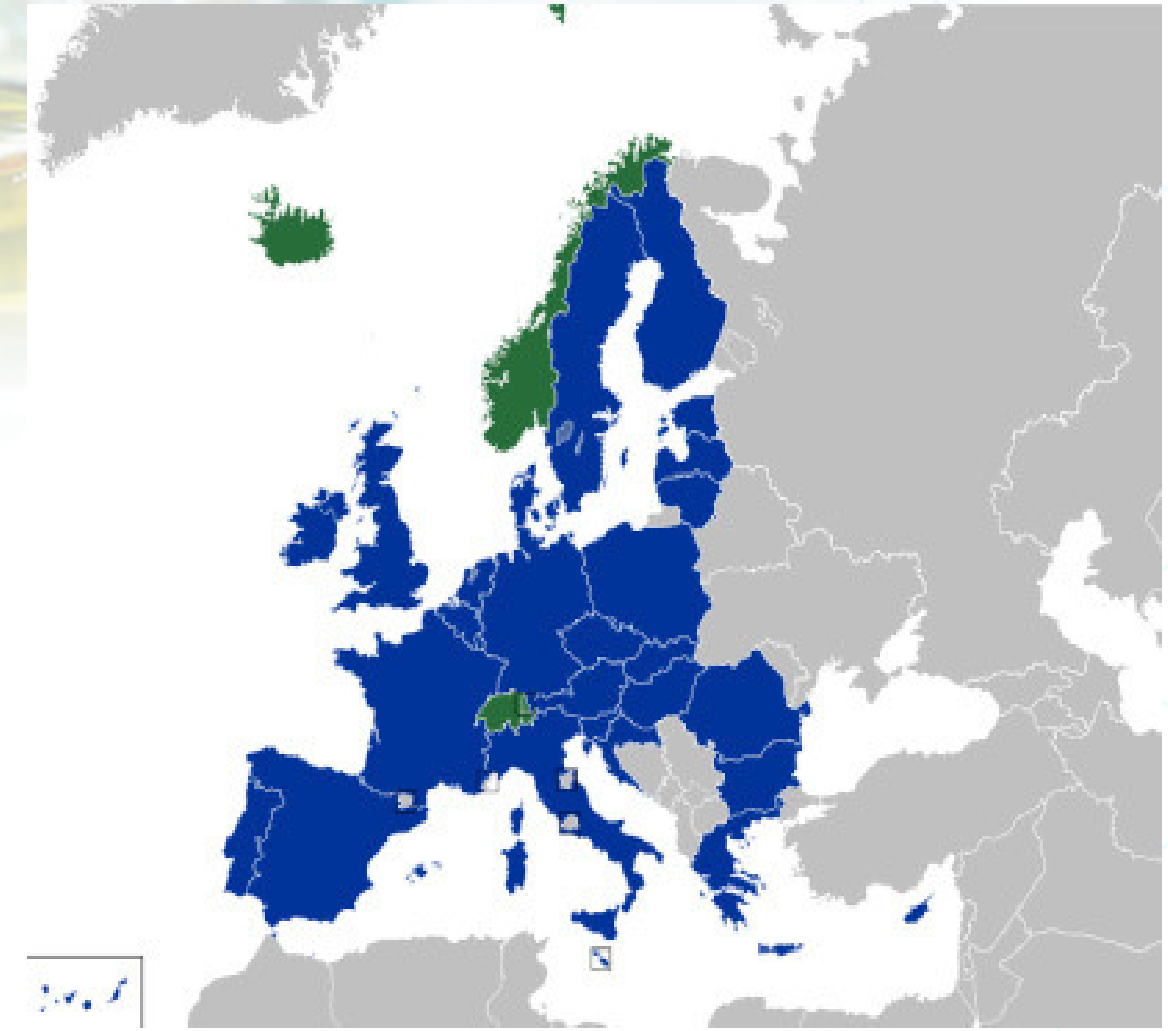
New European Union Pharmacovigilance Legislation
Status of Implementation

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Background

- Pharma Package
  - Rationalisation of pharmacovigilance legislation
  - Counterfeit medicines (now fake medicines)
  - Information to patients
- 2008
  - Consultation
- 2009
  - Reviewed by committees of the European Parliament & European Commission
- 2010
  - September – approved by European Parliament
  - December – approved by European Council
  - 31 December – Directive & Regulation published

Background

- European Regulation
  - Law applicable to all 28 member states of the EU
- European Directive
  - Has to be transposed into the national law in each of the 28 member states

