ARNOLD & PORTER LLP

Overview of Risk management: A EU perspective

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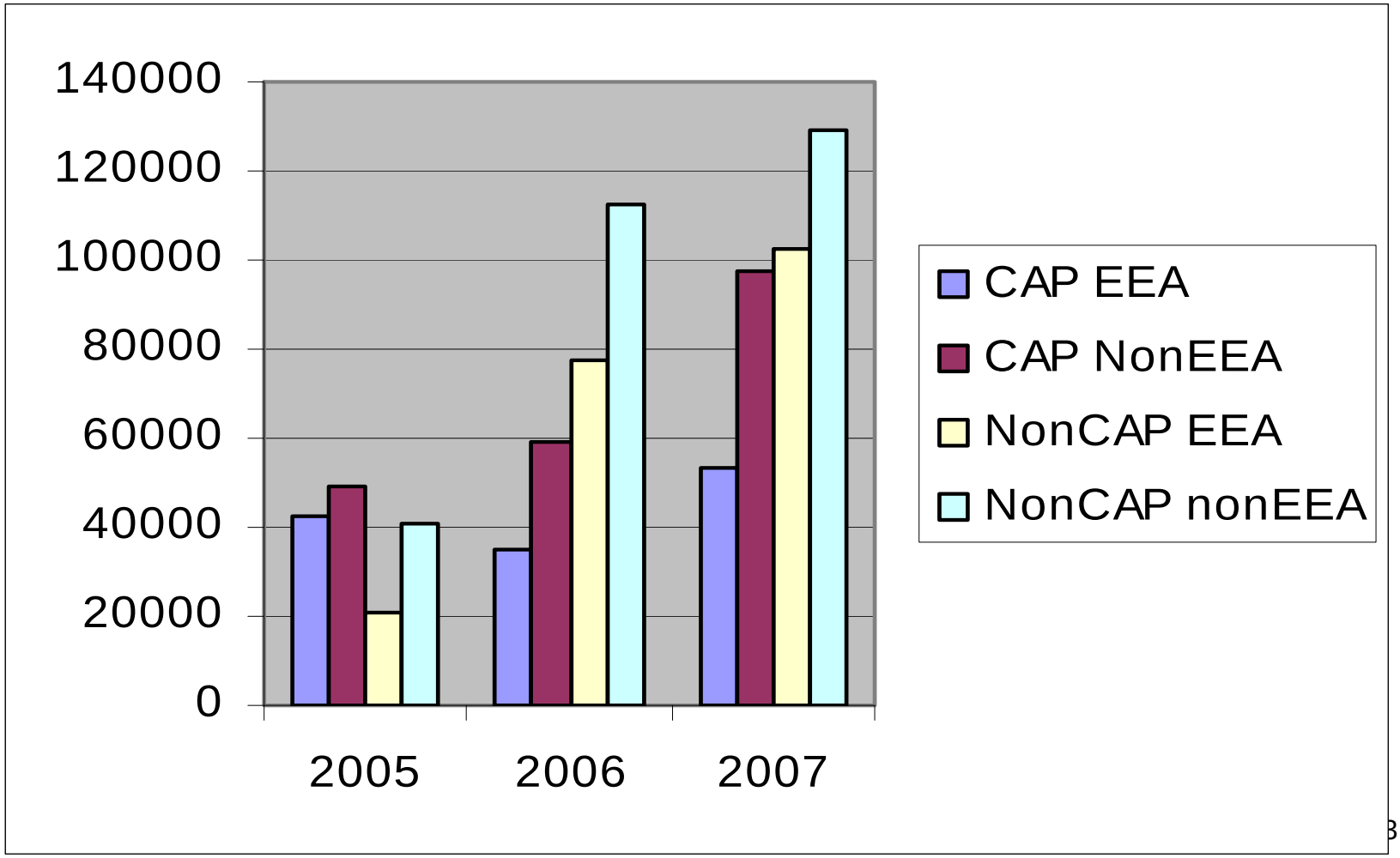
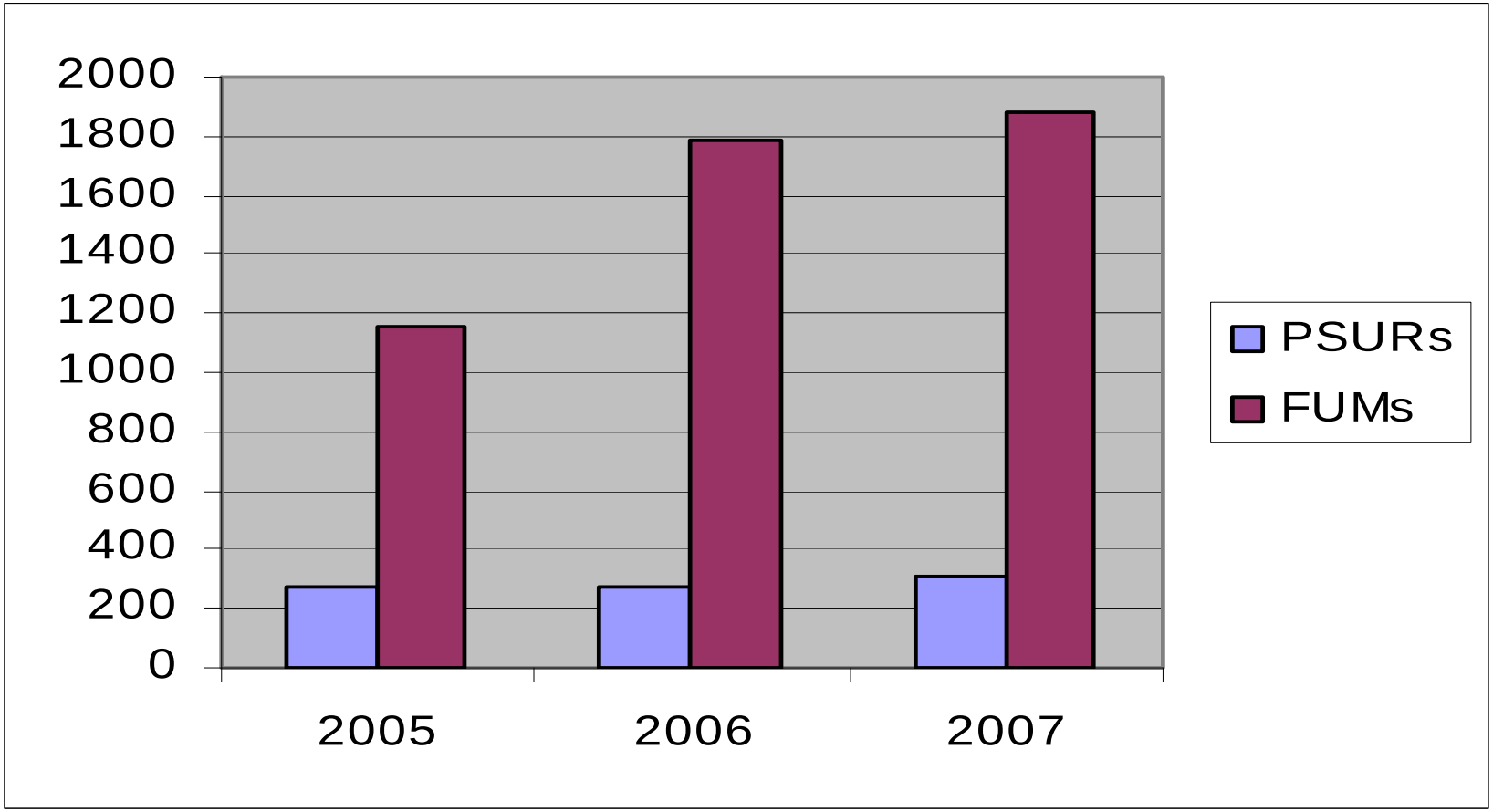
Current landscape following revision of pharmaceutical legislation

