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# EFPIA Position on Implementation of the ICH E17 Guideline on Planning and Design of Multi-regional Clinical Trials in International Markets

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## Executive Summary

Drug development now takes place on a global scale. The number of clinical trials has expanded rapidly over the last decade, and this increase is especially notable for Asia. In this context, the ICH E17 Guideline on Planning and Design of Multi-regional Clinical Trials (MRCTs)[1] is an important tool for global drug development and registration. To maximise the impact of the ICH E17 Guideline in streamlining and speeding up global drug development and registration, EFPIA recommends the following:

- Stakeholders including regulators and sponsors developing new treatments, should use the ICH E17 Guideline principles to optimize drug development at a global level.
- Promote greater awareness and use of existing ICH E17 training materials by all stakeholders.
- Adoption of strategies that pool patients across a region (for example, from Japan, South Korea, and China into an East Asian region) provided that ethnic factors are adequately understood and comparable and align with the recommendations of the ICH E5 Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data[2].
- Regulatory authorities should adequately implement the ICH E17 Guideline, and make sure to adapt their local laws and guidelines to the principles of the ICH E17 Guideline where appropriate.

## Introduction and Problem Statement

In today's globalized drug development environment, many companies favour MRCTs to generate data that can be accepted by multiple regulatory authorities to support approval of new medicines. As well as reducing unnecessary duplication of studies, MRCTs should reduce drug lag in key markets and improve patient access to new transformative treatments. However, evaluation of data generated with MRCTs for drug approval can pose a wide range of challenges for regulatory authorities on how to extrapolate foreign clinical data to a new region. As a result, work that started in June 2014 at the ICH level to provide harmonised and international guidance on General Principles for Planning and Design of MRCTs was finalised in November 2017 with the release of the ICH E17 Guideline[1] and its training materials[3] aimed at increasing MRCT data quality and acceptance by regulatory authorities of the ICH regions.

The ICH E17 Guideline describes how, with careful planning, new medicines can be developed globally from the outset. The guideline, which addresses strategic programme issues, should be used in conjunction with other ICH Guidelines, for example, E5, E6, E8, E9 (R1), E10 and E18. In addition,

extensive training materials including 7 modules have been developed to promote the efficient and consistent implementation of the E17 Guideline and are available on the ICH website[3]. The majority of ICH Regulatory Members have implemented the guideline[4], however, challenges remain for industry in relation to consistent implementation in practice of the principles of the guideline. The number of ICH Regulatory Members and Observers is increasing regularly[5], which represents an additional challenge in ICH guideline implementation.

A European Federation of Pharmaceutical Industry Associations (EFPIA) survey conducted in 2020 on the implementation of the E17 Guideline highlighted these challenges, such as the lack of awareness and use of the ICH E17 training materials by industry, as well as barriers to practical implementation of the guideline, including challenges with the use and acceptance of pooling strategies by regulators and the existence of local requirements that may be a barrier to full implementation[6].

## EFPIA's Recommendations to Increase the Full Use and Acceptance of the ICH E17 Guideline in International Markets

**Training**

- EFPIA supports promoting better awareness and use of the existing ICH E17 Guideline training materials[3]. This would result in a better understanding and implementation of the ICH E17 Guideline principles by both industry and regulatory authorities while widening industry understanding of the guideline beyond those working directly with clinical trials.
    - This could be achieved by inter-regional workshops where the practical details and benefits of the E17 Guideline to patients and regulatory authorities could be openly discussed.
- Existing ICH E17 Guideline training materials are general in nature and EFPIA supports their revision with the addition of more information including case examples in the future.

**Pooling Strategies**

- The ICH E17 Guideline introduced a new concept of a "pooled region/pooled subpopulation", where there is commonality in intrinsic and/or extrinsic factors known to potentially affect the treatment effect. The strategy for regions or pooled regions or pooled subpopulations should be pre-specified in the protocol for stratification, sample size allocation, and consistency evaluation.
- Pre-specified pooling of regions or subpopulations, based on established knowledge about similarities, may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
- Pooling patients from Japan, South Korea and China into an East Asian region can be a potential strategy, provided that ethnic factors, that potentially may modify the effects of the drug, are adequately understood and comparable. However, industry experience in applying such pooling strategies has been challenging so far.

