The new pharmacovigilance legislation in the EU

Elisabethann Wright, Partner, Hogan Lovells International LLP, Brussels

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Outline

– The new rules and requirements

– The black symbol

– Information requirements and next steps
The New Pharmacovigilance Legislation

• The new legislation is contained in two legislative instruments:

• Both adopted 15 December 2010
• Regulation (EU) No 1235/2010 entered in force on 2 January 2010 and applies from 2 July 2012
• EU Member States shall transpose and apply Directive 2010/84/EU by 21 July 2012
The new rules and requirements (I)

- EU Member States are required to take measures concerning a medicinal product if it is harmful:
  - not only in normal conditions but in any conditions OR if the risk-benefit analysis is not favourable under any conditions of use (not only authorized indication)

- Broader definition of adverse event:
  - A response to a medicinal product which is noxious and unintended, including in case of off-label use or misuse of the medicinal product
    - DELETED "... and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function."
The new rules and requirements (II)

• New definition of Post-Authorisation safety study:
  – Any study relating to an authorized medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures
• NO reference to conduct of study in accordance of the marketing authorization
The new rules and requirements (III)

- **New definitions:**
  - **Risk management system**: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.
  - **Risk management plan**: a detailed description of the risk management system.
  - **Pharmacovigilance system**: a system utilised by marketing authorisation holders and by EU Member States to fulfil the tasks and responsibilities listed in Title IX of the Community Code on medicinal products and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.
  - **Pharmacovigilance system master file**: A detailed description of the pharmacovigilance system utilised by the marketing authorization holder with respect to one or more authorised medicinal products.
The new rules and requirements (IV)

• Requirement to provide more detailed information in the marketing authorization application concerning the pharmacovigilance system:
  – detailed information on the QP for pharmacovigilance;
  – location of the pharmacovigilance master file;
  – statement of the applicant concerning the means used to fulfil the pharmacovigilance obligations;
  – risk management plan describing the risk management system to be implemented by the applicant and a summary of this plan;
  – the risk management plan must be proportionate to the identified and potential risks of the medicinal product and the need for post-authorization data and must be updated when appropriate.

• Applicant must submit summary of safety data, periodic safety update reports and suspected adverse reactions reports in relation to marketing authorizations granted in other EU Member States
The new rules and requirements (V)

• Marketing authorization holder should:
  – operate, maintain and regularly audit its pharmacovigilance system through the QP for pharmacovigilance;
  – establish and regularly update the pharmacovigilance system master file;
  – operate and update the risk management system for every medicinal product;
  – at the request of the competent authority of an EU Member State appoint a contact person in that EU Member State reporting to the qualified person for pharmacovigilance established in the EU;
  – submit Periodic Safety Update Reports including results of any studies with potential impact on the authorization and estimate of the population exposed to the product.

• The competent authorities of the EU Member States may conduct inspections of the pharmacovigilance system master file established and maintained by the marketing authorization holder.
Prior to marketing authorization

- The authorities may conduct pre-marketing pharmacovigilance inspections in order to verify the accuracy and successful implementation of the pharmacovigilance system described in the application for marketing authorization.
Conditional marketing authorizations

• Authorities may subject grant of a marketing authorisation to a number of conditions:
  – specific safety measure contained in the risk management plan;
  – conduct of post-authorization studies;
  – compliance with requirements concerning recording and reporting of suspected adverse events that are stricter than those contained in the Community Code on medicinal products;
  – "any other conditions or restrictions with regard to the safe and effective use of the medicinal product";
  – the existence of an adequate pharmacovigilance plan.
Following Authorization

• Marketing authorization holder should provide the European Commission or the competent authorities of the EU Member State with any new information that might influence evaluation of the benefits and risks of the medicinal product concerned:
  – both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation;
  – data on the use of the medicinal product where such use is not in accordance with the SmPC (off-label use).

• The European Commission or the competent authorities of the EU Member State may require the marketing authorization holder to provide the latest copy of the pharmacovigilance system master file
Renewal of marketing authorization

• Information to be submitted for renewal of marketing authorization should include:
  – evaluation of data contained in suspected adverse reactions reports and periodic safety update reports

• Exposure of an insufficient number of patients to the medicinal product may be a pharmacovigilance ground for the authorities to impose one additional five-year renewal of the marketing authorization:
  – the term "insufficient number of patients" is not defined in the Community Code on medicinal products;
  – expected to be assessed on case-by-case basis.
Post-authorization non-interventional safety studies

- Voluntary or required by the authorities;
- Draft protocol should be submitted to the newly established EMA Pharmacovigilance Risk Assessment Committee (PRAC) or to an EU Member State authority (if requested) for endorsement before initiation of the study or modification of the protocol;
- Initiated, organized or financed by the marketing authorization holder;
- Involve collection of data from patients or healthcare professionals;
- Should NOT have a promotional aim;
- Payments to healthcare professionals shall be restricted to compensation for time and expenses incurred;
- The marketing authorisation holder may be required to submit the protocol and progress reports to the competent authorities of the EU Member States in which the study is conducted;
- Results should be communicated to the authorities via PSURs;
- Final report should be sent to PRAC or the authorities of the EU Member States where the study took place.
Institutional changes – EMA PRAC (I)