- Approval based upon risk/benefit
- Stepping up on post-approval market surveillance
- Initial regulatory submission includes description of conduct of pharmacovigilance and risk management system
- Obligations to monitor and re-assess risk/benefit balance

Transmission of EU and non-EU ADR reports transmitted to the EMEA (2005-2007)

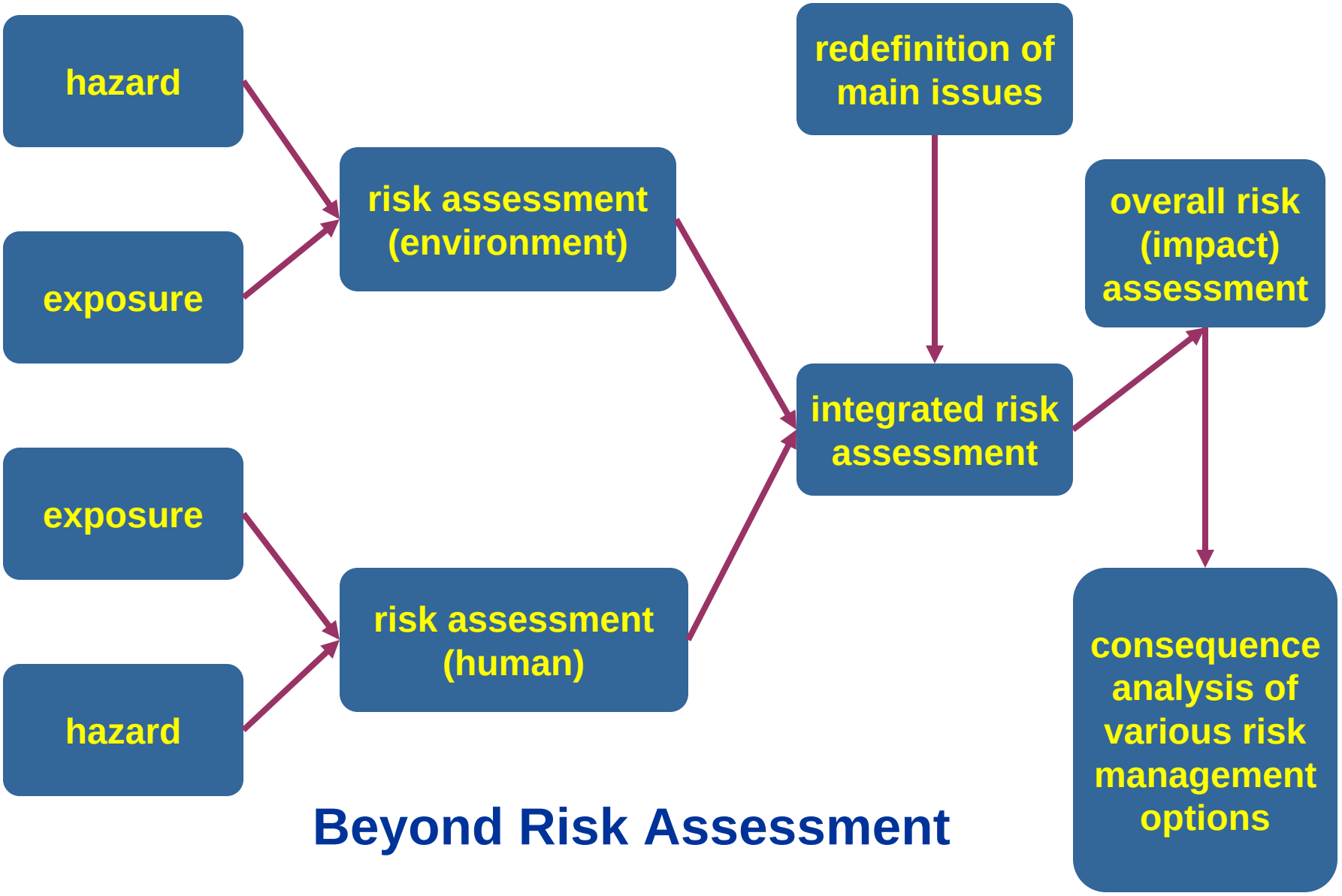


PSURs and Follow-up Measures (2005-2007)



