definition of ‘reasonable possibility’ = there is evidence to suggest a causal relationship between the drug and the AE
- Sponsor’s causality assessment prevails
- Day zero for expedited reporting: starts when the sponsor determines that the suspected adverse reaction or other information qualifies for reporting

European and US specific requirements

US specific requirements

IND reporting – aggregate reports

- Format: IND Annual Safety Report but waiver may be obtained for DSUR format – ICH E2F format adopted by FDA
- To be submitted within 60 days of the anniversary that the IND went into effect
- Less complex than DSUR

Non-binding but useful guidance for IND reporting:

Guidance for Industry and Investigators – Safety Reporting Requirements for INDs and BA/BE Studies

European and US specific requirements

US specific requirements

Postmarketing reporting – expedited reports

- Electronic format required to FAERS (FDA Adverse Reporting System)
- All serious and unexpected (according to FDA approved labelling) adverse experiences from all sources, domestic and foreign withing 15 days of receipt
- Solicited reports from postmarketing studies do only require expedited reporting if the applicant concludes that there is a reasonalbe possibility that the product caused the adverse experience

European and US specific requirements

US specific requirements

- **Clinical trial registration and results information submission**
  - Applicable trials for drugs and biologics: controlled investigations other than Phase I with at least one site in the US
  - Mandatory for all trials initiated after Sep. 2007 or initiated before that date but ongoing as of December 26, 2007
  - Trial information must be registered not later than 21 days after enrollment of the 1st participant
  - Trial results must be published not later than 12 months after the Primary Completion date
  - Registration on *clinicaltrials.gov*

European and US specific requirements

US specific requirements

- **REMs (vs RMPs in EEA)**
  - Required risk management plans that use risk minimisation strategies to ensure that benefits of certain prescription drugs (NDA & BLA) outweigh their risks
  - FDA can require a REMS before drug approval or if the agency determines that safety measures are needed beyond the professional labelling
  - Can be required for a single drug or a class of drugs
  - HCPs and distributors may need to follow specific safety procedures
  - Each REMS has specific safety measures unique to the safety risks of the drug or class of drugs
  - The risk must be a serious risk that is documented in the label

European and US specific requirements

US specific requirements

- *Factors considered when determining the need for a REMS*
  - Size of the population likely to use the drug
  - Seriousness of the disease
  - Expected benefit of the drug
  - Expected duration of treatment
  - Seriousness of known or potential adverse events
  - Whether the drug is new (new molecular entity)

European and US specific requirements

US specific requirements

- *REMS Elements*

- All REMS required for an NDA or BLA must contain a timetable for submission of assessments of the REMS • A REMS for an NDA or BLA may also contain any of the following elements:

  – Medication Guide or Patient Package Insert
  – Communication Plan
  – Elements To Assure Safe Use (ETASU)
  – Implementation System

- REMS for ANDA (generic) products may contain the following:

  – Medication Guide
  – Elements to Assure Safe Use (ETASU)
  – Implementation System

European and US specific requirements

EU specific requirements

QPPV – Qualified Person for Pharmacovigilance

- European role but same or similar concept introduced in many countries
- The MAH must appoint a QPPV and notify CAs and EMA
- Must be the single contact point for CAs and EMA with 24/7 availability
- The QPPV must be appropriately qualified (medically qualified or access to a medically quallified person)
- Must reside and operate in the EEA

European and US specific requirements

EU specific requirements

- Each PV system can have only one QPPV
- A QPPV may fulfill the role of QPPV for more than one MAH
- The QPPV is responsible for the establishement and maintenance of the MAH's PV system
- Ensures conduct of PV activities and submission of PV related documents is done in accordance with legal requirements and GVP
- Ensures quality, correctness and completeness of PV data

