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European Commission's Proposal to Re-Design Existing European Drug Safety Rules – *Outline of Major Changes*

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The Commission's Legislative Proposals

- Presented on 5 December 2007
- Proposals contain **very significant changes** to EU pharmacovigilance ('PV') legislation
- **Emphasis on**:
  - higher value activities: less focus on reporting, more on risk management
  - high risk products: more requirements for high risk products, less for low risk products
  - 'benefit risk' as key concept
- May offer **opportunities** for companies to improve drug safety for the benefit of the business as a whole

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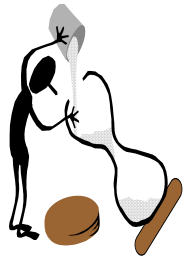
Timeline



- **March-May 2006:** Previous stakeholder consultation
  - Focus on strengths and weaknesses of current system
- **February 2007:** Vice-President Verheugen presented
  - *"Strategy to Better Protect Public Health by Strengthening and Rationalizing EU Pharmacovigilance"*
  - Part of that strategy covered *"proposals for changes to the legal framework"*
- **5 December 2007 – 1 February 2008:** Stakeholder Consultation (*82 contributions!*)
- **Q4 2008:** Commission aims to adopt proposals for the European Council and Parliament ("co-decision procedure")

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Previous Consultation Identified Weaknesses in EU PV Regime:

- Complex system
- Duplication of work
- Lack of clear roles and responsibilities
- Significant administrative burdens on industry and regulators
- Implementation not the same in all MS - negative impact on functioning of the internal market
- No fast and coherent EU action in response to drug safety alerts

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Legislative Strategy

- The Commission proposes:
  - a **Directive** of the European Parliament and the Council amending Directive 2001/83/EC
  - a **Regulation** of the European Parliament and the Council amending Regulation (EC) No 726/2004

- Article 101(b) of the proposals provide the legal basis for the Commission to adopt Good Vigilance Practices ('GVP')

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Structure of Presentation

Focus on six key aspects:

- *Risk Management System*
- *ADR Reporting*
- *PSUR Reporting*
- *Safety Assessment*
- *Key Safety Information*
- *Enforcement*

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1. Risk Management System

- Risk management system integrated into MA*:*

  "The risk management system shall be annexed to the marketing authorization"

- Risk management system key element in MS assessment of applications for MAs, together with data from pre-clinical tests and clinical trials (Article 21(4))
  - **Commission argues that:**

    "regulatory authority decision-making when authorizing products is directly linked to the robustness of post-authorization pharmacovigilance … this means ***products can be authorized earlier in their development****"*

Risk Management Conditions for MAs

- A MA may be granted subject to **conditions** included in the risk management system:
  - requirement to conduct PASS
  - additional adverse reaction recording/reporting obligations
  - conditions or restrictions of use

- MS Competent Authorities ('CAs') may provide that conditions should be met within certain **deadlines**

- **Note**: Continuation of the MA shall be **linked** to the fulfillment of conditions

- **Note**: Products subject to conditions shall be included in **list of intensively monitored products** (*more later*)

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Post Authorisation Safety Studies

- Clarified legal basis for Post Authorisation Safety Studies ('PASS'):
  - an authority that granted a MA may require a PASS *"**if there are serious concerns about the risks affecting the risk benefit balance** ..."*

- Amended definition of 'PASS':

  "A pharmacoepidemiological study or clinical trial with an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, or confirming the safety profile of the medicinal product"

- If PASS is required, it shall be a **condition for the MA**

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PV System Master File

- The PV System Master File ('SMF') is defined as:

  "A detailed description of the PV system utilized by the MAH to fulfill the tasks and responsibilities listed in [PV legislation]"

  – **Note**: It should be maintained on site and available for regulators and inspectors

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2. Changes to ADR Reporting

- **Key simplifications**:
  - All EU domestic reports go to Eudravigilance only
  - All serious third country reports go to Eudravigilance only
  - The EMEA to scan scientific literature (no longer MAH responsibility)
- **Note**: 15 day reporting for all EU source case reports

