Proposed Pharmacovigilance Legislation

A QPPV's View on the Practical Implications

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Disclaimer

The views expressed here are the current views of EFPIA, but shall in no way be binding for EFPIA.
Rationale for new legislation

In light of experience and following an assessment made of the EU pharmacovigilance system made by the Commission, it has become clear that new measures are necessary to improve how the EU rules operate on the pharmacovigilance of medicinal products.

Today’s proposals seek to change the existing EU legislation on pharmacovigilance (...). They aim at strengthening and rationalizing the EU pharmacovigilance system, with the overall objectives of better protecting public health, ensuring proper functioning of the internal market and simplifying the current procedures.

General comment

- EFPIA welcomes all measures contributing to the rationalisation and simplification of pharmacovigilance activities in Europe
- EFPIA welcomes the recommendations on:
  - Clarification of the roles and responsibilities for all parties
  - Recommendation for all ADR reports to be submitted to a single database, managed by a single data processing network
  - Adoption of a pharmacovigilance ‘master file’ system
- EFPIA supports transparency as a means of engaging stakeholders affected by the safety of medicines, as well as promoting the understanding and trust of the public, patients and healthcare professionals
EFPIA reservations

• EFPIA has several reservations:
  – Community Referral Procedures – Public Hearings
  – Transparency
  – Definition of ‘suspected adverse reaction’
  – Any additional national reporting requirements
  – Internal audit findings
  – Several technical issues

Areas of Concern
• Proposed that the assessment of Community Referrals by the Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) may result in public hearings (Directive 107k)

• EFPIA welcomes the concept of public hearings
  – Many international companies are already accustomed to such hearings, e.g. Advisory Committees in the USA

• However, a public hearing that focuses on risk, without considering benefit, may be problematic

• A public hearing that focuses on risk, without considering benefit, may be problematic:
  – Regulatory decisions on marketing authorisations are usually based on efficacy, safety and quality
    • Benefit-risk assessments are the responsibility of the Committee of Human Medicinal Medicines (CHMP) or the co-ordination group (depending on the registration procedure of the medicinal product)
  – A public focus on risk may result in an inaccurate perception of the benefit-risk profile, which could lead to untoward adverse public health consequences, e.g. should patients decide to abruptly discontinue treatment
Community Referrals - Public Hearings (3)

• Proposals
  – Need to clearly define how and where it would be appropriate to involve the PRAAC in a Community Referral and hold a public hearing
    • The criteria for initiating public hearings need to be clear, proportionate and based on significant scientific/public health reasons to ensure consistency and efficiency
  – Need to ensure that some recommendations can only be made after a benefit-risk assessment has been properly conducted e.g. not renewing a marketing authorisation

Transparency (1)

• Europe’s drive for a dynamic, knowledge-based, information society and its Treaty obligation to ensure a high level of health protection are complementary
  – EC’s White Paper on Health Strategy stated “…patients have a right to more quality information on available medicines, the ground of which they have been authorised and how they are monitored.”
• The EC’s proposals aim to strengthen the provisions on transparency and communication on medicines safety, to increase understanding and trust amongst patients and health professionals and improve the safe use of medicines
• While EFPIA fully supports these objectives, concerns arise on specific proposals related to the description of risk management systems, ‘opinions and decisions’ arising from the assessment of PSURs and post-authorisation safety study protocols
Transparency (2)

- Copies of ‘risk management systems’ (i.e. RMPs) to be publicly accessible via EMEA/Member State web portals (Regulation 26.3 & Directive 106.1)
- ‘Opinions and decisions’ arising from the PSUR assessment to be publicly available via EMEA safety web-portal (Regulation 26.10 & 28.6, Directive 107m)
  - Regulation Article 26.10 indicates that EMEA should publish only the conclusions of each report
- PASS protocols and results abstracts to be publicly available via the EMEA web-portal (Regulation Article 26.8)

Transparency (3)

