Update on E2D(R1)

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Overview

- Background on E2D
- New definitions and terminology
- Types of Individual Case Safety Reports (ICSRs): Spontaneous and Solicited
- Updated guidance by source of safety information (e.g., digital platforms, patient support programs)
- Expanded section on other types of post-market observations

E2D (R1): Post-Approval Safety Data: Definitions and Standards for Management and Reporting of Individual Case Safety Reports (ICSRs)

Background

- Original ICH E2D guideline adopted in 2003
- New post-market safety information sources have emerged (or are used more often) which vary in characteristics and contribution to post-market safety surveillance (e.g., patient support programs (PSPs) and social media)

Background

- The definitions and regulatory guidance in the original ICH E2D Guideline are no longer sufficient to provide guidance on current pharmacovigilance practices and needs
- ICH E2D(R1) EWG (Expert Working Group) was established in 2019 to revise E2D to support appropriate post-market safety surveillance

ICH E2D (R1)

- Recommendations are harmonized to the extent possible given differences in post-market safety reporting requirements among ICH regions
- Where applicable, this guideline notes where local and regional requirements may vary and, as such, marketing authorization holders (MAHs) should refer to relevant local or regional requirements
- E2D(R1) establishes a framework for current best practices of post-approval safety data management in a dynamic environment

ICH E2D (R1)

- These slides highlight only the significant updates and changes.
- Refer to the complete document for all other editorial changes and updates

The E2D(R1) Expert Working Group

- **Regulatory Authorities**
  - ANVISA, Brazil
  - EC, Europe
  - FDA, United States
  - MHLW/PMDA, Japan
  - NMPA, China
  - Roszdravnadzor, Russia
  - Swissmedic, Switzerland
  - TFDA, Chinese Taipei
  - TGA, Australia

- **Industry bodies**
  - EFPIA
  - IFPMA
  - IGBA
  - JPMA
  - PhRMA

Plenary Working Party (PWP)

MHRA, United Kingdom
Health Canada, Canada

Chapter 2: Definitions and Terminology

New Definitions:

- Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting (2.2)
- Expedited Report (2.3)
- Primary Source (2.4)

Chapter 2: Definitions & Terminology, Cont.

New Definitions:

- Digital Platform (2.7)
- Organised Data Collection System (ODCS) (2.8)
- Patient Support Program (PSP) (2.9)
- Market Research Program (MRP) (2.9)

All of these were areas of specific focus for the revisions in E2D(R1)

Chapter 3: Types of ICSRs

The concepts of Spontaneous Reports and Solicited Reports were moved from section ‘Sources of ICSRs’ to new section ‘Types of ICSRs’

- **Spontaneous Reports** A spontaneous report is a direct communication by an health care provider or consumer to an MAH, regulatory authority or other organization that describes one or more adverse events/adverse drug reactions in a patient who was exposed to one or more medicinal products and that was not gathered as part of an ODCS
- **Solicited Reports** are those derived from ODCS. For the purposes of reporting, solicited ICSRs are classified as ‘reports from study’ in E2B format and should have a causality assessment

Chapter 4 - Sources Of ICSRs

- Includes guidance on the management of safety communications by source

- Extensive updates to the literature section, in order to clarify important topics, including screening of medical and scientific journals by MAHs and vendors and clock start date (day zero)

Chapter 4.3: Digital Platforms

- Replaces original E2D Section “Internet”
- Defines what is meant by digital platforms as a data source
- Provides description of MAH responsibilities depending on digital platform ownership
- No obligation for MAHs to screen external digital platforms

Chapter 4.3: Digital Platforms

- **4.3.1 Digital Platforms under the MAH's responsibility**
  - MAHs should regularly screen digital platforms under their responsibility
  - Provides guidance on process for post-approval safety data management depending on nature of activity (i.e., spontaneous or solicited)

Chapter 4.3: Digital Platforms

- **4.3.2 Digital platforms not under MAH's responsibility**
  - Screen data using ODCS
  - Supports limiting the scope of screening for AEs
  - Clarifies the start of the time clock for reporting
  - Proposal to add a new value in E2B (ICSR reporting format) to identify cases from ODCS on Digital Platforms

Chapter 4.4: Patient Support Programs (PSPs)

- Provides definition
  - PSPs are considered ODCSs
  - Must include collection of medical information or program design is such that the program will likely receive medical information
  - Excludes delivery service; coupon card discounts
- Manage AEs/ADRs as solicited (i.e., study) reports
- Proposal to add new value in E2B to identify cases from PSPs

Chapter 4.5: Market Research Programs (MRPs)

- Provides definition
  - “MRPs are ODCSs which are used for planned collections of healthcare professional and/or consumer insights by an MAH, on medicinal products and/or a disease area, for the purpose of marketing and business development.”
- Manage AEs/ADRs as solicited reports
- Proposal to add new value in E2B to identify cases from MRPs

Chapter 5.1: What Should be Reported?

