Pharmacovigilance and risk management

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Pharmacovigilance and risk management

- Difficulties classically encountered by the SMEs in that area:
  - Limited resources which implies a best possible allocation of these resources
  - Limited number of products (authorised or under development) and high-tech products, therefore difficulties to perform signal detection
  - Scientific limitations (due to the rarity of the diseases for which some medicines are being developed)
  - Initiatives from the Agency to facilitate the implementation of the RMPs and the work of SMEs in particular

Legal obligations

- There are pharmacovigilance obligations <u>at all the steps of the life-cycle of a medicinal product</u>

1. Before the authorisation
   - Fundamental obligations of the sponsor of (interventional) clinical trials - Directive 2001/20/EC.
     - SUSAR reporting
     - Submission of the Annual Safety Report

Legal obligations

2. During the evaluation of a Marketing Authorisation Application (MAA)
   - Fundamental obligations of the sponsor (which may have an impact on the clinical safety evaluation of the MAA)
   - Description of the future pharmacovigilance system by the Applicant
   - Safety specification and preparation of the risk management plan

Legal obligations

3. After the granting of the Marketing Authorisation (MA)
   - Fundamental obligations of the sponsor (which may have an impact on the MA) +++
   - Fundamental obligations of the MAH described in the EU legislation (Directive 2001/83/EC and Regulation EC 726/2004)
     - Expedited reporting
     - Submission of the Periodic Safety Update Reports

Legal obligations

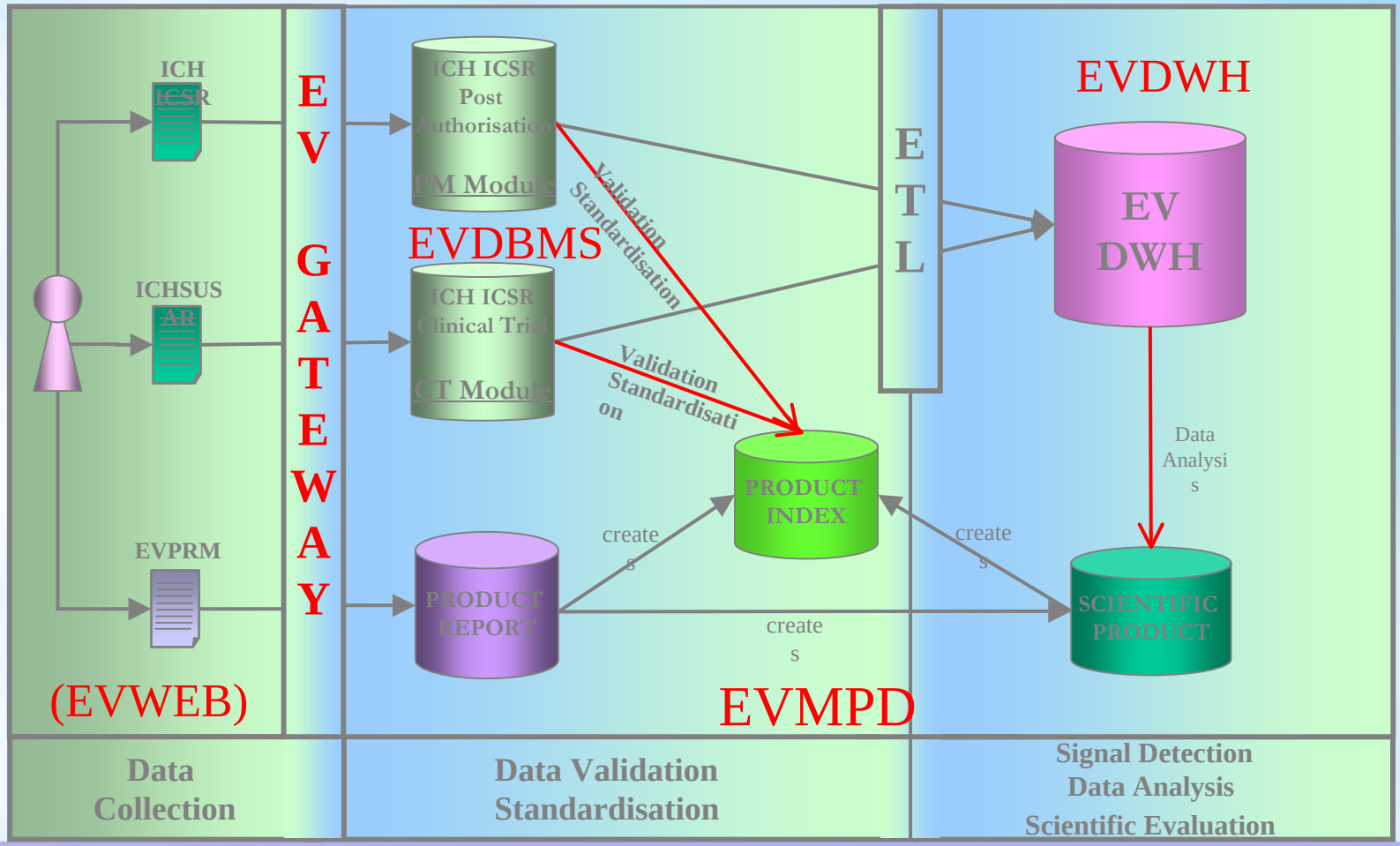
3. After the granting of the Marketing Authorisation (cont.)
   - Specific provisions which may be linked to the authorisation (e.g. conditional approval)
   - Implementation of the risk management programme
   - Renewal
   - Fulfilment of the post-authorisation commitments (pharmacovigilance follow-up measures)

