Regulatory Aspects of Pharmacovigilance

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Training Course Uppsala 2013

the UPPSALA MONITORING CENTRE

Agenda

- **Risk based approach to spontaneous reporting (incl clinical trials)** -> Pia Caduff-Janosa
- **The new EU PV legislation** -> Deirdre McCarthy
- **ICH E2C R2: PBRERs** -> Deirdre Mc Carthy
- **Discussion** 30 min

Requirements by Drug Regulatory Authority (DRA): MAH

- Marketing Authorisation Holders (MAH) must submit:
  - AE from clinical trials
  - PV Master File, PV/Risk Management Plans
  - Spontaneously reported ADR
  - ADR reports from Post Authorisation Studies (PASS)
  - Periodic Evaluations (PSUR/PRBER)
  - Ad hoc reporting (emerging signals, quality defects, supply bottle necks etc

Requirements by DRA: Health Care Professionals (HCP)

- Spontaneous ADR reports
- Suspected quality defects

→Not a legal obligation in every country

Patient/Consumer reporting

- A right, not a legal obligation

Requirements by DRA

- Principles and content are harmonized (ICH Guidelines, reports by CIOMS Working Groups)
- Format and timelines can differ between geographical areas

→ consult the applicable legislation

Useful Links

- http://www.ich.org/
  - http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
- http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad
- http://www.fda.gov/
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm

Individual Case Safety Reports (ICSR)

- Same risk based approached for pre- and postauthorisation reporting:

  → serious reactions first and documented as completely as possible

Seriousness (ICH E2A)

ADR

- Results in death
- Is life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability
- Is a congenital anomaly/birth defect

Medically Important

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as **important medical events** that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or **may require intervention to prevent one of the other outcomes listed in the definition above**. *These should also usually be considered serious.*

Severe ≠ Serious

- *Severe* is a clinical term that describes the intensity of a clinical event

- *Serious* is a regulatory term that defines reorting obligations and is related to the outcome

Examples

- Hexadactyly is serious (congenital anomaly) but not severe (cosmetic problem)

- Fever 40°C self resolving is severe but not serious

Clinical trials

- Interventional clinical trials must be authorized by ethical committee and DRA

→ changes to protocol etc must be submitted to DRA for approval

- Ethical committee and all investigators must be informed on findings that may adversely affect study participants

Reporting from Clinical Studies

- ICSRs: SUSAR (**s**erious, **u**nexpected, **s**uspected **a**dverse **r**eactions) only

- Development Safety Update Report DSUR: comprehensive safety evaluation of the clinical studies (all study centres!) as well as report on progression of studies

Spontaneous Reporting

Minimal reporting criteria:

- Identifiable reporter
- Identifiable patient
- Adverse reaction
- Suspected drug

- No hearsays

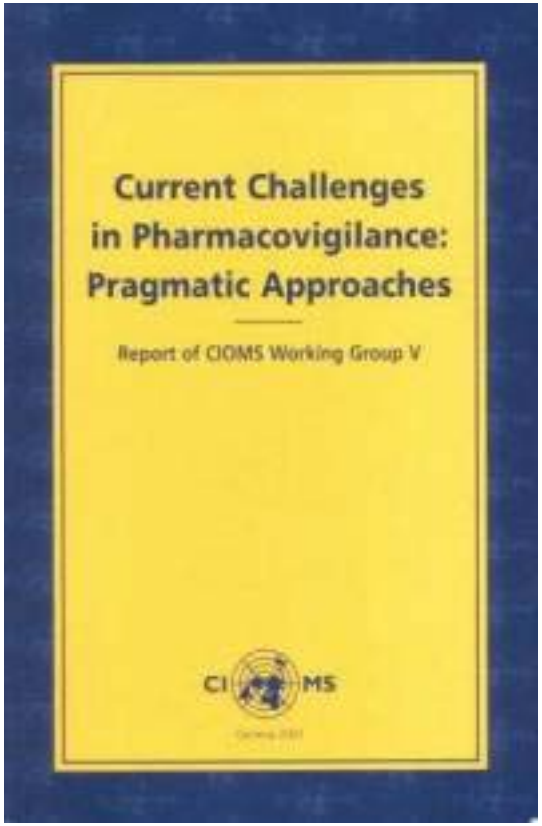
Good PV Practice

- Complete narrative
  - Chronology
  - Medical history
  - Investigations performed
  - Differential diagnosis
  - Action taken with drugs (dechallenge/rechallenge)
  - Outcome

