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

Regulatory Education for Industry (REdI)

2024 Annual Conference

May 29-30, 2024

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

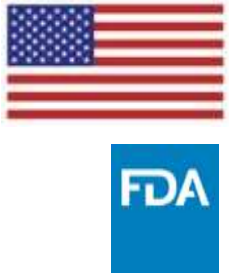
Expedited ICSR Definition*

- 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

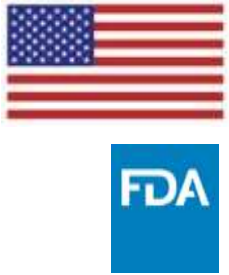
Provides guidance on the management of safety information by source:

- 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

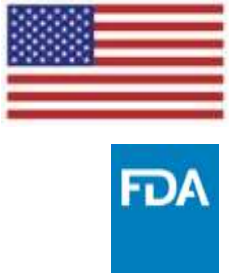
Chapter 5: What Should be Reported: Other Observations (5.1.3)

- 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)

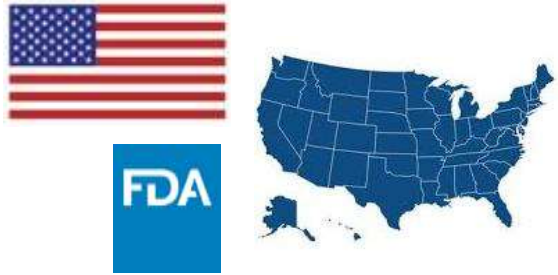
- Reports of other observations (occurring without associated adverse events/adverse drug reactions) should only be reported if required by local or regional regulations, guidelines, or other regulatory authority conditions.

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

U.S. FOOD & DRUG ADMINISTRATION

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 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

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

Table of Contents

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

Table of Contents

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

Table of Contents

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

Table of Contents

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

Table of Contents

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