• Creation of the Pharmacovigilance Risk Assessment Committee (PRAC)
• Remit: all aspects of the risk management of the use of medicinal products including:
  – Detection, assessment and minimisation of the risks;
  – Communication related to the risk;
  – Design and evaluation of post-authorisation safety studies and pharmacovigilance audit.
• Composed of:
  – one expert member and one alternate appointed by each EU Member State;
  – six experts appointed by the Commission (pharmacology and pharmacoepidemiology);
  – one representative of healthcare professionals appointed by the Commission after consulting the European Parliament;
  – one representative of patients' organizations appointed by the Commission after consulting the European Parliament.
• Three-years renewable mandate
Institutional changes – EMA's PRAC (II)

- PRAC will deliver opinions on referrals to EMA regarding evaluation of data relating to pharmacovigilance of an authorised medicinal product
- PRAC will conduct initial analysis and prioritisation of signals of new or changing risks or changes of the risk-benefit analysis of medicinal products authorized by the EU Member States
- PRAC shall receive and endorses draft protocols (and amendments) for non-interventional post-authorisation studies of medicinal products:
  - could object if the study is seen as promotional, if the protocol does not serves the declared objective, or if the study is a clinical trial;
  - may assess final reports and formulate recommendations regarding the terms of the marketing authorization.
- PRAC provides recommendations regarding EudraVigilance organization and functioning
CHMP

- CHMP rapporteur must cooperate closely with the PRAC rapporteur
- The CHMP will rely on PRAC's assessments and recommendations when agreeing and monitoring risk management systems
- CHMP positive opinions concerning the grant of marketing authorization should include:
  - recommendation on the frequency of submission of PSURs
  - details of any measures for the safe use of the medicinal product contained in the risk management system to be imposed as conditions of the marketing authorization
  - if appropriate, the written requirement to conduct post-authorisation safety studies or to comply with requirements on suspected adverse reaction recording or reporting stricter than those provided for in the EU law
CMD(h)

• The Co-ordination Group for Mutual Recognition and Decentralised Procedure - Human (CMD(h)) is given the explicit task to examine pharmacovigilance questions in relation to medicinal products authorized in the EU Member States
• The CMD(h) will agree to and monitor risk management systems relying on the scientific assessment and recommendation of EMA's PRAC
• The Executive Director of EMA and Commission representatives shall be entitled to attend all of CMD(h) meetings
• In case of absence of consensus, CMD(h) decisions will be taken by the majority of representatives of the EU Member States
New Requirement: Black Symbol

• Medicinal products subject to additional monitoring should carry a "black symbol"
• Black symbol should be included in the SmPC and the PIL of medicinal product
• Black symbol, plus an explanatory sentence to be selected by Commission on recommendation of PRAC
• Commission was expected to select the black symbol by 2 January 2012 – Nothing yet
Information Requirement for All Medicinal Products

- MAHs should, by invitation in PIL and SmPC, “encourage” healthcare professionals and patients to report adverse events:
  - explicit statements asking HCPs and patients to report any suspected adverse reaction;
  - provide detailed explanation of how to report by post, electronically and by other means.
- EU Member States should encourage patients, pharmacists and HCPs to report suspected adverse events
- EU Member State authorities and Commission should publish marketing authorizations, PIL and SmPC, and any conditions relating to the marketing authorization, without delay
  - ... as well as Public Assessment Report for the medicinal product and a summary in lay and accessible language
Obligation on EU Member States to publish SmPCs and PILs

• EU Member States are required to establish public web-portals containing SmPCs and PILs for medicinal products authorized in the EU Member States.

• Portals should also include:
  • public assessment reports;
  • summaries of risk management plans;
  • list of medicinal products subject of additional monitoring;
  • ways to report suspected adverse events in relation to medicinal products.

• EU Member State websites should be linked to EudraPharm database
EudraPharm database

• The EudraPharm database will provide comprehensive information on all medicinal products authorized in the EU by the European Commission and EU Member States.

• The database will, among other things, include:
  – SmPCs and PILs for centrally authorized medicinal products;
  – Public assessment reports for centrally authorized medicinal products;
  – Summary of risk management plans for centrally authorized medicinal products;
  – List of medicinal products subject to additional monitoring;
  – Information on how to report adverse events to the EU Member State national competent authorities.
Good Pharmacovigilance Practices (GVPs)

- The GVPs are a set of measures to be drawn up to facilitate the performance of pharmacovigilance obligations in the EU
- The GVPs will be divided in 16 modules
- In February 2012, EMA issued the first batch of seven modules of GVPs for public consultation
  - Public consultation process was open until 18 April 2012
  - EMA intends to finalise and publish these modules by July 2012
- The published modules include:
  - Pharmacovigilance systems and their quality systems;
  - Pharmacovigilance system master file;
  - Risk management systems;
  - Management and reporting of adverse reactions to medicinal products;
  - Periodic safety update report;
  - Post-authorisation safety studies; and
  - Signal management.
Next Steps (I)

- Commission shall adopt implementing measures and guidance on the new pharmacovigilance rules that are contained in the Directive and the Regulation.
- After a public consultation, the Commission is working on a Commission Implementing Regulation on the performance of pharmacovigilance activities:
  - Expected to be adopted in May 2012;
  - The Implementing Regulation will cover:
    - the content of the pharmacovigilance system master file;
    - pharmacovigilance quality systems;
    - post-authorisation studies;
    - format and content of risk management plans;
    - use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities.
Next Steps (II)

• By 31 December 2012 Commission shall present a report on the shortcomings of current SmPC and PIL content and, if necessary, present a proposal for improvement of the rules on SmPCs and PILs
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