ICH-E2C(R2) guideline and PBRER template: concept, principles and regulators' expectations

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Disclaimer and declaration of conflict of interest

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Declaration of Conflicts of Interest

No conflict of interest to declare

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PBRER Making & Assessment

ICH-E2C(R2) guideline and PBRER template: concept, principles and regulators' expectations

1	ICH-E2C(R2) guideline and evolution of PBRER
2	PBRER template: *General Concepts and Principles*
3	Regulators' perspective and expectations
4	Concluding Remarks

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PBRER Making & Assessment

ICH-E2C(R2) guideline and evolution of PBRER

PBRER = Periodic Benefit-Risk Evaluation Report

- PBRER aims to analyse balance of benefits and risks of a medicinal product, taking into account new information in the context of cumulative data. It is periodically submitted by marketing authorisation to regulatory authorities as a mandate in the post-authorisation phase.

Why do we need PBRER?

- **Clinical trial safety** data is **limited**: small number of patients, exclusion of at-risk/special population groups, short duration, tightly controlled doses and closely monitored patients.
- Thus, at the time of approval, **all ADRs** (ex: rare and delayed onset ADRs), **drug interactions** and issues related to **real-world use** of the drug are **not known** and **continuous surveillance** and **analyses of risks** in context of **benefits** is **vital** in post-marketing phase.
- PBRER ensures **continuous surveillance** of the **benefit-risk** of the product.

ICH-E2C(R2) guideline and evolution of PBRER

ICH= The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- ICH was established in 1990 with a mission to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner whilst meeting high standards. ICH currently has 18 regulatory and industry members, and 33 observers.

- **ICH Guidelines** have been developed to achieve harmonisation.

- The **ICH E2C(R2) Guideline for PBRER** provides a common standard for periodic benefit-risk evaluation reporting on marketed products among the ICH regions.

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- 1996: **ICH E2C:** Periodic safety Update Reports **(PSUR)** for marketed drugs → focus on new safety information in context of patient exposure, to determine if changes were needed to the RSI to ensure continued safe use.

- 2003**: ICH E2C(R1): PSUR** for Marketed Drugs (Addendum)→ additional guidance on inclusion of **'summary'** when a more comprehensive benefit risk analysis has been conducted.

- 2004: **ICH E2E**: Pharmacovigilance Planning →focus on Safety Specification and Pharmacovigilance Plan.

- 2010: **ICH E2F**: DSUR for periodic reporting on the safety of drugs under that continue to be under clinical development.

- 2012: **ICH E2C (R2): PBRER** → expands PSUR principle & shifts focus to **integrated benefit-risk evaluation, modular approach,** focus on new information in **cumulative context.**

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PSUR	PBRER
• Interval safety report focused on individual case reports • Includes case line listings and narratives. • Allows Summary, Bridging and Addendum reports.	• Cumulative benefit-risk report involving aggregate data evaluation. • No routine submission of case line listings or narratives. • No Summary, Bridging or Addendum reports. • Modular format.

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PBRER template: General Concepts and Principles

"The main objective of a PBRER is to present a comprehensive, concise and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit risk profile." **ICH E2C (R2)**

PBRER achieves this objective by:

- Summarising relevant **new safety information** that may impact the benefit risk balance.
- Summarising significant **new efficacy / effectiveness** information.
- Analysing the new information **in context of known benefit risk** profile of the drug
- Conducting an **integrated** benefit-risk evaluation where important new safety information has emerged.
- Outlining further **proposed actions** to optimise the benefit-risk profile.

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PBRER template: General Concepts and Principles

PBRER Format and Content

The full ICH Guideline E2C(R2) format should be used for all PBRERs

1	Introduction
2	Worldwide marketing authorisation status
3	Actions taken in the reporting interval for safety reasons
4	Changes to reference safety information
5	Estimated exposure and use patterns
6	Data in summary tabulations
7	Summaries of significant findings from clinical trials during the reporting interval
8	Findings from non-interventional studies
9	Information from other clinical trials and source
10	Non-clinical Data

