ICH E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

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Disclaimer

No conflicts of interest to disclose

Background on ICH

- A global harmonization effort
- Regulators and research-based industries across the globe
- Started in 1990
- Objectives:
  - To improve efficiency of new drug development and registration process
  - To promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness
- Accomplished through the development and implementation of harmonised Guidelines and standards

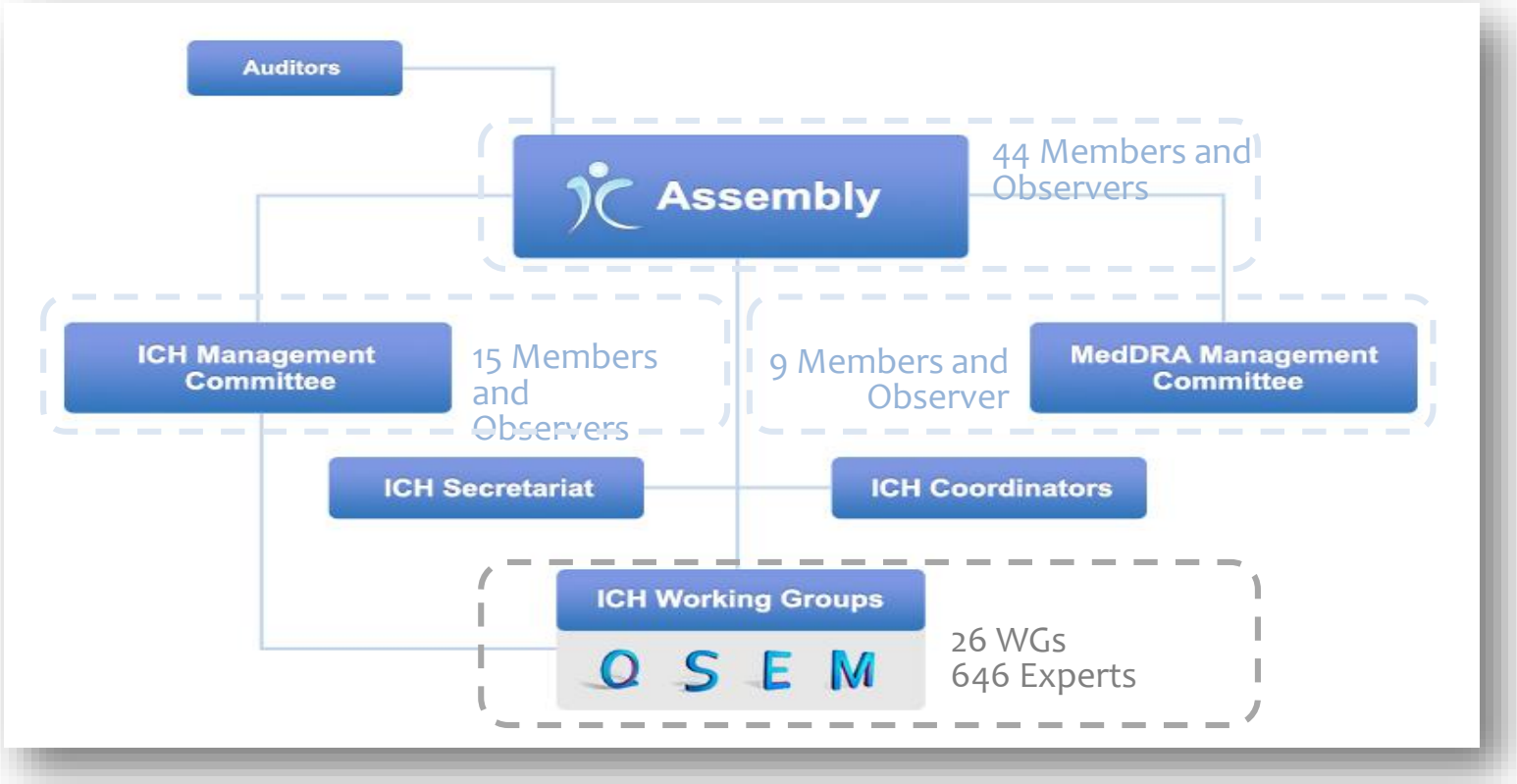
ICH Association

- The new ICH Association was officially established on 23 October 2015.

