The New PV Legislation – its Impact on PV & MI

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Content

• Scope of change

• Key areas
  - ADR reporting
  - DDPS to PSMF
  - RMPs and PSURs
  - Intensive monitoring
  - Post Authorisation Safety Studies (PASS)
  - Signal Detection
  - Provision of information

• Progress so far
SCOPE OF CHANGE
Scope of change (1)

- Authorisation requirements
- Risk Management Plan
- Legal basis for PASS + PAES
- Product information changes
- ADR reporting
- Signal detection and management process
Scope of change (2)

- PSURs
- Transparency and communication
- Committees and decision-making
- Enhanced coordination of inspections
- Pharmacovigilance audits
What is the impact on your organisation’s work?

The big picture

Key principles:
1. Proportionality; risk-based approach
2. Risks considered in the context of benefits
3. Considering outcomes and effectiveness of regulation

But what about the smaller picture, starting now?
Time to work on the details…
ADR REPORTING
Key Changes – ADR reporting
ADR reporting: consumers

- **More inclusive**: Patients (consumers) included as valid reporters of ADRs

Directive 2010/84/EU… Article 102. The Member States shall:

    …*take all appropriate measures to encourage patients, doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority; for these tasks, consumer organisations, patients organisations and healthcare professionals organisations may be involved as appropriate.*

- Technical enhancements to database to enable provision of patient ASPRs
Extended definition: to include harm from “noxious and unintended” reaction: ie, error, misuse, abuse, off-label

**Directive 2010/84/EU**

(Chapter 5) For the sake of clarity, the definition of the term ‘adverse reaction’ should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.
• Batch number and brand name to be reported for biologicals and vaccines

“Directive 2010/84/EU… Article 102. The Member States shall…[continued]

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product…and the batch number”
ADR reporting: role of Eudravigilance

Directive 2010/84/EU
Article 107(3)

MAHs shall submit to Eudravigilance:
all serious ADRs that occur in the Union and in third countries within 15 days........
All non-serious ADRs that occur in the Union within 90 days........
ADR reporting: transitional arrangements

• Until centralised reporting to Eudravigilance (likely 2015+), interim arrangements for Member States and EMA apply

**Directive 2010/84/EU**

*Article 2 – Transitional Provisions*

• Eudravigilance functionality to be met first
• Functional requirements to be drawn up by MSs and Agency
• Functionalities to be audited
• Article 107(3) applies 6 months after audit
DDPS: Master File changes

- DDPS no longer required
- Replaced by Pharmacovigilance System Summary and an on-site Master File, available on request
- PSMF must be in place by July 2015
- Provision of a process to enable early transition and removal of responsibility to maintain a DDPS in parallel
- Variations Classification Guideline to facilitate the above
National procedures

Application validation rules have been updated

• Only include Pharmacovigilance System Summary in new applications/renewals:
  - QPPV Name
  - QPPV Telephone Number
  - QPPV Email address
  - QPPV Address (the country where the QPPV resides and operates must be EU/EEA)
  - Location of the Pharmacovigilance Master File (physical (postal) address and must be EU/EEA.)
  - QPPV CV
  - Signed statement
Reducing the burden

Once a Master File is place:

- Submit Bulk IA\textsubscript{IN} Variations to add a Pharmacovigilance System Summary/ remove responsibility to maintain a DDPS
- Variations can be submitted at the point where the DDPS would require updating
- In future cross reference to Article 57 Database to further reduce variations
PERIODIC SAFETY UPDATE REPORTS
PSURs: The main changes

- Focus on benefit as well as risk
- No *routine* requirement for generics, homeopathics, THRs
- Creation of the EU reference dates list (EURD list)
- New template/modules described in GVP and Implementing Regulation
- No more *routine* line listings
- Greater work-sharing leading to single assessment
- Central repository to be created
PSURs: EURD List