11	Literature
12	Other periodic reports
13	Lack of efficacy in controlled clinical trials
14	Late-breaking information
15	Overview of signals: new, ongoing or closed
16	Signal and risk evaluation
17	Benefit evaluation
18	Integrated benefit-risk analysis for authorized indications
19	Conclusions and actions
20	Appendices to the PBRER

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PBRER template: General Concepts and Principles

PBRER SHOULD (BE):

- A single document for an active substance (including information on all approved indications, dosage forms and regimens). Fixed dose combination may be separate or combined; all relevant documents should be cross referenced.
- A single, stand alone document for the reporting interval, in context of cumulative information→ should include both interval and cumulative data.
- Based on International Birth Date (IBD) to determine data lock point
- More frequently prepared and submitted in early post marketing phase.
- Using the Company Core Safety Information (CCSI) to assess 'listedness'.
- Include **benefit** data related only to use in **approved indications**, but include all types of data on **safety and risk regardless of indication**.
- Include discuss new information in a **level of detail** proportionate to its potential impact on the benefit-risk profile.

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PBRER template: General Concepts and Principles

PBRER SHOULD NOT BE:

- The means or channel to provide initial notification of significant new safety information or efficacy information

- Used as a means to detect new safety concerns or issues. MAH should perform regular signal detection activities and literature monitoring to detect new safety concerns.

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Regulators' perspective and expectations

Common PBRER issues

- *Complete non-submission or late submission of PBRER*
- *Incorrect format of PBRER*
- *Exposure miscalculated and/or no explanation of calculation.*
- *Insufficient or erroneous analysis of new signals and inclusion of irrelevant information.*
- *Mismatch between data interpretation and PBRER conclusions*
- *Failing to refer to standardized MedDRA terminology*
- *Lack of analysis of cases of fatal cases or unlisted serious ADRs.*
- *Insufficient discussion of information on use in pregnancy, off-label use, drug interactions etc*
- *Inadequate review of literature.*
- *Omission of required information*
- *Previous requests from Regulatory Agencies not addressed.*

Regulators' perspective and expectations

Regulators' expectations

- Timely PBRER/PSUR submissions compliant with jurisdictional timeframes.
- PBRER format and content compliant with ICH-E2C (R2) guidelines.
- Complete review of all cases for PBRER interval.
- Fulfilment of regulatory requests and commitments based on previous PBRER submissions.
- PBRER must not only include interval data but also an evaluation of this data in context of cumulative information.
- Proactive proposals for appropriate risk management measures in the PBRER.
- Inclusion of effectiveness of specific risk minimisation measures
- ***During PV inspections:***
  - Consistency between case reports in safety database and PBRER.
  - Tracked and documented processes and QC for PBRER and its regulatory submission.
  - Documented evidence of completion of the actions/changes reported within the PBRER.

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Concluding Remarks

- PBRER provide a crucial opportunity to evaluate available benefit-risk at defined points in an approved products lifecycle.
- PBRER are gaining more importance as a necessary counterbalance to accelerated assessments and expedited authorisation of high priority drugs and vaccines, which have a nascent safety profile at approval.
- ICH-E2C (R2) guideline provides a common standard for PBRER reporting among ICH regions, and is a comprehensive and detailed reference for the purpose, concepts, principles, format and content of PBRER.
- Understanding and applying this guideline, in both preparing and assessing PBRER, is essential for meaningful evaluation and impactful optimisation of post-market benefit-risk profile of medicinal products.

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Thank you for your attention
спасибо за Ваше внимание
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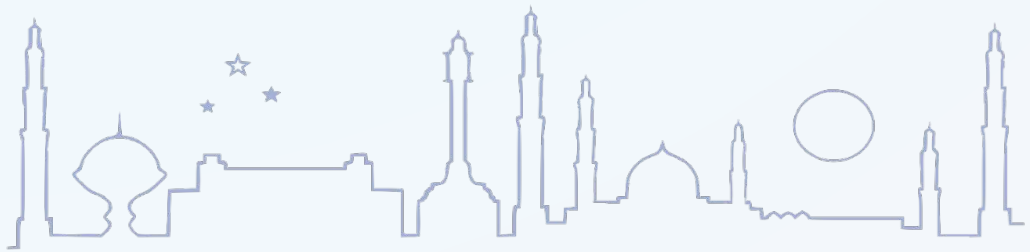

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