ICH E2D(R1)

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

Step 4

Step 4 document - to be implemented
09 September 2025

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Background

- **This document has been signed off as a *Step 4* document (15 September 2025) to be implemented by the ICH Regulatory Members**
- **This document was developed based on a Concept Paper (31 January 2020) and a Business Plan (18 November 2019)**

Background [continued]

- The 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) was established in 2019 to revise ICH E2D to support appropriate post-market safety surveillance

Background [continued]

- ICH E2D(R1) establishes a framework for current best practices of post-approval safety data management in a dynamic environment
- 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 regional and local regulatory authority's requirements
- These slides highlight only the significant updates and changes to the original 2003 ICH E2D Guideline. Extensive editorial changes have been made throughout the document. Refer to the complete document for all changes and updates

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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 ICH 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**
  - New definitions were added for **2.3 Expedited Report** and **2.4 Primary Source**

Chapter 2 - Definitions and Terminology (continued)

- New definitions have been provided for:
  - 2.7 Digital Platform
  - 2.8 Organised Data Collection System (ODCS)
  - 2.9 Patient Support Program (PSP)
  - 2.10 Market Research Program (MRP)

- All of these were areas of specific focus for the revisions within ICH 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’ as they are report types rather than sources

- **Spontaneous Reports** are direct communications by an HCP or consumer to an MAH, regulatory authority or other organization that describe 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 4.1 - Communications by HCPs and Consumers

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

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
- Provides helpful recommendation on classifying the Type of Report in ICH E2B for Literature ICSRs

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
- Clarifies the start of the time clock for reporting
- **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**
  - Provides guidance when accessing data on digital platform in context of Organized Data Collection System (ODCS)
  - Supports limiting the scope of screening for AEs/ADRs
  - Refers to a new value in E2B (ICSR reporting format) to identify cases from ODCS with source data from Digital Platforms
  - Provides guidance for managing AEs/ADRs identified on a digital platform outside the context of an ODCS

Chapter 4.4 - Non-interventional Studies

- Defines what is meant by non-interventional studies and describes primary data collection and secondary use of data
- Describes MAH responsibilities for review and reporting of AEs/ADRs depending on the type of data used (primary data collection versus secondary use of data)

Chapter 4.5 - Patient Support Programs (PSPs)

- PSPs are considered ODCSs
- PSPs include collection of medical information or program design is such that the program will likely receive medical information
- For the setup and conduct of PSPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS
- Manage AEs/ADRs as solicited (i.e., study) reports
- Refers to new value in ICH E2B(R3) (ICSR reporting format) to identify cases from PSPs

Chapter 4.6 - Market Research Programs (MRPs)

- MRPs are considered ODCSs
- For the setup and conduct of MRPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS
- Manage AEs/ADRs as solicited (i.e., study) reports
- Refers to new value in ICH E2B(R3) (ICSR reporting format) to identify cases from MRPs

Chapter 5.1 - What Should be Reported?

- Updates reporting guidance to allow harmonization with current regional or 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 regional or local requirements

Chapter 5.1.3 - Other Observations

- Expanded section to clarify reporting obligations for several scenarios:
  - Lack of Efficacy or Lack of Effect
  - Overdose, abuse, misuse, medication error, occupational exposure
  - Exposure to medicinal products associated with pregnancy or breastfeeding
  - Off-label use

Results of public consultation

- Approximately 450 comments were received during public consultation. The EWG reviewed every comment received
- Numerous revisions were made to provide greater clarity
- Additionally, a new section for non-interventional studies was introduced to address primary data collection versus secondary use of data
- Practical coding examples to illustrate use of new E2B(R3) values will be provided as training material

…And there's more!

- 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*

Considerations

- This Guideline refers to ICH E2A, E2B, E2C, E8, E19, M1, M14 where applicable
- To align the ICH E2D(R1) guideline with the ICH E2B(R3) reporting specifications, and to support stratification of cases by their source during signal detection and signal analysis, 3 new values will be added to ICH E2B(R3) data element, C.5.4 ‘Study Type Where Reaction(s)/Event(s) Were Observed‘

Conclusions

- This revised Guideline provides updated guidance on post-approval safety data management by better reflecting current practices and sources of safety data

- Additional training material will be developed to complement the Guideline

Contact

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

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