- EFPIA encourages regulatory authorities to fully leverage the concept of a "pooled region/pooled subpopulation" as set out in the ICH E17 Guideline to ensure the full benefit of the guideline can be applied in East Asia.

**Local Requirements**

- Local requirements are perceived by industry as a barrier to full implementation of the ICH E17 Guideline[6, 7]. In some cases, existing local requirements in ICH Regulatory Authority Members continue to mandate local subjects to be included in clinical trials for registration, contrary to the principles of the ICH E17 Guideline. Where local requirements exist that are contrary to the principles of the ICH E17 Guideline, the local laws and guidelines should be updated to incorporate/align with the concepts in the ICH E17 Guideline.

**Additional Factors**

- In cases where there may be additional guidelines in place, such as safety related guidelines that mandate certain number of patients, these should not override the concepts of the ICH E17 Guideline in relation to registration.

## Conclusions

The ICH E17 guideline is undoubtedly an important tool in global drug development. EFPIA recognise that it is one part of the overall drug development process to make new medicines available to patients globally. Despite sub-optimal use of pooling strategies, new medicines are getting approved in Japan and South Korea at about the same time as in other major markets, and China is taking a leap toward this ambition[8, 9]. EFPIA encourages all stakeholders to strive for full implementation of the ICH E17 Guideline principles, including the ability to pool subregions/subpopulations. Sharing experience and best practices could help and support the revision of the existing E17 Guideline training materials, which is also an important tool to foster development of MRCTs. This will ultimately support further development of MRCTs and their acceptance by regulatory authorities globally.

## Annex: Published Case Studies

Zhou *et al.* Asia-inclusive global development of pevonedistat: Clinical pharmacology and translational research enabling a phase 3 multiregional clinical trial. *Clin Transl Sci.* 2021;00:1-13.

Nielsen *et al.* Evaluation of Consistency of Treatment Response Across Regions—the LEADER Trial in Relation to the ICH E17 Guideline. Frontiers in Medicines. 2021;Vol 8:662775.

Ramamoorthy *et al.* Racial and Ethnic Differences in Drug Disposition and Response: Review of New Molecular Entities Approved Between 2014 and 2019. J Clin Pharmacol. 2021 Oct 4.
doi: 10.1002/jcph.1978 (online ahead of print).

## References

1. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) General Principles for Planning and Design of Multi-Regional Clinical Trials. (2017). Available online at: https://database.ich.org/sites/default/files/E17EWG_Step4_2017_1116.pdf (accessed 01 October 2021).
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E5 Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data. Available online at: https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf (accessed 01 October 2021).
3. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E17 Guideline training materials. Available online at: https://www.ich.org/page/efficacy-guidelines (accessed 01 October 2021).
4. Monitoring the Adequacy of Implementation and Adherence to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines. Available online at https://www.ich.org/page/ich-guideline-implementation (accessed 01 October 2021).
5. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) current members and observers, available online at https://www.ich.org/page/members-observers (accessed 01 October 2021).
6. European Federation of Pharmaceutical Industry Associations (EFPIA) survey on the implementation of the E17 guideline, June 2021. Available online at: Industry Survey on Implementation of ICH E17 Guideline (diaglobal.org) (accessed 01 October 2021).
7. ICH E17 Guideline on MRCTs, Catalyst for Simultaneous Global Development and Registration, June 2021. Available online at: ICH E17 Guideline on Multi-Regional Clinical Trials (diaglobal.org) (accessed 01 October 2021).
8. Centre for Innovation in Regulatory Science (CIRS) R&D briefing Number 81, New Drug Approvals in Six Major Authorities 2011 – 2020. Available online at: https://cirsci.org/wp-content/uploads/dlm_uploads/2021/06/CIRS-RD-Briefing-81-6-agencies-v5.pdf (accessed 01 October 2021).
9. Centre for Innovation in Regulatory Science (CIRS) R&D briefing Number 72, Trends in the Regulatory Landscape for the Approval of New Medicines in Asia. Available online at: https://cirsci.org/wp-content/uploads/2020/02/CIRS-RD-Briefing-72-Trends-in-the-regulatory-landscape-Asia.pdf (accessed 01 October 2021).