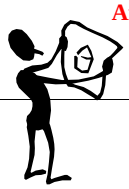
CIOMS IX and ICH E2C (R2)

An Update from the Horse`s Mouth

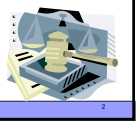


Val Simmons, MB BS FFPM
EU QPPV , Global Patient Safety

Lilly
Answers That Matter.

CIOMS and International Regulation

CIOMS I (1990)	Basis for ICH E2A and international regulatory standards and definitions, including CIOMS I form
CIOMS IA (1992)	Basis for ICH E2B
CIOMS II (1992)	Basis for ICH E2C (Periodic Safety Update Reports)
CIOMS III (1995)	Concept of CDS / CSI included in ICH E2C
CIOMS IV (1998)	Not formally incorporated into regulation but standard requested by EU authorities
CIOMS V (2001)	Basis for ICH E2D; included in Volume 9A
CIOMS VI (2005)	Concept of DSUR introduced
CIOMS VII (2007)	Basis for ICH E2F
CIOMS VIII (2010)	.....



NEW PUBLICATION

CIOMS

Council for International Organizations of Medical Sciences (CIOMS)

Practical Aspects of Signal Detection in Pharmacovigilance:

Report of CIOMS Working Group VIII

information technologists and statistical experts, working together, to deliver novel approaches to detect signals from these extensive and quickly growing datasets, and to manage them appropriately. In following this exciting story, this report looks at the practical consequences of these developments for pharmacovigilance practitioners.

The report aims primarily to provide a comprehensive resource for those considering how to strengthen their pharmacovigilance systems and practices, and to give practical advice. But the report does not specify instant solutions. These will inevitably be situation specific and require careful consideration taking into account local needs. However, the CIOMS Working Group VIII is convinced that the combination of methods and a clear policy on the management of signals will strengthen current systems.

Finally, in looking ahead, the report anticipates a number of ongoing developments, including

.....and now.....CIOMS IX

Practical Considerations for Development and Application of a Toolkit for Medicinal Product Risk Management

CIOMS IX
Introduction

- Regional requirements and divergences
  - implementation of ICH E2E
- Challenge of risk minimisation
  - burden on healthcare system
  - resources & cost effectiveness
  - effectiveness of tools?
- Need to develop
  - common principles
  - common objectives
  - proactive approaches and planning

CIOMS IX Membership

- Regulatory Authorities:

  EMA, France, Germany, Sweden, UK, US FDA, Japan (PMDA), Health Canada, TGA Australia,

- Biopharmaceutical industry and other stakeholders:

  Abbott, Amgen, AstraZeneca, Bayer Schering, Boehringer - Ingelheim, Eisai, GSK, Johnson & Johnson (Janssen), Eli Lilly, Novartis, Pfizer, Roche, Sanofi - Aventis, Japanese Pharmaceutical Manufacturers Association (JPMA), NDA Group

- CIOMS & WHO (Geneva)

CIOMS IX Outline

Chapter 1. Introduction, scope and background

Chapter 2. Current Landscape

Chapter 3. Identified Tools

Chapter 4. Tool Application

Chapter 5. Future Directions

Chapter 6. Recommendations

Other Chapters

Chapter 7. Glossary

Chapter 8. Appendices:

- 8.1.1 Membership
- 8.1.2. Regional Survey
- 8.1.3. Real life examples
- 8.1.4. Broader stakeholder input

Chapter 2. Current Landscape

- Current regulations and expectations
- Risk minimisation versus risk management
- Place of ICH E2E and its regional implementation
- Risk minimisation:
  - Need for harmonised principles
- 'Points to consider' approach
- Core principles
  - Including delivery

Chapter 3. Identified Tools

- Identify known risk minimisation tools
- Current Utilisation: Survey
- Tool Effectiveness – "Best Practices"
  - evidence-based
  - strengths and weaknesses
- Information, education, controlled distribution
- Controversial points:
  - safety studies,
  - observational registries
  - tool effectiveness

Chapter 4. Tool Application

- Safety Issue selection
  - **Levels of risk**
  - **Determinants of risk**
- Risk minimisation targets and objectives
- Considerations for tool selection
  - **Including burden on healthcare system**
- Outcome measures
  - **direct, surrogate**
- Process measures
- Application
  - **Global, regional, national**