Good PV Practice

- Suspected drugs
  - Substance and trade name
  - Formulation
  - Dosage
  - Route of application
- Concomitant drugs

Recommended Reading



Risk Management Plans @ DRA

- Integral part of marketing authorization submission

→ in most countries reviewed at authorisation

→ increasingly made public

→ replacing PSURs?

Changes to the EU PV legislation

Why change the pharmaceutical legislation?

- >10 year since last (major) change
- EU-enlargement
- Appraisal of the existing pharmacovigilance system
  - Fraunhofer-Report
- Industry's interests
- Broad consensus: the existing system and rules are complex and difficult
  - 'Simplification!'

Context

- Critical assessment of „scandals“ (?)
- New active substances
  - monoclonal antibodies, gene therapeutics etc.
- Huge data bases
  - ADRs, epidemiological databases etc.
- Increased interest of the public
- Globalisation of drug markets

Assessment of the Community System of PV

- Frauenhofer Institute for Systems and Innovation Research; 2006

- **General aim:**
- To analyse how the European central and EU Member States' medicines agencies collaborate with each other, the Marketing Authorisation Holders and other stakeholders, in monitoring the adverse effects of pharmaceuticals and to put forward recommendations
- Main components of PV systems:
  - Data collection
  - Data management
  - Signal Detection
  - Safety issue assessment
  - Decision making
  - Communication and action

Why the need for change?

- **European Commission Assessment Report estimated that:**

- *5% of all hospital admissions are due to adverse drug reactions*

- *5% of all hospital patients experience an adverse drug reaction*

- *Adverse drug reactions are the 5th most common cause of hospital death*

- *The legislation will save 5910 lives per year across the EU*

EU legislation

- New PV legislation was adopted by the European Parliament on 22 September 2010 and will come into force in July 2012.

- The legislation takes the form of a new Directive –amending the requirements of 2001/83/EC – and a Regulation that amends Regulation (EC) No.726/2004.

- Together these will bring about a number of changes to strengthen the way in which the safety of medicines for human use is monitored in the EU.

- **Three main areas of change:**
  - enhanced monitoring of the benefits and risks of medicines post-authorisation
  - replacement of the Pharmacovigilance Working Party with a Committee
  - an increased level of transparency of safety information.

New EU PV Legislation

Regulation	(EC) No 726/2004: for CAPs	**Chapter. 3**	**(EU) No 1235/2010 entered into force 2 July 2012**
Directive	2001/83/EC: for NAPs incl. MRP/DCP	**Title IX**	**2010/84/EU: entered into force 21 July 2012**
Guideline	Volume 9A of the Rules Governing Medicinal Products in the EU		**Good Pharmacovigilance Practices***

Acronym Key:
PV – Pharmacovigilance
CAP- Central Authorisation Procedure
NAP - National Authorisation Procedure
MRP - Mutual Recognition Procedure
DCP - Decentralised Procedure

**Volume 9A remains reference as applicable until transition period ends or until that specific GVP module published*

Good Pharmacovigilance Practices

Module XIII now to be incl in Module XII

Module XII, XVI Due Q1 2013. Module XI, XIV. Due Q2 2013

Final Modules I, II, III, IV, V, VI, VII, VIII IX, XV

Module	Module Title
I	**Pharmacovigilance systems and their quality systems**
II	**Pharmacovigilance system master file**
III	**Pharmacovigilance inspections**
IV	**Pharmacovigilance system audits**
V	**Risk management systems**
VI	**Management and reporting of adverse reactions to medicinal products**
VII	**Periodic safety update report**
VIII	**Post-authorisation safety studies**
IX	**Signal management**
X	Additional monitoring
XI	Public participation in pharmacovigilance
XII	Continuous PV, ongoing benefit-risk evaluation, regulatory action & planning of public communication
XIII	*Incident management no longer under development. All topics originally intended in this module now to be included in module XII.*
XIV	International cooperation
XV	**Safety communication**
XVI	Risk-minimisation measures: selection of tools and effectiveness indicators

