

Update on the ICH E2D(R1) Guideline

Craig Zinderman, MD MPH
Associate Director for Medical Policy,
Office of Biostatistics and Pharmacovigilance (OBPV)
CBER | US FDA

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Learning Objectives

- Understand the background and rationale for updating E2D
- Review the new definitions and terminology
- List the types of Individual Case Safety Reports (ICSRs)
- Comprehend updates to the guidance by information source (e.g., digital platforms, patient support programs)

ICH E2D (R1) Guideline:

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

ICH: INTERNATIONAL COUNCIL FOR HARMONISATION

Background

- Original ICH E2D guideline adopted in 2003
- Emerging post-market safety information sources
 - Sources are new or are used more often
 - Vary in characteristics and contribution to post-market safety surveillance

Background

- The definitions and regulatory guidance in the original Guideline are no longer sufficient to provide guidance on current pharmacovigilance practices and needs
- ICH E2D(R1) EWG (Expert Working Group)
 - Established in 2019
 - Revising 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 significant updates.
- Refer to the complete document for all editorial changes and updates

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

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)

ICSR Definition (part I)

- Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting (2.2)*
 - An ICSR is a description of an adverse event/adverse drug reaction, or other observation, in an individual patient at a specific point in time.

*See ICH E2D(R1) draft guideline, Section 2.2, for full details.

ICSR Definition (part II)

- An ICSR is a description of an adverse event/adverse drug reaction, or other observation, in an individual patient at a specific point in time.
- Minimum criteria for reporting an ICSR:
 - At least one adverse event/adverse drug reaction
 - At least one suspect or interacting medical product
 - An identifiable patient
 - At least one identifiable reporter

*See ICH E2D(R1) draft guideline, Section 2.2, for full details.

Expedited ICSR Definition*

- Expedited Report:
 - An ICSR that meets the requirements for reporting as soon as possible, but no later than 15 calendar days after day zero

*See ICH E2D(R1) draft guideline, Sections 2.2 (ICSR) and 5.2 (Reporting Timeframes), for full details

Expedited ICSR Definition*

- Day Zero
 - Date when any personnel of the MAH[‡] obtains sufficient information to determine that a case report fulfils the minimum criteria for reporting

*See ICH E2D(R1) draft guideline, Sections 2.2 (ICSR) and 5.2 (Reporting Timeframes), for full details

[‡] “Personnel of the MAH” includes third parties acting on the MAHs behalf

U.S. FDA Requirements: Expedited Reports*



Applicant (i.e., MAH) must submit:

- ICSRs for Expedited adverse event (AE) reports within 15 calendar days
 - Serious (death, hospitalization, life-threatening, disability, congenital anomaly, other)
- And*
- Unexpected (Unlabeled)

**21CFR314.80 for NDAs and 21CFR600.80 for BLAs*

U.S. FDA Requirements: Non-expedited Reports*



Applicant (i.e., MAH) must submit:

- Other ICSRs
 - For non-serious AEs; serious & labeled AEs
 - Periodic Adverse Drug Experience Report (PADER)
 - Quarterly for products <3 years old; Annually thereafter

**21CFR314.80 (NDAs) and 21CFR600.80 (BLAs). Non-expedited reporting requirement does not apply to AEs from studies, literature, and foreign marketing.*

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

New section created for concepts of Spontaneous and Solicited Reports (moved from section on ‘Sources of ICSRs’)

- **Spontaneous Reports:**

- Direct communications by health care providers or consumers to an MAH, regulatory authority or other organization
- Describe adverse events/adverse drug reactions in a patient who was exposed to a medicinal product(s)
- Not gathered as part of an ODCS

Chapter 3: Types of ICSRs

New section created for concepts of Spontaneous and Solicited Reports (moved from section on 'Sources of ICSRs')

- **Solicited Reports**

- Reports derived from ODCSs
- For the purposes of reporting, solicited ICSRs are classified as 'reports from study' in E2B format
- Should have a causality assessment

Chapter 4 - Sources Of ICSRs

Provides guidance on the management of safety information by source:

- Literature
- Digital Platform Section
- New Sections
 - Patient Support Programs
 - Market Research Programs
- Regulatory Authority Sources

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

U.S. FDA Requirements: Literature Reports*



Applicant (i.e., MAH) must submit:

- ICSRs for information in literature that the applicant receives or otherwise obtains if:
 - Expedited (serious and unexpected)
- And*
- Found in scientific literature either as case report or as the result of a formal clinical trial

**21CFR314.80 (NDAs) and 21CFR600.80 (BLAs)*

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
 - Proposes a new value in E2B (ICSR reporting format) for cases from ODCS on Digital Platforms

Chapter 4.4: Patient Support Programs (PSPs)



- PSP 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
- Proposes new value in E2B for cases from PSPs

U.S. FDA Requirements: Study Reports



- Manage AEs from PSPs as Study Reports[¥]
- Applicant must submit AEs from a postmarketing clinical study if
 - Expedited (serious and unexpected)
And
 - applicant concludes that there is a reasonable possibility that product caused the AE*

¥Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, March 2001

**21CFR314.80 for NDAs and 21CFR600.80 for BLAs*

Chapter 4.5: Market Research Programs (MRPs)

- MRP 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.”