Process

- Publication in Official Journal 31 December 2010
- Transposition over 18 months
  - Development of guidelines
  - Development of systems
  - Directive transposed into national laws – all member states
- Implementing measures regulation published end of June
- Effective from July 2012
- Full implementation will take well into 2016...
- First Good Vigilance Practice (GVP) modules issued June 2012

Guidelines

- Good VigilancePractice guidelines
  - Following modules have been issued:
    - I Pharmacovigilance systems and their quality systems
    - II Pharmacovigilance System Master File
    - III Pharmacovigilance inspections
    - IV Audits
    - V Risk management systems
    - VI Management and reporting of adverse reactions
    - VII PSURs
    - VIII Post-authorisation Safety Studies
    - IX Signal management
    - X Additional monitoring
    - XV Safety communications
    - XVI Risk minimisation measures

Guidelines

- Good VigilancePractice guidelines
  - Following modules to be issued:
    - XI Public participation in pharmacovigilance
    - XII Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication
    - XIII Not to be issued
    - XIV International cooperation

Pharmacovigilance & Quality Systems

- Module I of the GVP guidelines
- *All persons within the organisation should be involved in and support the pharmacovigilance system…*
- *All persons involved with the organisation should engage in continuous quality improvement…*
- *The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the pharmacovigilance activities and the quality system*

Pharmacovigilance & Quality Systems

- *…the marketing authorisation holder should ensure that structures and processes are in place, so that the QPPV can fulfil the responsibilities listed …*
- *…the marketing authorisation holder should ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant…*
- *When a marketing authorisation holder intends to expand its product portfolio … the QPPV should be notified early in the due diligence process…*

Pharmacovigilance & Quality Systems

- QPPV
- Local QPPV in some countries as well
- Sufficient number of competent, qualified & trained personnel
  - At the MAH
  - At the competent authorities

Pharmacovigilance & Quality Systems

- System audit to be conducted
- EMA's medicines portal to be regularly checked
- Documented evidence of investigations into any safety issue

Pharmacovigilance & Quality Systems

- Record management system needs to be described
- Record retention policy
  - System related documents retained for 5 years after retirement
  - Product related documents retained for 10 years after the MA has ceased to exist
- System in place to ensure maintenance of pharmacovigilance documents

Pharmacovigilance System

Master File

- Module II of the GVP guidelines
- Summary of system submitted with each new Marketing Authorisation Application
- PSMF maintained at one site in the EU
  - Location of QPPV or major pharmacovigilance activities
- Permanently available for inspection
- Provided within 7 days of request
- No template provided
- Requirement to notify authorities of significant changes
- To be implemented by July 2015

Pharmacovigilance System

Master File

- To include:
  - List of EU authorisations to include procedure, authorisation number, marketing status, availability outside the EU
  - Copies of contracts for significant pharmacovigilance activities
  - Record of audits over last 5 years plus open corrective actions
  - Metrics including timeliness of safety variation submissions
  - List of offices worldwide that may receive adverse event reports
  - Global information

Risk Management Plans

- Module V of the GVP guidelines
- Required for all new submissions
- Risk proportionate
  - Some sections not required for a new generic MAA
- RMP template issued October 2012
  - Modular format
  - Revised July 2013
- Summaries of RMPs to be published on EMA & NCA websites
  - But not yet
- Generic RMP should follow the innovator's
- To include a lay summary
- Risk minimisation activities include, e.g.:
  - Physician educational materials
  - Patient educational materials
  - Patient registries

Adverse Event Reporting

- In Module VI of the GVP guidelines, revised Sep 2014
- New definition of an adverse reaction:

  A response to a pharmaceutical product which is noxious and unintended ~~and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function~~.

  Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

  Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include overdose, misuse, abuse and medication errors.

Adverse Event Reporting

- All EU reports to be expedited
  - Serious within 15 days
    - Including all ex-EU serious reports
  - Non-serious reports within 90 days
- Single point of submission
- Interim measures confirmed
  - Frequent revisions
- Some agencies require submission of non-serious reports
- MAHs encouraged to monitor social media

Adverse Event Reporting

- Collect more information, e.g.
  - Age/age group for children & elderly
  - Indication – to characterise off-label use
- Adverse events associated with falsified medicines & defective medicines
  - Ensure processes are in place
- Medication errors, even if no associated AE, reportable
  - Collect but don't report

EudraVigilance & ICSRs

- National portals for HCP & patient reporting
- EudraVigilance to be developed & strengthened
  - Functional specification not yet written
  - Not fully functional until 2016
- Fully & permanently accessible
  - Appropriate access levels
  - Access policy not yet issued