Key differences in regulations

Key differences – post-marketing

	US	EU
Single case reports		
Classification	Report serious unexpected (all countries)	Report all serious (spontaneous and solicited)
Source	HCP and consumer	HCP and consumer
Causality	Report irrespective of causality	Only report at least possibly related cases
Aggregate Reports	**'PADERs'**	**'PSUR's /'PBRER's**
Timelines	Quarterly for 3 years	Six-monthly for 2 years
	Annually thereafter	Annually for 2 years, 3 yearly thereafter

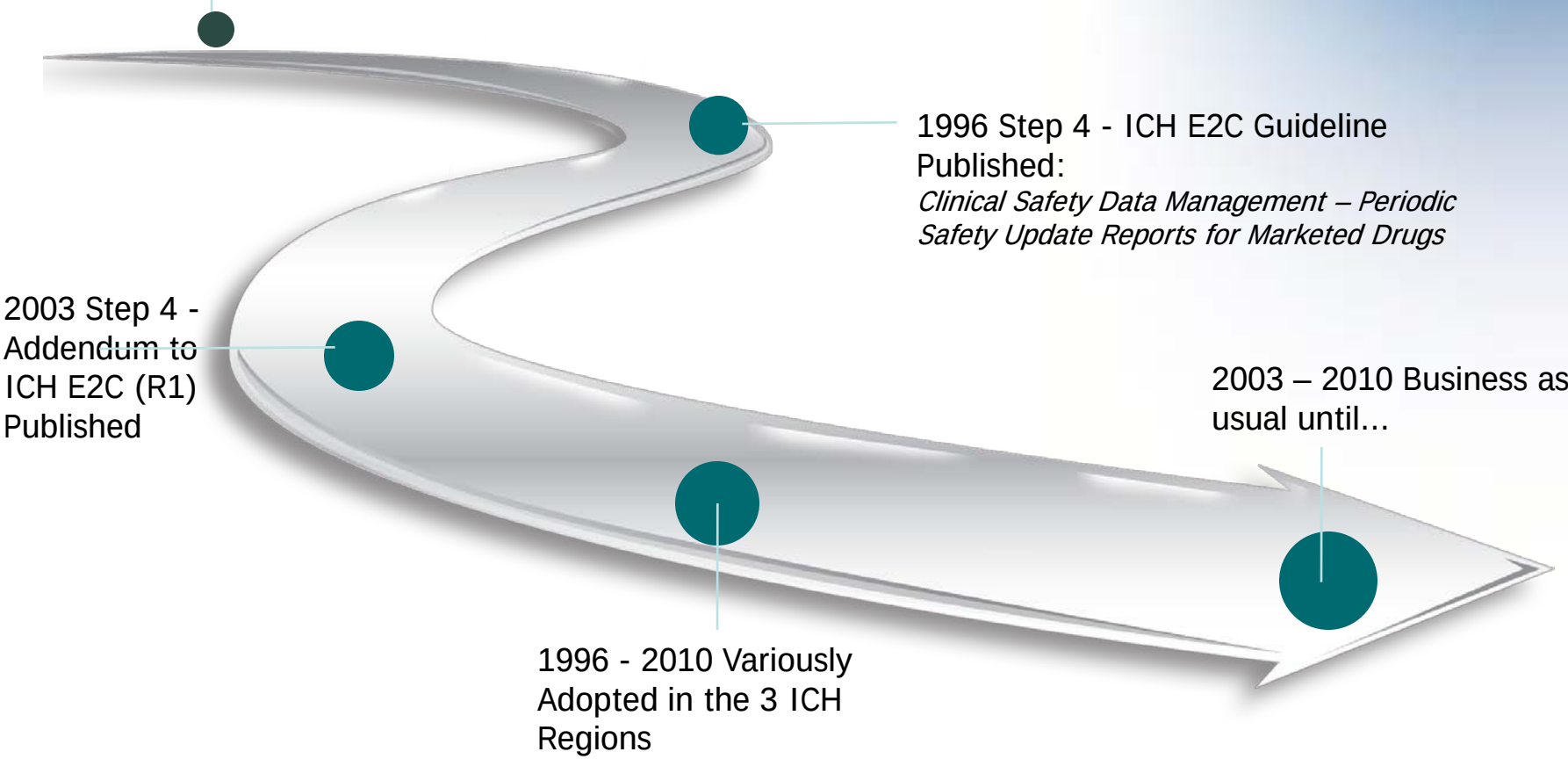
Key differences continued

	US	EU
Literature searching		
Frequency	Monthly	Weekly
Search for	Case reports only	Case reports and other safety data
Report forms	MedWatch (3500)	E2B Files or CIOMS I
	VAERs	
Risk Management Programs	REMS (RiskMAPs)	EU-RMPs
QPPV	No	Yes
PV System Master File	No	Yes

ICH E2C (R2)

Periodic Benefit Risk Evaluation Report (PBRER)

History



Acronym Key:
PSUR – Periodic Safety Update Reports

Why change PSURs?

- Previously, risk management guidance was based solely on managing risks.
- However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit.
- In assessing the risk-benefit balance at the time of authorisation, the assumption is made that these benefits and risks apply to the whole target population.
- However, there may be subsets of patients for whom the risk is greater than that for the target population as a whole or in whom the benefit may not be as great.

Why change PSURs?

- In addition, **efficacy** in the clinical trial setting may not reflect the true **efficacy** of the medicinal product in everyday medical practice and so the risk-benefit balance of a medicinal product as assessed at the time of authorisation will inevitably change post-authorisation.

Rationale & Vision

Rationale

- ICH E2C originally created in 1990s
  - Guideline has not kept apace with regulatory/technology advances
- Overlap of content of ICH Guidelines E2C(R1), E2E and E2F
- Lack of modular approach