- Updates reporting guidance to allow harmonization with current local requirements with respect to seriousness, expectedness
- Other Observations (5.1.3): Expanded to include several scenarios and clarify reporting obligations
  - Lack of Efficacy
  - Overdose, abuse, misuse, medication error, occupational exposure
  - Use of medicinal products in pregnancy/lactation
  - Off-label use

ICH E2D(R1) Major Milestones

Expected completion date	Milestone
Feb 2024	***Release for public consultation*** ***ICH Efficacy Guidelines:*** *ICH Official web site : ICH Efficacy Guidelines* ***Public Consultation:*** *https://www.ich.org/page/public-consultations*
July 2024	Regulatory Consultation and Discussion
May 2025	Adoption of ICH Harmonized Guideline by Regulatory Members of the Assembly

Questions?

https://www.ich.org/page/public-consultations

Explanatory note on proposed changes ICH E2B(R3)

- An explanatory note supports the E2D(R1) Step 2 public consultation by explaining the proposed updates to ICH E2B(R3)
- Alignment of ICH E2B(R3) with the ICH E2D(R1) guideline will require clarification and updates to two existing ICH E2B(R3) data-elements
  - Addition of new values to an existing data element can be accommodated as per established ICH E2B(R3) maintenance process and do not require a revision procedure
- The proposed updates may change following comments received during public consultation of the E2D(R1) guideline and subsequent implementation discussions with the E2B(R3) Expert Working Group

Chapter 4.2: Reporting from Literature

- Updated recommendations on screening literature to improve harmonization
- Clarifies the start of the time clock for reporting literature ICSRs
- Clarifies expectations for reporting when the specific brand or trade name of the product is ambiguous or unknown
- Provides recommendations to include important findings from literature in Periodic Safety Reports, when applicable

…And there's more!

- Adds new section in Sources of ICSRs for "Communications from HCPs and consumers"
- Provides guidance on cases obtained from a regulator's publicly available AE/ADR database
- Clarifies start of time clock for reporting
- Adds new Section on Duplicate Management

REMINDER: *Refer to the complete document for all the changes and updates*

Proposal for new ICH E2B Values

Type of Report ICH E2B(R3) C.1.3	**Study Type Where Reaction(s) / Event(s) Were Observed** ICH E2B(R3) C.5.4 (only populated if Type of Report = 2, (ICH E2B(R3) C.1.3)) *
1 = Spontaneous report 2 = Report from study * 3 = Other 4 = Not available to sender (unknown)	1 = Clinical trials 2 = Individual patient use(e.g. 'compassionate use' or 'named patient basis') 3 = Other studies (e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring) *4 = Patient Support Programme* *5 = Market Research Programme* *6 = Organised Data Collection System with source data from a digital platform*

* Value '2=report from study' and the data element 'study type where reaction(s)/event(s) were observed' is used for studies as well as other ODCSs

Table of Contents

Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

1 INTRODUCTION *(updated)*

2 DEFINITIONS AND TERMINOLOGY *(updated)*

2.1 Basic Terms:
- 2.1.1 Adverse Event (AE) *(updated)*
- 2.1.2 Adverse Drug Reaction (ADR) *(updated)*
- 2.1.3 Serious AE/ADR *(updated)*
- 2.1.4 Unexpected AE/ADR *(updated)*
- 2.1.5 Other Observations *(new)*
- 2.1.6 Reporting Terminology *(new)*

2.2 Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting *(new)*

2.3 Expedited Report *(new)*

2.4 Primary Source *(new)*

Table of Contents

Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

2 DEFINITIONS AND TERMINOLOGY (continued)

2.5 Healthcare Professional (HCP) *(updated)*
2.6 Consumer *(updated)*
2.7 Digital Platform *(new)*
2.8 Organized Data Collection System (ODCS) *(new)*
2.9 Patient Support Program (PSP) *(new)*
2.10 Market Research Program (MRP) *(new)*

3 TYPES OF ICSRs *(new)*
3.1 Spontaneous Reports *(new)*
3.2 Solicited Reports *(new)*

Table of Contents

Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

4. **SOURCES OF ICSRs** ***(updated)***
   - 4.1 Communications by HCPs and Consumers ***(new)***
   - 4.2 Literature ***(updated)***
   - 4.3 Digital Platforms ***(new)***
     - 4.3.1 Digital platforms under the responsibility of the MAH ***(new)***
     - 4.3.2 Digital platforms not under the responsibility of the MAH ***(new)***
   - 4.4 Patient Support Programs ***(new)***
   - 4.5 Market Research Programs ***(new)***
   - 4.6 Regulatory Authority Sources ***(new)***
   - 4.7 Other Sources ***(updated)***

Table of Contents

Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

5. STANDARDS FOR REPORTING *(updated)*
   - 5.1 What Should Be Reported? *(updated)*
     - 5.1.1 AEs/ADRs *(updated)*
     - 5.1.2 Important Safety Findings *(new)*
     - 5.1.3 Other Observations *(updated)*
       - 5.1.3.1 Lack of Efficacy *(updated)*
       - 5.1.3.2 Overdose, abuse, misuse, medication error, occ. exposure *(updated)*
       - 5.1.3.3 Use of medicinal products in pregnancy/lactation *(new)*
       - 5.1.3.4 Off-label use *(new)*
   - 5.2 Reporting Timeframes *(updated)*

Table of Contents

Post-Approval Safety Data: Definitions And Standards for Management and Reporting of Individual Case Safety Reports

6. GOOD CASE MANAGEMENT PRACTICES *(updated)*
   - 6.1 Assessing Patient and Reporter Identifiability *(updated)*
   - 6.2 The Role of Narratives *(updated)*
   - 6.3 Clinical Case Evaluation *(updated)*
   - 6.4 Follow-up Information *(updated)*
     - 6.4.1 Other Observations *(new)*
       - 6.4.1.1 Overdose, abuse, misuse, medication error, occupational exposure *(new)*
       - 6.4.1.2 Use of medicinal products in pregnancy/lactation *(updated)*
   - 6.5 Contractual Agreements *(updated)*
   - 6.6 Duplicate Management *(new)*
   - 6.7 How to Report *(updated)*

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