• Every substance and ID code (& formulation) listed
• EU reference date = earliest licence date
• Frequency determined by current benefit-risk knowledge
• Development and publication of harmonised birthdates to support PSUR submission published 1 October 2012 and updated monthly
• Becomes legally binding in April 2013
• Interim list of generics for which PSUR reporting is required in the meantime
PSUR changes: impact on MHRA

• Maintaining role in worksharing in EU network in transition to single assessment

• Supporting information provision in line with introduction of the EURD list and its derogations

• Current Situation:
  • Over compliance
  • National licences, generics not required
PSURs: still to be determined

- EMA shall hold PSUR repository (MAHs to submit to EMA 12 months after repository has been established)

- Single assessment

- Details of submitting safety issues to NCAs in the absence of PSURs is being developed.
RISK MANAGEMENT PLANS
Risk Management Plans

- From July 2012 all new marketing authorisation applications to include a Risk Management Plan

- A lay summary must be included which can be published

- Content of RMP should be proportionate to the risks

- Normally all parts of the EU-RMP should be submitted

- In line with the principle of proportionality certain parts or modules can be omitted for generics, unless requested by NCA
What this means in practice

• RMP is now a required part of the dossier

• However, proportionate approach is welcome, sensible and possible

• Content of RMP could be minimal for products with a well-established safety profile

• Very often there will be no RMP for the reference product – “important risks” should therefore be based on issues with warnings in section 4.4 of SmPC or which warrant a contraindication in section 4.3

• Routine Pharmacovigilance and routine risk minimisation (through labelling in SmPC/PIL) will often be sufficient
RMP Changes: impact on MHRA

• Revised processes for validation of applications
• Increased resource to manage RMP assessments
• Introduction of triaged workflow to introduce proportionate RMP assessment according to application type
• Technical IT enhancements to database in order to manage and track applications and RMP assessments
• Summaries to be published on NCA/EMA website
POST AUTHORISATION SAFETY STUDIES
Post-authorisation Safety Studies

• Post-authorisation safety/efficacy studies may be a new obligation (condition) on or after granting a marketing authorisation

Post-authorisation safety study: definition

Any study relating to 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.
Objectives of a PASS

• To quantify potential or identified risks
• To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (eg pregnant women, specific age groups, patients with renal or hepatic impairment)
• To provide evidence about the absence of a risk
• To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (eg indications, dosage, co-medication, medication errors)
• To measure the effectiveness of a risk minimisation activity.
PASS & PAES - progress so far

- Implementation of the PASS procedure for protocols approval and results management for CAPs started July 2012
  - First protocol at October Pharmacovigilance and Risk Assessment Committee (PRAC)
- Guidance for PASS protocol submission: published October 2012
- Consultation on PAES Commission awaited
ADDITIONAL MONITORING
Black Triangle Scheme
“Directive 2010/84/EU…

(10)...some medicinal products are authorised subject to additional monitoring. This includes all medicinal products with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance.”
Additional Monitoring

- Similar to UK Black Triangle Scheme
- List to be maintained by EMA and include:
  - all new active substances
  - any biological product
  - others subject to consultation with PRAC
- Removal from list reviewed at 5 years – can be extended subject to PRAC agreement
- Black symbol – EC have confirmed PRAC ‘s recommendation for a black triangle
- First additional monitoring list expected in April 2013 alongside publication of the new template
SIGNAL DETECTION
Signal detection

- Member State obligation to analyse monthly EU signals for established medicines
- Supporting EU-wide procedures and the formal procedure overseen by PRAC
  - UK is signal lead for ~100 products
- Continual review of internal signal thresholds, including assessment of foreign data
Progress so far…

• Operation of signal management process established July 2012

• New EU signal detection processes started July 2012; signal work-sharing list published

• Start of signal management through PRAC with multiple signals through first 4 months (September onwards)
Eudravigilance – 3419 substances

- 420 CAPs on URD (signals monitored by EMA)
- 2999 on existing signals monitoring list e-RMR
- 1751 unallocated to a lead member state for signals
- 89 have a PSUR frequency of 5 years or less
### e-RMRs

The image contains a table from a Microsoft Excel spreadsheet titled "Copy of Draft-eRMR for MS [Read-Only]". The table appears to be a list of active substances with columns for various specifications and values. The specific details of the table are not visible due to the image resolution, but it is likely related to pharmaceutical substances and their properties.