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Changes to ADR Reporting (cont'd)

- **Patients to report** suspected ADRs:
  - for medicines under intensive monitoring: to MAH
  - for other drugs: to relevant national CA

- **Medication errors** to be reported
- **Public access** to individual adverse reaction reports in Eudravigilance

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Medicines Under Intensive Monitoring

- EMEA to establish and maintain **list of medicines under intensive monitoring**
  - names of products and active ingredients
  - any product subject to conditions or restrictions shall be automatically added to list
  - removal from the list linked to risk management plan conditions (if risk benefit balance remains positive after assessment of additional data)

- SPC, package, and package leaflet for products under intensive monitoring to provide:

  "This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported"

Changed Causality Assessment

- Article 101(e) introduces a lower causality threshold for reports:
  - "where the MAH considers that a causal relationship is at least a reasonable possibility, and this shall include:

    (a) Reports where the patient or Healthcare Professional has made a statement that a causal relationship between the event and the product is considered to be at least a reasonable possibility; and

    (b) Reports where … the temporal relationship between the exposure to the medicinal product and the adverse reaction means that a causal relationship cannot be excluded."

3. PSUR Reporting

- Periodic Safety Update Reports ('PSURs') shall:
  - contain scientific evaluation of risk benefit balance
  - contain summaries of data relevant to risk benefit
  - not routinely contain listings of individual cases
  - contain data on volumes of sales and, if available, data on volume of prescriptions
  - be submitted electronically

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Exemptions from PSUR Reporting

- PSURs not required for:

✓ generics (Article 10)

✓ active ingredients in well-established medicinal use for ten years with an acceptable level of safety (article 10a)

✓ homeopathic medicinal products (Article 13-16)

✓ traditional herbal medicinal products (Articles 16a-16i)

4. Safety Assessment for Nationally Authorized Products

- **Centralize at EU level** the safety assessment for nationally authorized products (Article 101(k))
- **Mandatory** community assessment if certain criteria ("**triggers**") are met, i.e. if MS:
  - considers suspension or revocation of a MA
  - considers suspending marketing or distribution of product
  - considers refusing renewal of MA
  - is informed by the MAH that it considers withdrawing a product on safety grounds

Safety Assessment for Nationally Authorized Products (cont'd)

- Triggers (cont'd), if MS:
  - considers that new a contraindication or a restriction to indications is necessary
  - conducts inspection and finds "serious deficiencies"
- Detailed procedure:
  - Public hearing
  - Assessment by new "Committee on Pharmacovigilance"
  - CHMP opinion (made public)
  - Commission decision (binding)

Transparency and Communications

- EMEA to coordinate important safety announcements between CAs

- EMEA to establish a safety web portal to make available safety data, including:
  - agreed risk management plans
  - list of all QPPVs
  - reference dates for PSURs
  - agreed PASS protocols
  - the initiation of a Community assessment of safety issues, including data related to public hearings

5. Key Safety Information

- Introduction of a new presentation of “key safety information”
  - the Summary of Product Characteristics (SPC) shall contain “**key safety information** about the medicinal product and **how to minimise risks**”
  - the Package Leaflet shall contain the same data presented in a box surrounded by a **black border**
- **Note:** link to risk minimization

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6. Enforcement

- Enforcement of risk management:

  "The MS shall ensure that laws, procedures and resources are in place to allow enforcement of measures included in risk management plans …"

  "… effective, proportionate and dissuasive penalties…"

- *CAs shall send all **inspection reports** to the **EMEA***

- *Criteria for suspension, revocation, withdrawal or variation of MA by CAs simplified:*
  - *if risk benefit balance is not positive*
  - *(if composition of product is not as declared)*

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Conclusions

- Very significant changes to EU drug safety legislation

- Focus:
  - less reporting, more risk management
  - less duplication, more centralization
  - benefit-risk as key criteria

- Implications:
  - monitor developments in 2008 carefully
  - higher value PV?
  - opportunities and risks

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Thank you!

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