PV EU Regulations

Module 9 Topic 8

EU Regulations

- New pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council in December 2010.
- Accompanied by the implementing regulation # 520/2012, a legally binding act, published by the European Commission in 19 June 2012 that provides details on the operational aspects for the new legislation:
- Things have been changed from passive to proactive

EU Regulations (contd)

- PV plan including risk management plan will now be a part of new drug applications
- A new set of guidelines (Good PV Practice) for the conduct of pharmacovigilance in the EU is under development.
- These guidelines are organised into 16 modules, the first seven GVP modules came into force on 2nd July 2012

(GVP Modules, a Summary. Clinical Research Advisor, Sept. 2012)

Aims of the new legislation

- To make roles and responsibilities clear;
- To minimise duplication of effort;
- To free up resources by rationalising and simplifying adverse drug reaction (ADR) reporting and periodic safety update report (PSUR) reporting;
- To establish a clear legal framework for post authorisation monitoring

EMA PV legislation 2010

Impact of the regulations

- Reporting directly into EUDRA Vigilance
- Post-authorisation safety and efficacy studies could be a condition for authorisation
- Authorisation could be withdrawn for non compliance
- Risk-management systems are required for all newly authorised medicines

Impact of the regulations

- PSURs will change to PBRERs. Will need a risk benefit analysis to be a part of the document
- Maintainance of PV Master File
- All pharmacovigilance referrals are discussed by the new Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP) or the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)

PSURs

- There will be a single assessment for the same active substance or a combination of active substances
- Routine PSUR reporting is no longer necessary for products with low risk or for old or established products unless concerns arise
- PSUR reporting is electronic following the establishment of an EU repository. PSURs are sent directly to the European Medicines Agency
- The construction is modular so that sections can be used as is for other regulatory submissions e.g. risk management plan

EMA PV legislation 2010

PSURs to PBRERs

- Periodic Benefit-Risk Evaluation Report(PBRER) E2C(R2)
- Retains most of the basic elements of the PSUR
- Compared to the PSUR, the PBRER has more information on:
  - Clinical trials and observational studies
  - Signals that are new, ongoing, or closed
  - Risk evaluation and effectiveness of risk minimization
  - Benefit evaluation
  - Benefit-risk analysis for approved indications

PSURs to PBRERs

- The PBRER is a more comprehensive document
- The construction is modular so that sections can be used as is for other regulatory submissions e.g. risk management plan
- More work to prepare and more work to review

ICH E2C R2

Need for Risk Benefit

- As **society has shifted to a view** that medications should have **virtually no risks**, the inevitable effect has been to **reduce the flow** of important new drugs
- But society must be careful to weigh the benefits of effective new drugs for diseases that until now have been poorly treated, versus the added risks of the new medications. **If we focus too much on the risks of drugs, and do not balance those risks against the benefits, fewer drugs will be approved** and reach patients in need. That is a risk in and of itself

Christoph Westphal, Boston Globe, June 28 2010,

Benefit Risk balance, CIOMS

- It is a frustrating aspect of benefit-risk evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data and that might permit straightforward quantitative comparisons of different treatment options, which in turn might aid in decision-making
- Rarely is it possible to express the relationship between benefits and risks quantitatively with simple units of measure (as a ratio or difference, for example), although attempts have been made

Benefit-Risk Balance for Marketed Drugs : Evaluating Safety Signals, Report of CIOMS Working Group IV 1998

Signal and Risk Evaluation

- Summary of safety concerns
- Signal evaluation
  - Evaluation of Risks and New Information
- Characterisation of Risks
- Effectiveness of risk minimisation

COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012 of 19 June 2012

Benefit Evaluation

- Important Baseline Efficacy and Effectiveness Information
  - Summarises information available at the beginning of the reporting period.
- Newly Identified information on Efficacy and Effectiveness In approved indications
- Characterisation of Benefits
  - Integration of baseline information with any new information.
  - If significant information or benefit profile is significantly decreased, a concise but critical evaluation needed.

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Integrated Benefit/Risk Analysis

- Benefit-risk Context –
  - Medical Need and Important Alternatives
- Benefit-risk Analysis Evaluation
  - For each indication and population
  - the key benefits and risks considered in the evaluation should be specified
  - Consider context of use
  - Explanation of the methodology and reasoning used to develop the benefit-risk evaluation
  - Take into account strengths, weaknesses and uncertainties in the evidence

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Actions and Conclusions

- Provide a conclusion on Benefit-risk
  - For each approved indication
  - By subgroups where relevant
- Assess need to change the CCDS/labelling and propose changes where appropriate.
- Include preliminary proposals to optimise or further evaluate Benefit-risk balance (e.g additional pharmacovigilance or risk minimization activities).
- Incorporate into the RMP

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ICSRs

- The basic element in PV
- Changes due to new regulations GVP module VI
- Adverse Reaction to include response to normal dose as well as misuse and abuse, medication error, overdose, occupational exposure
- Expectedness no longer relevant
- To be submitted electronically on Eudra Vigilance database
- Internationally Standardised reporting format across regulators. agreed terminologies,formats and standards

ICSRs some changes

- Validation checks incorporated in the database and erroneous reports will be rejected (e.g. age cannot be >120 yrs, weight not > 500 kgs)
- Identification of duplicates
- Data checked for quality
- Clean data can be accessed by regulatory authorities, HCP, patients, consumers, marketing authorisation holders at different levels
- EMA itself will scan literature, load identified ICSRs in the database and publish a list of the literature reviewed and the active substances covered.

Pharmacovigilance System Master File

- A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.
- To be maintained electronically.
- Not submitted along with mkting application
- Can be reviewed by authorities anytime

Pharmacovigilance System Master File (contd)

- Reduced documentation
- Will help do away with DDPS (Detailed Description Of Pharmacovigilance System) over time
- Tool for QPPV to
  - oversee and manage system
  - Ensure compliance with requirements
  - Identify risks and help mitigate them

Major elements of the PV master file:

- Lists products , route of authorisation of each product, presence on the market and indication of special monitoring measures
- Information about QPPV – job description, qualifications etc, contact details, backup arrangements and national contacts if present
- Organisational structure and sites of PV activities, including third parties

Major elements of the PV master file: (contd)

- Location, functionality and responsibility for computer systems
- Contracts and agreements for key activities
- Description of the key processes, data handling and records of the pharmacovigilance system
- Description of the quality system
- Description of record keeping and archiving.
- Change log, Notification of significant changes as reqd
  - http://www.ottosen.com/pharmacovigilancesystemsmasterfiles download dec12

In Summary

- Change from reactive to proactive
- The PBRER is a more comprehensive document than the PSUR – more work to prepare and more work to review
- Company will have to constantly review the change, if any, in the risk benefit situation of the product based on multiple inputs

In Summary (contd)

- Will have to inform authorities and implement the risk minimisation plan
- Onus is squarely on company for present and future
- Will need more manpower and high degree of support from expert personnel
- Possibility of outsourcing addressed in master file