The page also includes a logo for the MHRA ( Medicines and Healthcare Products Regulatory Agency).
Future challenges

• Potential benefits of more Eudravigilance data BUT
  - Training required
  - Time consuming system
  - Under developed thresholds
  - No drill down ability
  - Not true data mining
Feedback from regulators

- Communication of validated signals
  - When is a signal ‘validated’?
  - Consistency across EU network needed

- Robust tracking and management required (auditable)
- What about signals from industry?
MEMBER STATE RESPONSIBILITIES AND COMMUNICATIONS
Communications and transparency

• National web portals to host range of transparency documents:
  - SPCs and PILs
  - Summaries of Risk Management Plans
  - Public Assessment Reports (including conditions)
  - Products under additional monitoring
  - ADR reporting forms
• EMA web portal expected to host further information relating to:
  - PASS abstracts, protocols and study reports
  - Committee details
• Various levels of access to EudraVigilance
• There will be EU public hearings on drug safety
• → You will have access to wider information/data, but so too will others!
New PV Legislation - ‘take all appropriate measures’

“Directive 2010/84/EU… Article 102. The Member States shall:

….take all appropriate measures to encourage patients, doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority; for these tasks, consumer organisations, patients organisations and healthcare professionals organisations may be involved as appropriate.”

Need to raise general awareness of legislation
Yellow Card strategy – revised

Raise awareness and understanding of the Yellow Card Scheme and increase reporting

Facilitation

Increasing access to the scheme to meet the needs of reporters e.g. integration with clinical systems

Clarity

What to report and when

Impact

How Yellow Card reporting makes a positive difference

Promotion

Develop and maintain promotion and communication strategies for the scheme

Two complementary sets of activities

- healthcare professionals
- the public
UK spontaneous reports 2012

Extensions to Scheme:
- Coroners (1969)
- Pharmacists (April 1997 & Nov 1999)
- Nurses, midwives and health visitors (2002)
- Patient reporting pilot scheme UK-wide (2005)
- Patient reporting established – Feb 08

Sources of direct health professional reports 2008 - 2012
Electronic reporting direct from HCPs

- SystmOne (GP system) (15-20% England GP practices)
  - Reported >2,200 since end of November 10
  - Over 1700 received in one year
  - ~50% increase in GP reporting

- UKMI Centres went live in 2010

- Pilot ongoing with Cerner - Newcastle NHS Trust

- NHS information Standard – ISB 1582 electronic Yellow Card reporting
  - GP Systems of Choice
Updated reporting site
Yellow Card App

- Facilitation of Yellow Card reporting through development of Apps
  - Initial development of website formatted for smart phones and tablets
  - Development of Yellow Card mobile app
New pharmacovigilance legislation, July 2012

In July 2012, new pharmacovigilance legislation come into effect across the EU as a result of changes set out in:

- Regulation (EU) No1235/2010 (external link)
- Directive 2010/84/EU (external link)

The changes introduced by the Directive will be transposed into UK law in the Human Medicines Regulations 2012, which also consolidate nearly all other UK medicines legislation. In February 2012, we published a formal consultation on our proposals for transposition (MLX 374). The MHRA’s response to this consultation presents a summary of the responses we received to MLX 374 and key issues raised. It also highlights significant changes we made in response:

Public consultation (MLX 374): Transposition of Pharmacovigilance Directive 2010/84/EU - The MHRA’s response (50Kb)

The legislation will be underpinned by an EC Implementing Measures Regulation and a series of modules on Good Pharmacovigilance Practice.