Chapter 5. Future Directions

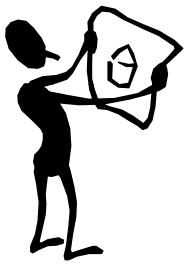
- Professional training:
  - **RM Specialist**
- New communication platforms
  - **web- based;**
  - **E- detailing; expert systems**
- New models
  - **visual presentation, simulation**
  - **patient orientated**
- Biomarkers
- Pharmacogenetics
- eHR
- External Collaborations

New Chapters

- Risk Management Governance
  - **Process Overview**
  - **Roles and Responsibilities**
  - **Management Controls and Governance**
  - **Design**
  - **Execution**
  - **Assessment**
- Failure Modes and Effects Analysis (FMEA)

Real Life Examples

- Clozapine and agranulocytosis
- Isotretinoin teratogenicity
- Oxycontin and abuse potential
- Other examples discussed



General Discussion Points

- Non-ICH countries
- Benefit/risk planning
- Risk characterisation & quantification
- Minimisation versus mitigation
- Stakeholder input
- Scope (chemical entities, vaccines, OTCs, devices)
- Measuring RM effectiveness
- Chapter overlap
- Role of the patient

.....anticipated delivery??

Q4 2012

ICH E2C (R2)

A Pressing Need for Harmonisation

Future European Pharmacovigilance Legislation

REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 15 December 2010
amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 15 December 2010
amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

Future PSURS in Europe

- PSURs should provide greater emphasis on analysis of benefit-risk profile, rather than detailed presentation of individual case reports; to include
  - **scientific evaluation of the benefit-risk profile,**
  - **summaries of relevant scientific/clinical data**
  - **available sales/prescription data**
- Frequency of submission shall be specified in the MA
- Routine PSURs will not be required for products of 'low risk' or where reporting would be duplicative
  - **e.g. generic products**
- Submitted electronically

Future PSURS in Europe

….but whatever happened to international harmonisation????

….but then the EMA produced a Concept Paper

Draft ICH Concept Paper for the Review of ICH E2C

March 2010

Industry Position

- (B)RMP considered to be the pivotal safety document from industry to regulators
- EFPIA supportive of re-opening ICH E2C in principle
- Caveats :
  - **Rationalisation with E2E and avoiding overlap with information contained in the Safety Specification; removal of redundant information**
  - **Consider in the light of modern PV standards including electronic submission of ICSRs**
  - **Focus on aggregate data and NOT individual case reports & line listings**
  - **Focus on simplification and streamlining**
- Consider a modular approach

……which is why we ultimately ended up in Japan....

ICH Brainstorming Session
Fukuoka

November 2010

…… the outcome of which was a Final Concept Paper

Periodic Safety Update Reports for Marketed Drugs E2C(R2) and gap and potential improvement analysis of ICH E2C, E2E and E2F

8 December 2010

Endorsed by the ICH SC on 10 December 2010
EFPIA as Rapporteur

ICH E2C (R2) Concept Paper Proposals

- Draft a new ICH guideline E2C(R2) covering periodic benefit risk evaluation reporting
- Deliver a plan to the ICH Steering Committee for review of other ICH guidelines based on :
  - an evaluation of the ICH pharmacovigilance documentation
  - a gap and potential improvement analysis of ICH E2C, E2E* and E2F

*** Safety Specification**

ICH E2C Concept Paper Proposals

Issues to be Resolved

- The new ICH guideline will ensure that reports have the role of being **periodic benefit risk evaluation reports**.
  - **safety evaluation**
  - **evaluation of all relevant available information (all use)**
  - **benefit risk evaluation**
    - **benefit risk will be within the approved indication(s)**
    - **not a formal or quantitative analysis**
- A key question:
  - **level of information**
    - **benefit and benefit risk**
  - **how the B/R evaluation is structured**

ICH E2C Concept Paper Proposals

Issues to be Resolved

- The guideline should have a modular approach :
  - **sections that can be separated & submitted independently or combined with other documents**
  - **maximises the utility of the content and minimise duplication**
  - **support use of different modules for different regions and potentially across different documents**
  - **flexibility at different times in the lifecycle of a product.**
- Expert Working Group to consider if B/R evaluation should be a separate module
  - **use module in other documents?**