Policy triggers for the current European risk management rules and strategy

- G10 Medicines Report 2002
- EMEA 2002 proposals for establishing a risk management strategy concentrating on centrally authorised product and referrals
- UK initiative for a “excellence” model for the future conduct of pharmacovigilance
- Result of high profile drug withdrawal and certain public health issues surrounding certain products in 2000s



Beyond Risk Assessment

Purpose of risk management strategy

- Risk management strategy goes far beyond collection and analysis of safety reports

- An essential part of risk management is to attempt to foresee the possible problems a compound may encounter when it comes into general use
  - secondary pharmacological effects
  - formation of reactive metabolites
  - failure to observe contraindications
  - mistakes in dose
  - serious concurrent diseases and their treatment
  - genetic polymorphisms

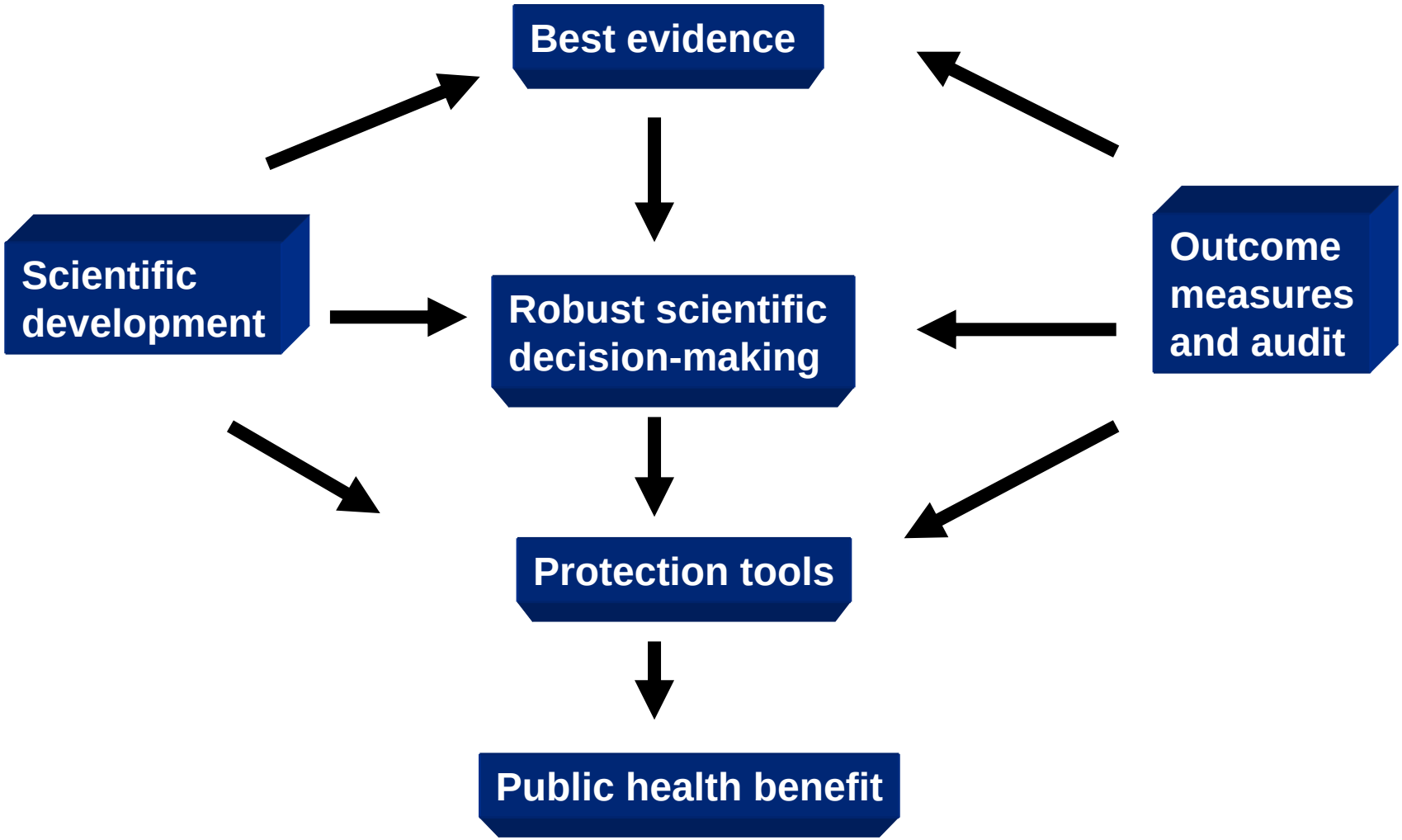
Risk management

- A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a specific product, including the assessment of the effectiveness of those interventions

Need for a European strategy for pharmaceuticals

- Agreement by Heads of Agencies in 2002
- Working Group established to develop a EU wide strategy for risk management:
  - builds on existing resources and expertise and co-ordinating role of the EMEA
  - supports consistent, robust decision making
  - ensures accessible information on drug safety including information exchange between agencies
  - avoids duplication
  - is demonstrably effective in protecting public health

Evidence base for pharmacovigilance



Best evidence being considered

- Mechanisms and procedures to stimulate spontaneous reporting from health professionals
- Collaborative efforts to design and apply tools to generate signals
- Avoiding duplication in management of PSURs
- Registries and follow up programmes
- Automated data sources for performing pharmacoepidemiological studies
- On grant of MA agreement on safety study protocols
- NCAs and companies to implement electronic reporting through EudraVigilance

Process driven

- **Pharmacovigilance specification**