PSURs

- In Module VII of the GVP guidelines
- Not called Periodic Benefit Risk Evaluation Report in the legislation
- Regular PSURs will not always be required for generic medicines!
  - European Union list of Reference Dates published
  - 10% of generic actives require a regular PSUR
- Renewals
  - Addendum to the clinical overview (ACO) required for all MAs

PSURs

- Single assessment via EMA
  - Fees payable
- Any resulting measures adopted through a single EU-wide procedure
- Portal for electronic submission
- DLP 90 days before submission, 70 days for 12 month PSURs
- Renewals to be submitted no later than 9 months before renewal date

PSURs

- Format changed
  - ICH PBRER format
  - No line listings
  - Greater focus on benefit-risk assessments
    - New section on signal detection
    - New section on changes in efficacy/effectiveness
    - New section on changes to benefit:risk profile
  - New template
  - Modular
    - Sections can be used in the RMP (and vice versa)

PSURs

- Phases of transition
  - For PSURs submitted after 21 July
    - Old format
    - Plus critical evaluation of benefit-risk profile
    - DLP plus 90 days
  - For PSURs submitted after 10 January 2013
    - New format
  - For PSURs to be submitted after 1 April 2013
    - To EURD list, updated monthly
  - From August 2013
    - Submit via EMA portal for CAP actives
    - PSUR Work Sharing list revived for others
  - From November 2014
    - All to be submitted for single assessment

PSURs

- Volume of PSURs significantly reduced
- But reports more complex
- Positive impact upon budget
- But, EMA assessment fees
  - To be invoiced 3 months in advance of the DLP

Renewals

- CMDh Best Practice Guide on the Processing of Renewals in the Mutual Recognition and Decentralised Procedures, CMDh/004/2005/Rev. 9, Apr 2013
  - Third revision in 6 months!
  - Describes format of module 2.5 ACO
  - Similar to PSUR but includes history of inspections
  - Signed by the clinical expert and to include a clinical expert statement

Post-authorisation Safety Studies

- In Module VIII
- Can be imposed at any stage in a product's life cycle:
  - Condition of marketing authorisation – conditional approval
  - Response to a safety concern
- GVP cross refers to Volume 10 for a clinical study
- GVP has guidance on non-interventional studies
- MAH has 30 days to request to submit written observations
- Joint study if safety concern applies to more than 1 active
- Potential significant financial implications

Signal Management

- In Module IX of the GVP guidelines
- Explicitly mentioned in the legislation for the first time
- EudraVigilance tools to be used by member states & MAHs
- PRAC to manage
- Work sharing of signal detection by European agencies

PRAC

- Pharmaceutical Risk Advisory Committee
  - Responsible for all aspects of risk management of medicines
  - 1 member per member state, 6 appointed by the Commission, 1 member to represent HCPs & 1 member to represent patients
  - Concern that national agencies are unnecessarily referring issues to the PRAC

Inspections

- GVP Module III
  - New concepts include:
    - Pre-authorisation inspections
    - Information sharing on planned and conducted inspections
    - Inspections of vendors

Audits

- GVP Module IV
  - Risk based approach
  - No defined periodicity
  - Independence of audits
  - Strategic and tactical audit plan required
  - Critical and major findings to be in the PSMF until closed
  - Audit plan and results of audit to be communicated to senior management

Additional Monitoring

- Described in Module XI of the GVP guidelines
- Similar to UK Black Triangle Scheme
- List to be maintained by EMA
  - All new actives authorised since 1 January 2011
  - All biological products authorised since 1 January 2011
  - Others in consultation with PRAC
- Stay on list for 5 years
- Symbol ▼
- Information to be included in PIL

SmPCs & PILs

- Format to be revised
- Specifically to emphasise important safety information
- European Commission to prepare proposal for revising SmPCs & PILs
- Text on suspected ADR reporting for SmPC & PILs in revised QRD template and in Module XI
- SmPCs to be updated with new statement

Safety Communications

- Module XV
  - Focus on emerging safety information
  - Recommends two way interaction in designing safety communications
  - PRAC should be consulted on DHPCs (Dear Healthcare Professional Communications)

Literature Monitoring

- EMA shall monitor selected literature for selected actives
  - To be determined
  - Large list(?) yet to be published
- MAHs will not have to report ICSRs for these actives from this literature
- For other actives/literature, MAH will have to submit a copy of the clinical paper
- MAHs will have to monitor the same literature for these actives
  - For PSURs
  - For signal detection
- No date for when the EMA plans to take on this responsibility, deferred until resources available

EMA Medicines Portal

- All SmPCs & PILs for authorised products
- Committee information
  - Including PRAC, minutes, recommendations etc
- RMPs
  - Summary, eventually
- Substances under additional monitoring
- Locations of PSMFs
- PSUR submission
- Protocols & abstracts for PASE
- MAH to check for updates

