ICH
harmonisation for better health

E2D(R1)

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

Step 2 document - to be released for comments

5 February 2024

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal notice

Background

Step 2

- **This document has been signed off as a *Step 2* document (5 February 2024) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper (31 January 2020) and a Business Plan (18 November 2019)**
- **Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: May 2025**

Background [continued]

Step 2

- Original ICH E2D guideline was adopted in 2003
- New sources of post-market safety information 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)
- The definitions and regulatory guidance in the original ICH E2D document are no longer sufficient to provide guidance on current pharmacovigilance practices and needs
- ICH E2D(R1) EWG (Expert Working Group) established in 2019 to revise E2D to support appropriate post-market safety surveillance

Background [continued]

Step 2

- This updated guideline provides recommendations that 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 the relevant local or regional regulatory authority's requirements
- E2D(R1) establishes a framework for current best practices of post-approval safety data management in a dynamic environment
- These slides highlight only the significant updates and changes to the document. Extensive editorial changes have been made throughout the document. Refer to the complete document for all other editorial changes and updates

The E2D(R1) Expert Working Group

Step 2

- **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

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Chapter 1 - Introduction

- The ICH E2D guideline was originally based on the contents of ICH E2A
- The introduction was updated to reflect the current focus of E2D: guidance on definitions and standards for post-approval individual case safety reporting, as well as good case management practices

Chapter 2 – Definitions and Terminology

- Key changes include:
  - New definitions **2.1.5 Other Observations** and **2.1.6 Reporting Terminology** have been added
  - New definition (2.2) was added for **Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting**
  - New definitions were added for **2.3 Expedited Report** and **2.4 Primary Source**

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' as they are report types rather than sources

- **Spontaneous Reports** A spontaneous report is a direct communication by an HCP or consumer to an MAH, regulatory authority or other organization that describes one or more AEs/ADRs 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 2 – Definitions and Terminology (continued)

- New definitions have been provided for:

2.7 Digital Platforms

2.8 Organised Data Collection System (ODCS)

2.9 Patient Support Programs (PSP)

2.10 Market Research Program (MRP)

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

Chapter 4 - Sources Of Individual Case Safety Reports

- Includes guidance on the management of safety communications by HCPs and consumers by source to regulatory authorities or other Organisation (e.g., WHO) and marketing authorisation holders (MAHs)
- 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 4.2 - 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

Chapter 4.3 - Digital Platforms

- Replaces original E2D Section 3.1.3 Internet
- Defines what is meant by digital platforms as data source
- Provides description of MAH responsibilities depending on digital platform ownership
- No obligation for MAHs to screen external 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 [continued]

- **4.3.2 Digital platforms not under MAH's responsibility**
  - Screen data using Organized Data Collection System (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 (see next slide)

Proposal for new ICH E2B Values

Step 2

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

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 (ICSR reporting format) to identify cases from PSPs (see slide 18)

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 (i.e., study) reports
- Proposal to add new value in E2B (ICSR reporting format) to identify cases from MRPs (see slide 18)

Chapter 5.1 What Should be Reported?

- Updates reporting guidance to allow harmonization with current local requirements with respect to seriousness, expectedness
- Added a new Section: **5.1.2 Important Safety Findings**

  Safety findings which do not qualify for ICSR reporting and which may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health should be communicated as soon as possible to the regulatory authorities in accordance with local or regional requirements

Chapter 5.1.3 Other Observations

- Expanded section to include several scenarios:
  - Lack of Efficacy
  - Overdose, abuse, misuse, medication error, occupational exposure
  - Use of medicinal products in pregnancy/lactation
  - Off-label use
- Clarification of reporting obligations

… And there's more!

Step 2

- Added new section in Sources of ICSRs for "Communications from HCPs and consumers"
- Provided guidance on management of cases obtained from a regulator's publicly available National or Regional AE/ADR database
- Clarified start of time clock for reporting
- Added new Section on Duplicate Management

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

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

Contact

- **For any questions please contact the ICH Secretariat:**

admin@ich.org