Chapter 4.5: Market Research Programs (MRPs)

- Manage AEs/ADRs from MRPs as solicited reports
- Proposes new value in E2B for cases from MRPs

Chapter 5: What Should be Reported?

- Updates reporting guidance to allow harmonization with current local requirements with respect to seriousness, expectedness

Chapter 5: What Should be Reported?

- 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 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: What Should be Reported:

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

Chapter 5: What Should be Reported:

Other Observations (5.1.3)



- Reports of other observations (occurring without associated adverse events/adverse drug reactions) should only be reported if required by local or regional regulations, guidelines, or other regulatory authority conditions.

U.S. FDA Requirements: Other Observations



- Off-label use, medication error, use in pregnancy:
≠ AE
 - No requirement to submit as ICSRs unless occurring with an AE

U.S. FDA Requirements: Lack of Effect



- Adverse drug experience* † :
 - Any AE associated with the use of a drug in humans, whether or not considered drug related, including...
...any failure of expected pharmacological action.

**21CFR314.80 for NDAs and 21CFR600.80 for BLAs*

†Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, March 2001

Chapter 6: Good Case Management

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 in pregnancy/lactation (*updated*)

6.5 Contractual Agreements (*updated*)

6.6 Duplicate Management (*new*)

6.7 How to Report (*updated*)

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

ICH E2D(R1) Major Milestones

- ICH Step 3: Regulatory Consultation and Discussion
 - Open for public comments through June 2024
 - ICH Website: <https://www.ich.org/page/public-consultations>
 - Federal Register (March 14, 2024):
<https://www.federalregister.gov/documents/2024/03/14/2024-05381/e2dr1-post-approval-safety-data-definitions-and-standards-for-management-and-reporting-of-individual>

ICH E2D(R1) Major Milestones

- Expert Working Group discuss and review comments
 - Starting in July 2024
- Final Guideline anticipated May 2025

Summary

- ICH E2D(R1):
 - Includes new and updated definitions (e.g., ICSR, ODCS, PSP)
 - Clarifies and adds new guidance for key information sources (e.g., literature, Digital Platforms, PSPs)
 - Updates guidance on other safety observations (e.g., lack of effect, off-label use, use in pregnancy)
- Draft is open for public comments

Challenge Question #1

The main reason for ICH to update E2D:

- A. Compare and contrast use of large language models like ChatGPT, BERT, and LLAMA, for post-market safety reporting
- B. New information sources have emerged (or are used more often) which vary in characteristics and contribution to post-market safety surveillance (e.g., PSPs, and social media)
- C. New participants (i.e., Health Canada and MHRA) have joined ICH
- D. To align E2D with related ICH post-market reporting guidelines which have been recently updated (i.e., ICH E2B(R3) and ICH E2C(R2)).

Challenge Question #2

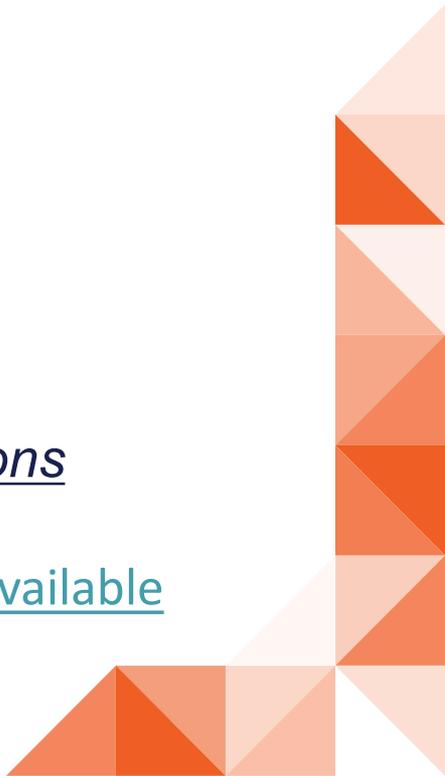
An ICSR is an adverse event, or other observation, in an individual patient at a specific point in time. Which of these is **NOT** one of the four minimum criteria for reporting ICSRs:

- A. At least one adverse event/adverse drug reaction
- B. At least one suspect or interacting medical product
- C. At least one Serious *And* Unexpected (i.e., unlabeled) AE
- D. An identifiable patient
- E. At least one identifiable reporter

Questions?

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

[Federal Register Notice: E2D\(R1\) Draft Guidance Available](#)



Back-Up Slides



Proposal for new ICH E2B Values

Type of Report	Study Type Where Reaction(s) / Event(s) Were Observed
ICH E2B(R3) C.1.3	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, pharmacoconomics, intensive monitoring) <i>4 = Patient Support Programme</i> <i>5 = Market Research Programme</i> <i>6 = Organised Data Collection System with source data from a digital platform</i>

- 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

Explanatory note on proposed changes ICH



E2B(R3)

- An explanatory note supports the E2D(R1) Step 3 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

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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*)

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- 2 DEFINITIONS AND TERMINOLOGY (continued)
 - 2.5 Healthcare Professional (HCP) *(updated)*
 - 2.6 Consumer *(updated)*
 - 2.7 Digital Platform *(new)*
 - 2.8 Organised 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)*

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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)*

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- 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)*

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- 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)*