  http://www.ich.org/ichnews/press-releases/view/article/ich-announces-organisational-changes.html
- The Articles of Association are published on the ICH website.

  http://www.ich.org/about/articles-procedures.html
- The ICH Association is a non-profit legal entity under Swiss law with the aim to focus global pharmaceutical regulatory harmonisation work in one venue.

ICH Governance



Source: www.ich.org

The ICH Process

Source: www.ich.org

Overview of ICH Guidelines

- Over 60 Guidelines on technical requirements on:
- Safety – 14 Guidelines
- Quality - 23 Guidelines
- Efficacy – 21 Guidelines
- Multidisciplinary - 6 Guidelines

- Electronic Standards for the Transfer of Regulatory Information (ESTRI)
- CTD/eCTD
- MedDRA (standardised medical terminology)

Source: http://www.ich.org/products/guidelines.html

ICH - Finalized Guidelines

Safety, Total = 14

- S1A – S1C: Carcinogenicity studies (3)
- S2: Genotoxicity studies (1)
- S3A – S3B: Toxicokinetics and Pharmacokinetics (2)
- S4: Toxicity Testing (1)
- S5: Reproductive toxicology (1)
- S6: Biotechnology products (1)
- S7A – S7B: Pharmacology studies (2)
- S8: Immunotoxicology studies (1)
- S9: Nonclinical evaluation for anticancer pharmaceuticals (1)
- S10: Photosafety evaluation (1)

Quality, Total = 23

- Q1A – Q1E: Stability (5)
- Q2: Analytical validation (1)
- Q3A – Q3D: Impurities (4)
- Q4 – Q4B: Pharmacopoeias (1)
- Q5A – Q5E: Quality of biotechnology products (5)
- Q6A – Q6B: Specifications (2)
- Q7: Good Manufacturing Practice (1)
- Q8: Pharmaceutical development (1)
- Q9: Quality risk management (1)
- Q10: Pharmaceutical quality system (1)
- Q11: Development and manufacture of drug substances (1)

Efficacy, Total = 21

- E1: Clinical safety (1)
- E2A – E2F: Pharmacovigilance (5)
- E3: Clinical study reports (1)
- E4: Dose-response studies (1)
- E5: Ethnic factors (1)
- E6: Good Clinical Practice (1)
- E7, E8, E9, E10, E11-E11A: Clinical Trials (5)
- E12: Clinical evaluation by therapeutic category (1)
- E14: Clinical evaluation (1)
- E15: Definitions in Pharmacogenomics (1)
- E16: Qualification of Genomic Biomarkers (1)
- E17: Multi-Regional Clinical Trials (1)
- E18: Genomic Sampling (1)

Multidisciplinary, Total = 6

- M3: Nonclinical safety studies (1)
- M4, M4Q, M4S, M4E: CTD (4)
- M7: Genotoxic impurities (1)

Other ICH Products

Safety	
▪ S3A : Toxicokinetics and Pharmacokinetics (Q&As)	▪ S9: Nonclinical evaluation for anticancer pharmaceuticals (Q&As)
Quality	
▪ Q3D: Impurities (Training) ▪ Q6A : Specifications (Decision Trees)	▪ Q7: Good Manufacturing Practice (Q&As) ▪ Q8, Q9, Q10 - Q&As ▪ Q11: Development and manufacture of drug substances (Q&As)
Efficacy	
▪ E2B, E2C : Pharmacovigilance (Q&As, Specifications and related files, ESTRI) ▪ E3: Clinical study reports (Q&As) ▪ E5: Ethnic factors (Q&As)	▪ E7: CT in Geriatric Population (Q&As) ▪ E14: Clinical evaluation (Q&As)
Multidisciplinary	
▪ M1: MedDRA terminology & PtC ▪ M2: Electronic standards (Recommendations - ESTRI) ▪ M3: Nonclinical safety studies (Q&As)	▪ M6: Gene Therapy (Considerations) ▪ M8: eCTD