- There is a need to have a good knowledge of these requirements (i.e. knowledge of the EU regulations and corresponding implementing texts) +++

Implementation of the electronic reporting of ICSRs / SUSARs

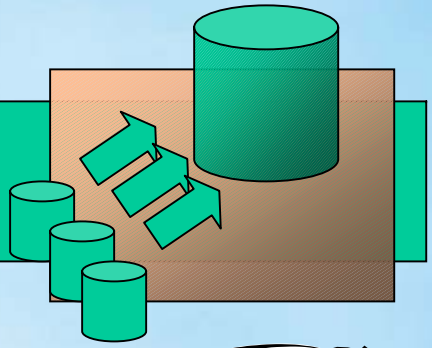
- All the adverse drug reactions reports (or individual case safety reports) must be transmitted electronically in the EU according to internationally agreed standards (ICH standards incl. MedDRA)
- These ICSRs must (but not only) be transmitted to EudraVigilance

What is EudraVigilance?

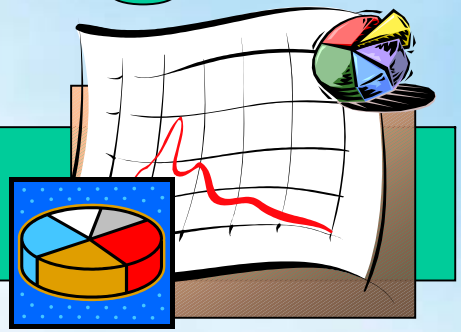


What is EudraVigilance?

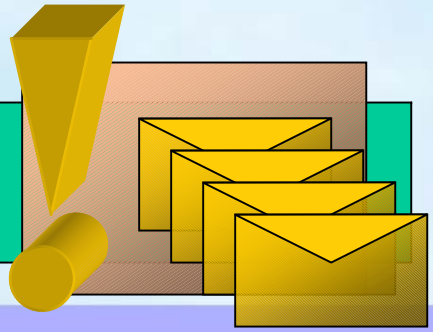
The EudraVigilance Data Warehouse



The EudraVigilance Analysis Toolkit



The EudraVigilance Information Delivery System



Implementation of the electronic reporting of ICSRs / SUSARs

- Need to register first to EudraVigilance
- There is a web application (EVWeb) for the electronic transmission of ICSRs which can be used by SMEs
- Need to undertake a 3 days EudraVigilance training
- Possibility to obtain a waiver for the MedDRA license
- Populate the EVMPD +++
- Pls visit our website http://eudravigilance.emea.europa.eu or contact us eudravigilance@emea.europa.eu

The Risk Management System

- Guideline on Risk Management Systems for Medicinal Products for Human Use (Doc. Ref. EMEA/CHMP/96268/2005)
- « a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions »

The need for a risk management

- New marketing authorisation involving:
  - New active substance
  - A similar biological medicinal product
  - Generic/hybrid where safety concern requiring additional risk minimisation activities has been identified with reference medicinal product

The need for a risk management

- Significant changes to Marketing Authorisation (unless agreed not needed)
  - New pharmaceutical form
  - New route of administration
  - Significant change in an indication/patient population
- On request from a Competent Authority
- On company initiative e.g. safety issue with a marketed medicines
- Update to previous EU-RMP