- EFPIA position:
  - Technical documents are designed for competent authorities, not the general public; they may also contain commercially confidential information
  - To avoid misinterpretation, inappropriate expectations or undermine the Committee’s opinion/decision making process in any way:
    - Only reader-friendly summaries of technical documents should be posted on public websites
    - Only final assessment conclusions, recommendations and decisions should be posted on public websites
Definition of Suspected ADR (1)

• ICH E2A (1995) many companies have managed spontaneous reports as having implied suspected causality, while maintaining a need for specific causality assessment of clinical trial case reports
• ICH E2D (2003) many companies have used the same causality categories for assessment of case reports from all ‘solicited’ sources
• EC proposes new definition of suspected ADR for adverse events from spontaneous sources & PASS: An adverse reaction in respect of which a causal relationship between the event and the medicinal product cannot be excluded
  – Directive 2001/20/EC ENTR/CT3: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Definition of Suspected ADR (2)

• EFPIA concerns
  – Proposed definition differs from that applied in other ICH regions or in other settings (e.g. clinical trials)
  – Different definitions will result in a different thresholds for the identification of ADRs from clinical trials and post-marketing studies
  – Leads to a risk of confusion in the area of safety data management, within pharmaceutical companies and the competent authorities, with the potential for adverse consequences on the quality of data being collected for safety surveillance and public health protection purposes
• Consistency in safety data management is essential if safety surveillance activities are to be effective: EC’s proposal should be clarified, to maintain consistent definitions across clinical trial and post-marketing safety regulations
No additional national requirements (1)

- Currently, national pharmacovigilance rules accompany EU rules; even centrally authorised products can be subject to additional national requirements
  - Although often similar, various national rules are not uniform, resulting in a complex architecture of national pharmacovigilance systems in a variety of different languages
- Measures aimed at rationalising, simplifying and harmonising the European PV system should be implemented uniformly across Europe: important for the benefit of patients and to ensure maximum consistency and optimal use of available resources
  - Regulation (Recital #5) states “Member States should therefore not impose on marketing authorisation holders any additional reporting requirements”

No additional national requirements (2)

- Application by Member States of a single set of EU PhV rules without additional national requirements would:
  - Still allow competent authorities to maintain national databases to handle local reports, but all to the same standard
  - Still allow for national evaluation and surveillance of safety data
  - Facilitate a single robust database for safety signal detection purposes
  - Facilitate prevention of multiple duplicate reports
  - Ensure that each task is done once, not 27 separate times
    - Should be more cost-effective as Member States would not have to invest locally in signal detection and evaluation functionality
No additional national requirements (3)

- Critical success factors would include:
  - Immediate access and control of local case reports by individual competent authorities
  - Acceptable service level agreements in terms of system reliability and availability, as well as data protection
  - Interoperability of the central database (EudraVigilance) with national databases, particularly in terms of data quality, analysis and signal detection capabilities
- EFPIA position:
  - All parties should accept use of a single set of PhV rules, and a single standard for quality and language of report
  - All expedited reports should be sent to a single portal with immediate and reliable access for all individual Member States

Internal audit findings

- Proposed that MAHs must perform regular audits of their PhV systems: a note of the main findings of these audits must be appended to the PhV system 'master file' ready for inspection by the competent authorities (Directive 104.2 & 108b)
- EFPIA supports the concept of regular internal audits, but we are concerned that the proposal to inspect records on internal findings may compromise the ability of internal audits to improve the marketing authorisation holder’s pharmacovigilance system
- EFPIA proposes that the PhV system master file should include information about MAH's procedures for internal audits and specific internal pharmacovigilance audit programmes (past 5 years and future) but not the findings themselves
Intensive Monitoring

- Medicinal products will be subject to ‘Intensive Monitoring’ if they require PASS or have conditions/restrictions regarding safe and effective use
  - Product labelling to include the following: “This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority>”
- Concern: if such statements are limited to certain products, affected patients could be unduly alarmed
- Proposal: it would be more appropriate to encourage the reporting of adverse reactions for all medicinal products

Summary of Essential Information

- ‘Summary of Essential Information’ section in SmPC and PILs to accompany every medicinal product placed on EC market; to be placed in a ‘black box’ with an identifying symbol
- May lead to readers taking notice of only selected information, shifting the focus away from other meaningful information: could create confusion among patients and have unintended negative consequences for public health