ICH E2A

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS FOR
EXPEDITED REPORTING
E2A

Current *Step 4* version

dated 27 October 1994

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

ICH E2A – Expedited Reporting Safety

- Defines “adverse event” (or “adverse experience”)
- Defines “adverse drug reaction”
- Defines “unexpected adverse drug reaction”
- Defines “serious adverse event or adverse drug reaction”
- Defines “expectedness” of an adverse drug reaction
- Discusses “causality” assessment in case reports

FDA's Revised Premarket Safety Reporting Rule

- FDA published amended safety reporting regulations for investigational new drugs (INDs) on 29 September 2010
- Reason for amended regulation: misapplication of the "reasonable possibility" standard
  - FDA was receiving adverse event reports from clinical trials for which there was little reason to believe that the drug cause the event

FDA's Revised Definition of Suspected Adverse Reaction

- "Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."
- Consistent with ICH E2A
- The sponsor needs to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.
- For some events, a single case may be sufficient to meet the definition of "suspected adverse reaction." In other cases, one or more occurrences may be necessary to establish a reasonably possibility. Finally, in some cases, aggregate analysis is needed.

Definitions – Adverse Event

- Adverse Event (or Adverse Experience)
  - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

  An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition – Adverse Drug Reaction

- Adverse Drug Reaction (ADR)
  - In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

  The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Definition – Unexpected Adverse Drug Reaction

- Unexpected Adverse Drug Reaction
  - An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

Definition of Serious Adverse Event or Serious Adverse Drug Reaction

- A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:
  - results in death,
  - is life-threatening,

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

  - requires inpatient hospitalisation or prolongation of existing hospitalisation,
  - results in persistent or significant disability/incapacity, or
  - is a congenital anomaly/birth defect.

Definition of Serious – Other Considerations

- "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.*
- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse."

Definition of Expectedness of an Adverse Drug Reaction

- The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:
  - 1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. (See section III.F. and ICH Guideline for the Investigator's Brochure.)
  - 2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Expedited Reporting – Single Cases

- Serious + Unexpected ADRs = expedited reporting
- “All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) should always be specified.”

ICH E2A – Causality Assessment

- Required for case reports from clinical investigations
- “Reasonable suspected causal relationship”
- Notes that there is no standard international nomenclature
- “The expression ‘reasonable causal relationship’ is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship”.
- For marketed products (spontaneous reports), there is usually implied causality

Other Observations

- For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
- A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).

Reporting Time Frames

- Fatal or Life-Threatening Unexpected ADRs
  - 7 calendar days after sponsor's first knowledge that a case qualifies for initial notification
  - Complete report an additional 8 calendar days later
- All Other Serious, Unexpected ADRs
  - 15 calendar days after sponsor's first knowledge that a case qualifies

Minimum Criteria for Reporting

- Identifiable patient
- Suspect medicinal product
- Identifiable reporting source
- Event or outcome that can be identified as serious and unexpected
- For clinical investigation cases, a reasonable suspected causal relationship

Managing Blinded Cases

- For serious adverse reactions judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind.
- Recommend maintaining the blind for study personnel responsible for analysis and interpretation at the study's conclusion
- If mortality or other serious outcome is the primary efficacy endpoint, recommend reaching agreement with regulators in advance concerning serious adverse events that would be treated as disease-related and not subject to routine expedited reporting.

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Questions


FDA
U.S. FOOD & DRUG
ADMINISTRATION