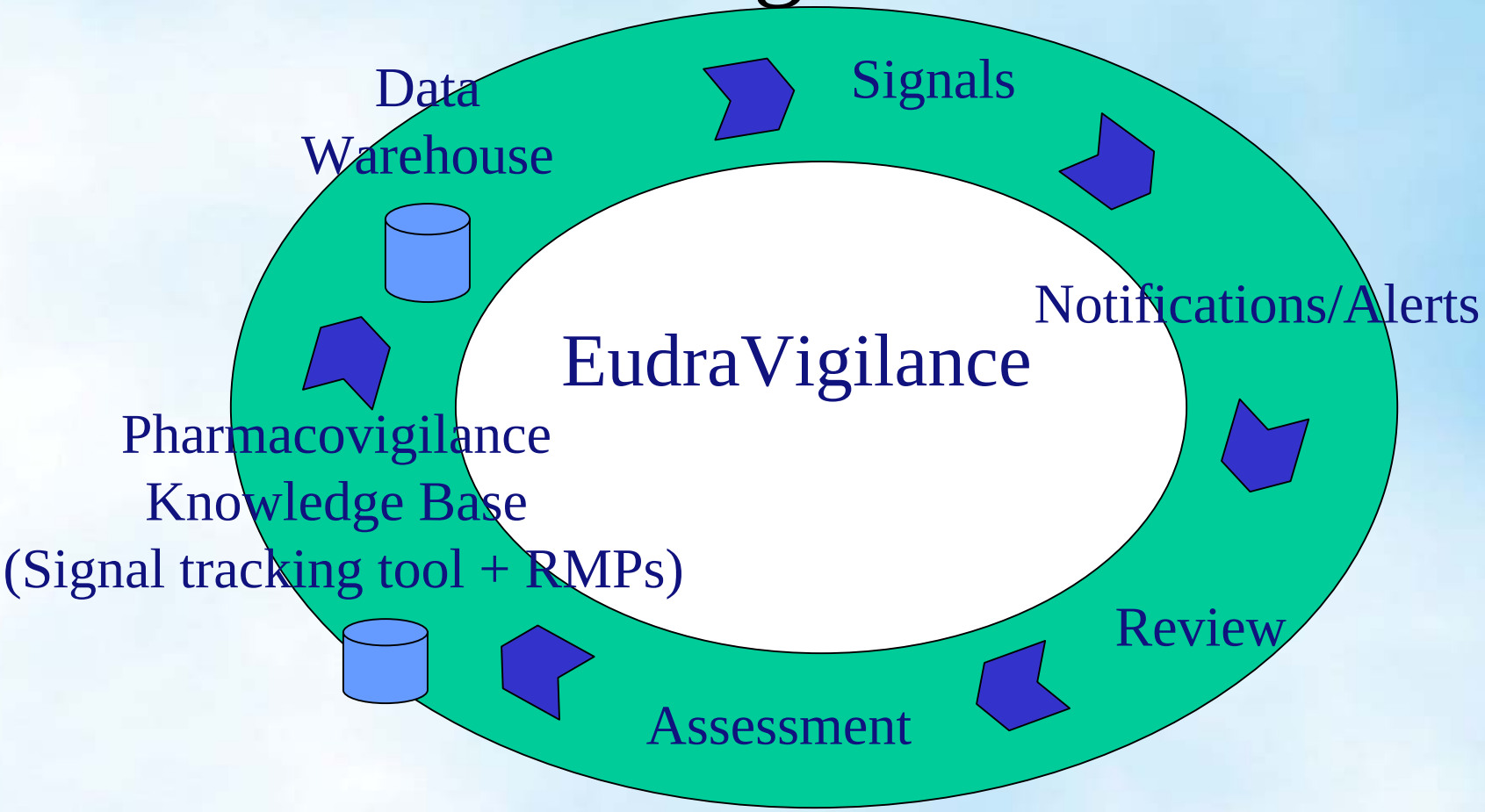
The content of a EU risk management (EU-RMP)

- Part I (ICH E2E)
  - Safety specification
  - Pharmacovigilance Plan
- Part II (EU specific)
  - Evaluation of the need for risk minimisation activities
  - if a need for additional activities: Risk minimisation plan
- The template for EU risk management plan contains these documents plus an Annex 1 (interface between EU-RMP and EudraVigilance). This template is published on the EudraVigilance website: http://eudravigilance.emea.eu.int/human/EURiskManagementPlans.asp

Feedback on RMPs

- The RMP shold be a short stand-alone document (20-40 pages) sometimes too long with too many details
- Safety spec: tend to focus on known risks rather than what is NOT known. Kaplan-Meier curves to clarify exposure
- PhV plan: Too much emphasis on routine PhV activities rather than additional studies which are needed. When safety studies are planned: purpose, key elements of design and timeframe for protocol
- Risk minimisation plan: JUSTIFICATION when considerer not needed. Value of drug utilisation studies.

EudraVigilance and risk management



Key points

- Gain a good knowledge of the EU regulations and relevant implementing guidelines (soon publication of revised Volume 9A of the rules governing medicinal products in the EU – pharmacovigilance)
- Contact the relevant persons to get some advice and support (PTL, EV, Risk management team, ..)
- Discuss the possible controversial issues during the pre-submission meeting (including risk management plans)
- EudraVigilance Information Days and trainings (see EV website)

Future prospects

- Technical validation of the EudraVigilance Data Warehouse (Data Analysis System) including quantitative methods and roll-out to the NCAs
- Implementation of the EudraVigilance access policies in accordance with the new EU legislation (appropriate access is considered for the MAHs)

Relevant texts and guidelines

Volume 10

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm

EudraLex (rules governing medicinal products in the EU)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

Pharmacovigilance guidelines (CHMP working parties – pharmacovigilance)

http://www.emea.europa.eu/index/indexh1.htm

EudraVigilance and guidelines relevant to the electronic transmission of ICSRs in the EU

http://eudravigilance.emea.eu.int/human/index.asp

ICH guidelines

http://www.ich.org/cache/compo/276-254-1.html