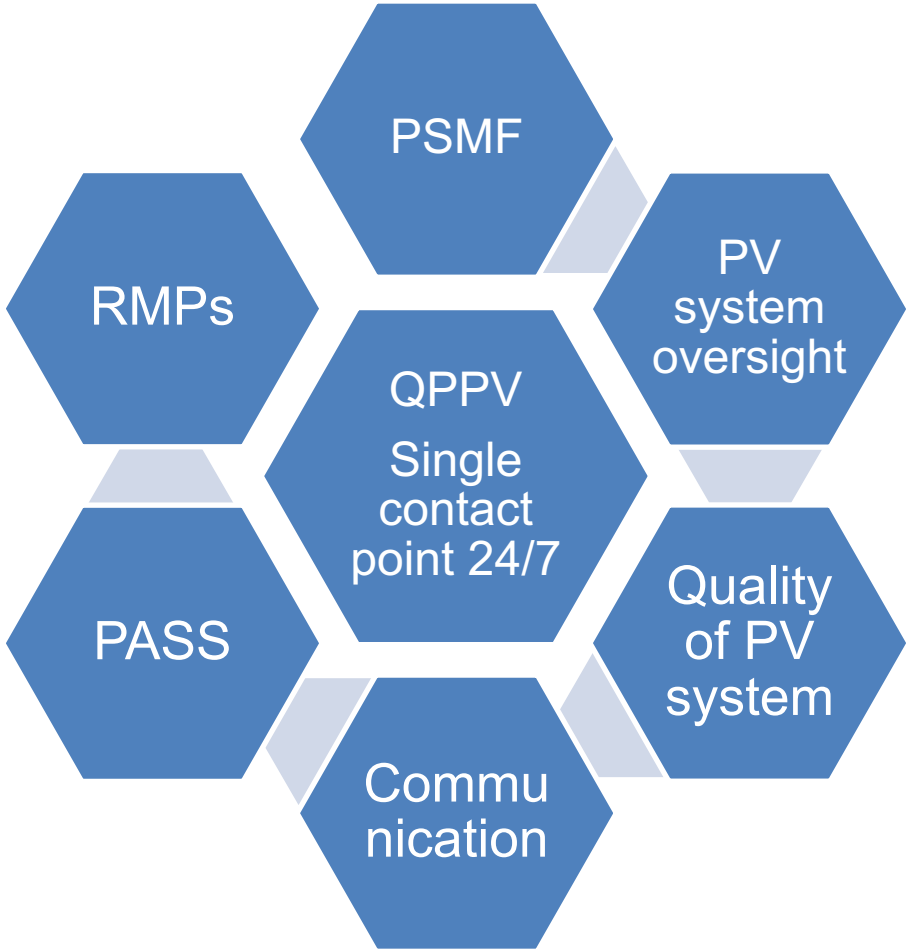
European and US specific requirements

EU specific requirements

- Must have access to the PSMF and have sufficient authority to ensure that the information contained in the PSMF reflects accurately the current PV systerm under his responsibility
- Must be aware of conditions or obligations related to MA and risk minimisation measures
- Must be aware of RMPs and PASS & review protocols of PASS

European and US specific requirements

EU specific requirements



European and US specific requirements

EU specific requirements

Pharmacovigilance System Master File (PSMF)

- No need to include the PSMF in any dossier
- Only Summary of PV System will be included in dossier
- Health Authorities can request PSMF to be provided within 7 days
- PSMF will be used for evaluation of PV system of MAH before dedicated PV inspection
- The full PSMF must be in place before the summary is submitted
- Must be accessible to the EU QPPV

European and US specific requirements
EU specific requirements

What is the PSMF?

- **Body text:**

Everything about the PV system and anything that might impact:

- QPPV
- Organisation & structure
- Sources of Safety data
- Computer sytems and databases
- Performance (compliance data)
- Quality system

European and US specific requirements

EU specific requirements

- **Annexes (data that might change rapidly):**
- QPPV CV/tasks delegated, extra contract details
- List of partners, contracts and agreements
- Sources of safety data
- Computer Systems
- List of SOPs, work instructions, user guides
- Performance indicators & compliance results
- Audit schedules, list of completed audits, CAPAs
- Products lists
- Log book (history of changes)

European and US specific requirements

EU specific requirements

The PSMF is often a source of major inspection findings

- Incorrect/missing information
- Lacking back up procedures
- Unclear organisational structure
- Unclear processes or not covering all activities
- Incomplete list of service providers/products/contractual agreeemnts
- Incomplete compliance data
- …

European and US specific requirements
EU specific requirements

1 Qualified Person Responsible for Pharmacovigilance

- 1.1 Information about the EU QPPV
- 1.2 Information about the Deputy EU QPPV
- 1.3 Location of the Pharmacovigilance System Master File
- 1.4 Back-up arrangements
- 1.5 Out of office hours arrangements
- 1.6 List of delegated activities
- 1.7 National Qualified Persons Responsible for Pharmacovigilance

European and US specific requirements
EU specific requirements

2, Organizational structure of Marketing Authorization Holder

- **2.1 Overview and governance structure**
- **2.2 Global Pharmacovigilance**
- **2.3 Affiliate Organizations**
- **2.4 Central functions other than GPV contributing to PV**
  - 2.4.1 Regulatory Affairs
  - 2.4.2 Medical Affairs
  - 2.4.3 Clinical Development
  - 2.4.4 Pre-Clinical Development
  - 2.4.5 Quality Assurance
  - 2.4.6 Information Technology
  - 2.4.7 Library and Information Resources