EU Medicinal Product Dictionary (xEVMPD)

- EMA to establish a list of all medicinal products authorised in the EU
- MAHs to submit electronically to EMA information for all their products authorised in the EU by July 2012
- To use international standard format
  - Identification of Medicinal Products – IDMP
  - 40+ data elements
  - Detailed guidance issued March 2012

xEVMPD

- Update of current records from June 2014
  - To be completed by end of 2014
  - Update current records within 30 days
- To be used to calculate pharmacovigilance service fees
- Implement ISO IDMP July 2016
- Quality review conducted by EMA
  - 18% of records have errors
  - So what?

xEVMPD

- A description of the (invented) name of the medicinal product
- A description of the therapeutic area(s), which shall include:
  - ATC Code for the medicinal product
- The designation of additional monitoring for biological medicinal products, and all other medicinal products where applicable, after 2 July 2012
- Details of the marketing authorisation holder
- Name, address and contact details of the Qualified Person Responsible for Pharmacovigilance (QPPV)
- Location of the Pharmacovigilance System Master File
- Details of the marketing authorisation and the marketing status, which shall include:
  - Marketing authorisation procedure
  - Country of marketing authorisation
  - Marketing authorisation number
  - Authorisation date
  - Marketing authorisation status
  - Mutual-recognition procedure number/decentralised-procedure number
  - Authorisation number for centrally authorised medicinal products as specified in the Commission Decision
  - Orphan drug designation
  - Date of withdrawal of the medicinal product from the market, where applicable

xEVMPD

- A description of the clinical particulars, which shall include:
  - Therapeutic indication(s)
- A detailed description of the active substance(s), excipient(s), adjuvant(s) and their specific characteristics which shall include:
  - The molecular structures, taxonomic and anatomical information and physical properties taking into account the nature of the substance as applicable; this shall include any modifications known to alter the molecular structure of the underlying material
  - The constituents and amounts of the substance as applicable
  - The expression system for biologicals/biotechnological derived substances
  - The manufacturer of the substance
  - The manufacturing steps necessary for the production of the substance including the critical processes, analytical data and specifications
  - The monograph references including the grade of the substance
  - For polymers, the monomers used to prepare the polymer including their proportion, the type of polymer or co-polymer and representation of the molecular weight and type of molecular weight
  - Any available (international) code used to identify a substance

xEVMPD

- A description of the strength of the active substance(s)
- A description of the medical device(s) in accordance with Regulation (EC) No 1394/2007 as applicable
- The pharmaceutical dose form
- The route(s) of administration
- Description of the packaging information
- An electronic copy of the following documents, as applicable, including date of the last revision, document reference number(s) and document language(s)
  - Summary of Product Characteristics
  - Manufacturing Authorisation Holder responsible for Batch Release
  - Conditions of the Marketing Authorisation
- Labelling
- Package Leaflet

Amending Legislation

- 27 October 2012, new Pharmacovigilance Directive 2012/26/EU (amending Directive 2001/83/EC)
  - Enters into force on 16 November 2012
  - Member States must transpose the new provisions into national law by 28 October 2013
- 14 November 2012, new Pharmacovigilance Regulation (EU) No 1027/2012 (amending Regulation 726/2004)
  - Enters into force on 4 December 2012 and applies from 5 June 2013
- The Directive and the Regulation constitute a response to the Mediator (benfluorex) case in France

Amending Legislation

- Voluntary withdrawal MAHs must explain reasons for:
  - Suspension/ceasing marketing of a product
  - Withdrawal of the product from the market
  - Requesting withdrawal of the marketing authorisation
  - Not applying for a renewal of a marketing authorisation
- On the basis of the explanation received the competent authority may initiate a referral
- Withdrawal for safety concerns must not be disguised as commercial activity

Costs

- Fees
  - EMA can raise money
    - In addition to fees imposed by national agencies
  - 2012 proposals:
    - €1000 per product entry in xEVMPD
    - €80,500 assessment fee per PSUR
  - 2014 agreed:
    - €67 per product entry in xEVMPD service fee – 20% discount for generics
    - €19,500 assessment fee per PSUR
    - Referrals €179,000 to €295,400
- Future
  - Reduced costs to MAHs (?)
  - Savings to society - €237mn to €2.4bn

Costs

- Service fee is per chargeable unit:
  - Active substance or combination
  - MAH
  - Country
  - Pharmaceutical form
  - Therefore, Dr Reddy's Sildenafil 25mg, 50mg and 100mg tablets in the UK is one chargeable unit



European Pharmacovigilance Legislation - current status - Oct 2014