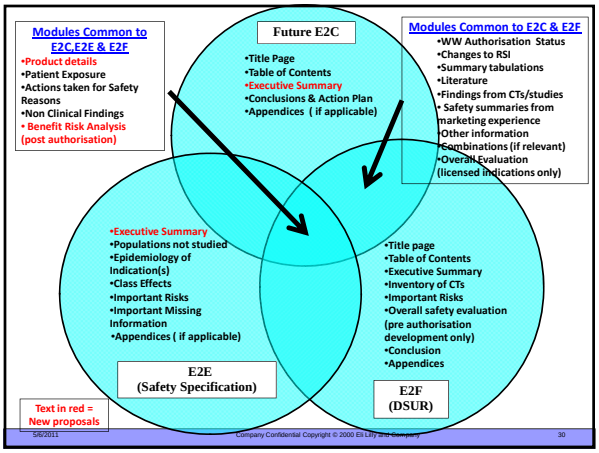
ICH E2C Concept Paper
Regulatory Constraints

- **Europe** : consistency with the content & implementation timing of the new PV legislation
- **FDA** : consistency with the current legislation & regulation; guidance can be amended
- **MHLW** : consistency with current legislation

Comparison of ICH E2C, E2E* and E2F

Section	E2C	E2E	E2F	Comment
Title page	Y	N	Y	Document specific
Table of Contents	Y	N	Y	Document specific
Executive Summary	N	N	Y	Document specific; consider for all documents
Introduction	Y	N	Y	**Replace with Product Details module (consider tabular format)**
WW Authorisation Status	Y (table)	N	Y (summary)	Is this really needed??? If so, use E2F (summary) format.
Changes to Reference Safety Information (RSI)	Y (CCDS)	N	Y (IB or local label)	**Changes to RSI Module (split by DCSI/CCDS; IB & CCDS as appendices)**
Patient Exposure (CT & PM)	Y (interval)	Y	Y (cumulative)	**Patient Exposure Module (split by CT & PM: cumulative and interval (PM)data)**

*Safety Specification only



ICH E2C (R2)
Draft Guideline Structure

Title Page

Executive Summary

1. Introduction
2. Worldwide Marketing Authorisation
3. Actions taken in the Reporting Period for Safety reasons
4. Changes to Reference Safety Information
5. Estimated Exposure
   - **5.1 Cumulative Subject Exposure in the Development Programme**
   - **5.2 Cumulative and Interval Patient Exposure from Marketing Experience**

ICH E2C (R2)
Draft Guideline Structure

6. Summary of Data from Studies
   - 6.1 Interventional Clinical Trials
   - 6.2 Non-interventional Studies
   - 6.3 Non-clinical Data
   - 6.4 Literature
7. Summary of Data from Marketing Experience
   - 7.1 Data from Spontaneous Reporting
   - 7.2 Literature
8. Summary of Data from other Sources

ICH E2C (R2)
Draft Guideline Structure

9. Risk Evaluation
   - 9.1 Link to Safety Specification
   - 9.2 Signals newly identified, ongoing or closed in the reporting period
   - 9.3 Newly identified important risks
   - 9.4 Effectiveness of Risk Minimisation (if applicable)
10. Benefit Evaluation
    - 10.1 Important Efficacy Information
      - **10.1.1. Strength of the evidence and limitation of the data**
    - 10.2 Newly identified Efficacy information

ICH E2C (R2)
Draft Guideline Structure

11. Integrated Benefit/Risk Analysis for approved indications
    - 11.1 Introduction
    - 11.2 Importance of benefits and risks
    - 11.3 Discussion on the benefit-risk balance
12. Conclusions and potential actions
13. Appendices to the PSUR

ICH E2C (R2) - Timelines

Completion Date	Deliverable
April 2011	• Draft Guideline sections
April 2011 – June 2011	• Discussion of open topics • Review of draft texts
ICH Meeting, June 2011	• Finalisation of ICH E2C(R2) guideline structure • Continued review of draft text • Draft gap analysis and plan for revision of ICH E2E and E2F
Proposed 2nd Interim face to face meeting	• Agreement on a final draft of ICH E2C (R2) to allow achievement of step 2 in Q4 2011
ICH Meeting Q4, 2011	• **Step 2 Guideline** • Final draft gap analysis of ICH E2E and E2F and final draft proposals for revision
November 2012	• **Step 4 Guideline**

New CIOMS & ICH initiatives

- CIOMS X
  - **Considerations for applying good meta-analysis practices to clinical data within the biopharmaceutical regulatory process**
- ICH E2A (R1)
  - **Clinical Safety Data Management: Definitions and Standards for Expedited Reporting**
  - **Draft concept paper**
  - **To be presented to ICH Steering Committee (June 2011)**
  - **Step 4 proposed Q4 2012**