European and US specific requirements

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2.5 Cross-functional teams and committees

2.6 Subcontracted pharmacovigilance activities

- 2.6.1 ICSR processing
- 2.6.2 Interventional clinical trials
- 2.6.3 Medical writing and other medical services
- 2.6.4 Market Research Programs and Patient Support Programs

2.7 Commercial partners

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EU specific requirements

3 Sources of safety data

- 3.1 Principles
- 3.2 Overview of main sources of safety data
  - 3.2.1 Spontaneous reports
  - 3.2.2 Medical Information
  - 3.2.3 Scientific literature
  - 3.2.4 Digital media
  - 3.2.5 Clinical trials
  - 3.2.6 Non-interventional studies and programs
  - 3.2.7 Product quality complaints
  - 3.2.8 Commercial partners

European and US specific requirements
EU specific requirements

4 Computerized systems and databases

- 4.1 Pharmacovigilance database
- 4.2 Medical Information database
- 4.3 Product quality complaint database

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EU specific requirements

5 Pharmacovigilance processes

- 5.1 Continuous monitoring of product benefit-risk profiles
- 5.1.1 Ongoing safety surveillance and signal detection
- 5.1.2 Signal validation, assessment and action
- 5.2 Risk management systems

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EU specific requirements

- 5.3 ICSR collection, follow-up, assessment and reporting
  - 5.3.1 Description of ICSR workflow
  - 5.3.2 Data reconciliation and aggregate reporting
  - 5.4 Periodic safety reporting
  - 5.5 Communication of safety concerns and implementation of safety variations
  - 5.6 PV relevant information associated with product quality complaints 5.7 Responses to requests for information from regulatory authorities

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6 Pharmacovigilance system performance

- 6.1 Documentation of non-compliance, monitoring of performance and compliance, and business continuity
- 6.2 Monitoring methods for specific pharmacovigilance activities
  - 6.2.1 Reporting of ICSRs
  - 6.2.2 Periodic safety reports
  - 6.2.3 Safety variation submissions
  - 6.2.4 Safety related commitments
- 6.3 Significant deviations identified apart from audits or inspections

European and US specific requirements
EU specific requirements

7 Pharmacovigilance quality system

- 7.1 Document and record control
  - 7.1.1 Standards and requirements
  - 7.1.2 GPV Central Archive
  - 7.1.3 Local Archiving
- 7.2 Procedural documents / SOPs
- 7.3 Training

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7.4 Auditing

- 7.4.1 Global function audits
- 7.4.2 Affiliate audits
  - 7.4.3 Business partner PV audits
- 8 Maintenance of PSMF

European and US specific requirements

EU specific requirements

RMP – Risk Management Plans

The RMP is a document that contains

- Pharmacovigilance specifications
- Pharmacovigilance activities
- Risk minimisation activities

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EU specific requirements

Objectives of an RMP

- Identify or characterise safety profile
- How to characterise further
- Describe measures take to prevent or minimise risks including the assessment of the effectiveness of these measures
- Document post-autorisation obligations

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EU specific requirements

Types of RMP

- New molecule/new drug/new indication/new population
  ➔ Full RMP
- Known molecule but not a generic/copy: submission based on literature and minimal studies
  ➔ FULL RMP
- True generic
  ➔ ABBREVIATED RMP (Modules SI to SVIII can be omitted; part III & IV can be omitted if not in reference product RMP; part VI should be based on SmPC)

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EU specific requirements

Content and structure

PART I: Product overview

- Invented name(s) in EEA
- Autorisation procedure
- Brief description of the product
- Indications in the EEA
- Posology and route of administration
- Pharmaceutical form(s) and strenght(s)

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EU specific requirements

Content and structure

PART II: safety specification

- Gap analysis
- Summary of safety concerns
- Impact on the BR balance of the product

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Module SI

- Epidemiology of the indications & target population

Module SII

- Established risks & potential for unidentified risks

Module SIII

- Limitations of the human safety database

Module SIV

- Populations not studied

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EU specific requirements

Module SV

- Post-autorisation experience

Module SVI

- Additional EU requirements

Module SVII

- Identified and potential risks

Module SVIII

- Summary of safety concerns

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EU specific requirements

PART III: Pharmacovigilance plan

- Must be approved with regulators prior to approval

PART IV: Post Autorisation Efficacy studies

- Not needed for many applications but may be requested by authorities

PART V: Risk Minimisation measures

- For each identified risk & should include measurement of effectiveness of these measures

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EU specific requirements

PART VI: Summary of the RMP

- Tables summarising the safety concerns and risk minimisation measures
- Summary for the public

Annexes