Find out more about the implementation of the legislation in the introduction page below.

We have developed a series of questions and answers (Q&As) (below), from the MHRA’s perspective, to support marketing authorisation holders (MAHs) with the introduction of the new legislation. Information is grouped into six themes. This information will be developed over the coming weeks and months, and MAHs are advised to keep an eye out for updated information.

A Q&A document on the new Pharmacovigilance legislation is also available from the European Medicines Agency (EMA) (external link)

For further questions or comments specifically regarding MHRA’s implementation of the new legislation, email pv2012@mhra.gsi.gov.uk. Please note, however, that not all enquiries will be answered directly and may instead be used to develop further questions and answers on this webpage. The EMA also has an email for enquiries regarding the legislation: p-pv-helpdesk@ema.europa.eu
Web-Portal

• National web-portal to be established containing:
  - Public Assessment Reports and Summaries
  - SPCs and PILs
  - Summary Risk Management Plans
  - List of substances under additional monitoring
  - Information on how to report and electronic reporting forms
  - Important information for the public
Drug Analysis Prints (DAPs)

DAPs contain complete listings of all suspected adverse drug reactions or side effects, which have been reported by healthcare professionals and patients to the MHRA via the Yellow Card Scheme. Each DAP lists all of the reactions reported by health professionals and patients for a particular medicine.

Go to the Drug Analysis Prints (DAPs)

Drug Safety Update (DSU)

Drug Safety Update is our monthly newsletter for healthcare professionals, bringing you information and clinical advice on the safe use of medicines.

Go to Drug Safety Update (DSU)

Public Assessment Reports

The MHRA’s assessment of a medicine is available in a Public Assessment Report (PAR), albeit with commercially or personally confidential information removed. PARs are typically prepared for products that were granted licences after 30 October 2005. We also publish safety Public Assessment Reports, which summarise the evaluation of a safety issue that has been identified with a medicine and the action taken to ensure that any risks are minimised and the benefits always outweigh them.

Go to the Public Assessment Reports (PARs)

Summaries of Product Characteristics (SPCs) and patient information leaflets (PILs)

This page contains product information. Every medicine pack includes a patient information leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics - a description of a medicinal product's properties and the conditions for its use.

Go to the Summaries of Product Characteristics (SPCs) and patient information leaflets (PILs)

Summaries of Risk Management Plans

A Risk Management Plan (RMP) is a document which describes all the available knowledge about the safety and efficacy of a medicinal product.

Go to the summaries of risk management plans

Yellow Card

The Yellow Card Scheme is run by the MHRA and the Commission on Human Medicines (CHM), and is used to collect information from both health professionals and the general public on suspected side effects or ADRs to a medicine. Its continued success depends on the willingness of health professionals to report ADRs.

Go to the Yellow Card

Help viewing PDFs:

- Help viewing PDF files
- Download Acrobat Reader for free
- Adobe text conversion tools
Where have we got to?
Feedback for Industry

- Transition to PSMF
- ‘Over compliance’
  - Submission of non-required PSURs
- Variable implementation of ADR reporting requirements
  - Clarity on transitional measures
- Black triangle list – watch out!
- Off label use
- Solicited vs. spontaneous
- PSPs
What does it all mean for you?

• **Rationalisation**: how might life get easier? PSURs… DDPS… Modular structures

• **Challenges**: what obstacles lie ahead? PASS… Communications… Clarity…

• **Implementation**: what is your team’s/organisation’s plan?
  - Training
  - Communication (internal and external)
  - IT
  - Risk
Summary

• After a long time in the making the new system is alive
• Member States have had to engage as fully as industry
• Still a number of outstanding issues and transition
• Q&As are on MHRA and EMA websites to help you
• Are we there yet?
Plenty more to do…

I've finished all of my objectives for the rest of the year.

What happens now? Do you double my salary, or do I take the rest of the year off?

You were wrong, Wally: there is harm in asking.

Oops.
Any Questions?