- Resources diverted away to duplicative document production, rather than focusing on risk management activities that could promote public health

Vision

- New ICH guideline will ensure that the reports have the role of being periodic benefit-risk evaluation reports.
  - Safety evaluation
  - Evaluation of all relevant available information (all use)
  - Benefit-risk evaluation

Objective of the new PBRER

- To present a comprehensive and critical analysis of new or emerging information on the risks and, where pertinent, new evidence of benefit to enable an appraisal of overall benefit risk.

- To contain an evaluation of new relevant information that became available to the MAH during the reporting interval, in the context of cumulative information:
  - Examine whether new information is in accord with previous knowledge of the benefit risk profile
  - Summarises relevant new safety information that may impact the benefit risk profile
  - Summarises any important new efficacy and effectiveness information
  - Conduct an integrated B/R evaluation (where new important safety information has emerged)

Acronym Key:
PBRER - Periodic Benefit Risk Evaluation Report
MAH - Market Authorisation Holder
B/R – Benefit Risk

'All drugs are dangerous,

Some may also be useful'

N. Moore, BMJ, 2005, 330;539-40

A lot to consider!

PSUR, DSUR and RMP

Common Ground-sections of documents that can be shared

PSUR section	Share with RMP	Share with DSUR
Worldwide MA Status		Yes
Action taken for safety reasons	Yes	Yes
Cumulative exposure in clinical trials/postmarketing	Yes	Yes
Cumulative tabulations of SAEs from Clinical Trials		Yes
Completed/ongoing clinical trials, LTFU, Other therapeutic use, new data related to combo therapies		Yes
Finding from non-interventional studies		Yes
Information from other sources		Yes
Non clinical data		Yes
Literature		Yes
Lack of efficacy in clinical trials		Yes
Late breaking information		Yes
Conclusions & actions		Yes

Questions?

Thank you

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