DIA QPPV Forum – Apr 09

www.diahome.org
Marketing Authorisation Application

- To include:
  - Proof that the applicant has the services of a QPPV
  - Member State where the QPPV resides
  - Contact details for the QPPV
  - Statement signed to confirm that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX
  - Reference to the site where the pharmacovigilance system Master File for the medicinal product is maintained
  - Any authorisation obtained in another Member State, including a summary of the data contained in periodic safety reports and adverse reactions reports, or in a third country to place the medicinal product on the market
Pharmacovigilance Master File

• Analogous to Detailed Description of Pharmacovigilance System
• ‘Key elements’ to be submitted with each MAA
• Copy to be made available to EU competent authorities within 7 days of request

Scientific Literature

• EMEA to monitor published literature for ‘selected’ products, to identify ADRs for entry onto EudraVigilance
• MAHs still to monitor (world-wide) literature for safety surveillance purposes
ADR Reporting

- All suspected ADRs to be submitted electronically to EudraVigilance only (i.e. not Member States)
- Serious ADRs within 15 days; non-serious ADRs (EU only) within 90 days
  - To include overdose and medication error reports that result in ADRs
- Competent authorities to facilitate ‘consumer’ reporting, including web-based structured forms
- MAHs to access ‘regulatory authority’ ADRs via EudraVigilance
  - Necessitates active screening of EudraVigilance for ADR reports

Expedited Notification of Benefit-Risk

In particular, he shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is not in accordance with the summary of the product characteristics.
Periodic Safety Update Reports

• To provide analysis of benefit-risk balance, not a “detailed presentation of individual case reports”
  – Routine PSURs not required for products of ‘low risk’ or where reporting would be duplicative (e.g. generic products)
• To include:
  – Summaries of data relevant to the benefits and risks of the medicinal product
  – Scientific evaluation of the risk-benefit balance of the medicinal product
  – All available sales and prescription volume data
• To be submitted electronically

Post-Authorisation Safety Studies

• Amended definition: *Any study with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.*
• Competent authorities may require PASS as condition of marketing authorisation
  – Authority to specify rationale, objectives and timeframe for submission/conduct
• ‘Harmonised guiding principles’ to be introduced (excluding post-authorisation clinical trials) to ensure PASS are non-promotional
PASS cont’d

• Provisions to be applied equally to studies initiated by MAH and competent authorities
• MAH to submit study protocol and allow 60 days for competent authority to comment
  – Competent authority will have right to object to initiation of the study: letter of approval will be required before the study can commence
• PASS study results to be made publicly available via EMEA web-portal

Transparency

• EMEA/Member States maintain ‘safety web-portals’
• To include publicly available copies of:
  – List of locations where MAH Master Files are sited
  – MAH contact information for pharmacovigilance enquiries
• Healthcare professionals and patients to be given ‘appropriate’ access to EudraVigilance
• EudraVigilance data to be publicly available in aggregate format, with explanation how to interpret data
  – Individual ADR reports may be requested by the public, subject to data privacy rules
Initiation of Article 107

- Article 107i lists situations that may warrant its initiation, including: (e) it considers that new contraindications, a reduction in the recommended dose, or a restriction to the indications is necessary.
- Article 107i should be reserved for situations in which the marketing authorisation is at imminent risk of being revoked or suspended; other public health concerns where a Community interest is involved can be adequately handled via the Article 31 Referral Procedure.

GPvP & Medicinal Product Information

- Commission to adopt and publish guidelines on Good Pharmacovigilance Practice.
- MAH will be required to submit medicinal product information electronically (for EudraPharm and EudraVigilance Medicinal Product Dictionary).
Pharmacovigilance fees

• EMEA to charge fees for:
  – PSUR assessment: € 6100
  – Assessment of RMPs: € 12100
  – Pharmacovigilance referral procedures: € 72,800
• Regardless of authorisation procedure
• 50% of fee to be passed on to Member State competent authorities who undertake actual work