  - structured method for documenting the established risks of a drug and the potential for unidentified risks at the time of MA
- **Pharmacovigilance plan**
  - to collect data relevant to safety profile of a product after marketing
  - to demonstrate safety and identify harm
- **Risk minimisation 'toolkit'**
  - strategies to reduce risk to individual patients and populations

- Product-specific taking account of product characteristics and patient population

Risk management plans

- NCE and biotech derived products
- Orphan medicinal products
- Significant changes in established products (new form/route of administration)
- Established products introduced to new populations or significant new indications
- Established products when reclassified from POM to non-POM

Risk minimisation toolkits

- All products require high quality pharmacovigilance and product labelling
- Some may require specific intervention to minimise risk, e.g. information for prescribers, pharmacists, nurses and patients
  - patient educational programmes
  - healthcare provider education programmes
  - certification programmes for prescribers and pharmacists
  - additional education fora
- Special packaging requirement
- Controlled access and/or product distribution channels

What is in the horizon? Challenges

- Consultation on pharmacovigilance strategy
  - discussion by Pharmaceutical Committee in 2007
  - rationalising risk management planning
  - compliance
  - applicability to already authorised products
- Paradigm for assessing risk/benefit balance
- Convergent approach in risk management affecting drug/device combination products
- Paediatric Regulation
- Advanced Therapy Medicinal Products Regulation
- Biological products (including biosimilars)
- Products for emerging infectious diseases

Ongoing efforts at ERMS 2008-2009

- Exploring methodologies in conduct of pharmacovigilance
- Applying a more proactive conduct of pharmacovigilance
- Striking right balance between timely patient access to new medicines and knowledge needed on safety profile at grant of MA along with most robust post-authorisation measures
- Strengthening quality assurance within the EU PV system to improve the overall quality (output)
- Increased transparency and improving communication on safety of medicines