ICH Reflection paper

Strategic Approach to International Harmonization of Technical Scientific Requirements for Pharmacoepidemiological Studies Submitted to Regulatory Agencies to Advance More Effective Utilization of Real-World Data

Background

In recent years, the sophistication of pharmacoepidemiological studies conducted in various countries worldwide has advanced dramatically alongside more active use of Real-World Data (RWD). Many regulatory agencies and industries are now conducting epidemiological safety assessments based on data gathered during the post-marketing stage. In the last 10-years, the only ICH activity related to pharmacovigilance has been the revision of the PSUR guideline (E2C)[1], and ICH currently has no forum in which to facilitate the exchange of information related to pharmacoepidemiological studies, such as issues faced by epidemiologists in their daily work. Therefore, best practices, relevant know-how, and personnel experiences related to pharmacoepidemiology concerns are not being adequately shared among the different regulatory agencies, resulting in a lack of communications among regulatory agencies and industries.

Some regulatory guidelines related to epidemiological evaluation during the post-marketing stage have been already published in each region, such as the FDA, United States Guidance for Industry "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data"[2], the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidances[3] related to the planning and execution of pharmacoepidemiological studies, and the PMDA "Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases"[4], among others.

However, there is currently no ICH guideline that focuses on pharmacoepidemiological studies. Although the Appendix of the current ICH E2E Guideline[5], "Pharmacovigilance Planning", discussed typical designs for pharmacoepidemiological studies, the primary focus of ICH E2E is how to develop an effective pharmacovigilance plan that suitably describes product safety profiles and also offers a roadmap for how to monitor products. Regarding RWD, the ICH Reflection on "'GCP Renovation: Modernization of ICH E8 and Subsequent Renovation of ICH E6"[6] has stated that ICH plans to develop guidelines for non-traditional trials which will focus on data reliability/integrity in clinical trials. This reflection paper, however, primarily focuses on pharmacoepidemiological issues in the post marketing stage. ICH guidelines to address issues related to pharmacoepidemiology will be needed to further promote international harmonization in this area. Such guidelines play a critical role in regulatory decision-making pertaining to the post-marketing setting.

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[1] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf
[2] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf
[3] http://www.encepp.eu/standards_and_guidances/index.shtml
[4] https://www.pmda.go.jp/safety/surveillance-analysis/0011.html
[5] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf
[6] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/GCP_Renovation/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf

This reflection paper proposes a strategic approach to international harmonization of technical scientific requirements for pharmacoepidemiological study data submitted to regulatory agencies.

Objectives

The goal of this reflection paper is to harmonize the technical scientific requirements related to pharmacoepidemiological studies submitted to regulatory agencies. Harmonization in this area facilitates utilization of RWD and promote a globally-harmonized approach in post-marketing safety-related regulatory actions based on the most current scientific evidence.

Examples of possible areas for harmonization:

Short Term Objectives:

- Glossary used for pharmacoepidemiological studies intended for regulatory submission
  - Harmonizing terminology related to regulatory submission in the area of pharmacoepidemiology
  - Facilitating information exchange between regulatory agencies and industries

- Format of study protocols/reports intended for regulatory submission
  - Harmonizing structure and format of protocols and reporting documents (but not Common Technical Document; CTD)
  - Promoting global submissions by industries and facilitating drug safety assessment by regulatory agencies

Long Term Objectives:

- General principles for pharmacoepidemiological study for regulatory submission
  - Harmonizing general approach for planning and design of pharmacoepidemiological study (e.g., data-source selection, patient selection, exposure definition, outcome definition, primary analysis, etc.)
    - Harmonizing general approach for planning and design of pharmacoepidemiological study (e.g., data-source selection, patient selection, exposure definition, outcome definition, primary analysis, etc.)
  - Increasing usefulness/acceptability of pharmacoepidemiological studies in global regulatory submission

Discussion for scope

Harmonization of technical scientific requirements would primarily be focused on pharmacoepidemiological studies for drug safety in post-marketing study, an area which many regions already have sufficient experiences. The harmonization in this area will also contribute to more efficient, and potentially broader, utilization of RWD for medicines regulation.

Hybrid/innovative types of pharmacoepidemiological studies have been becoming more common in recent years. However, initial discussion in this area should focus on more typical study designs for making a consensus smoothly in ICH, but their applicability may also be considered when appropriate.

Strategic approaches

For achieving the objective, a step-wise approach is proposed as described below.

	Workload	Deliverable	Timing*
1st Stage	• Information exchange for mutual understanding of situations including contents of local guidelines in each region (mainly e-mail/TC based) • Considering the specific areas and opportunities for international harmonization	• List of Harmonizable areas in ICH	2019.Q4 -2020.Q2
2nd Stage	• Prioritizing harmonization area as ICH guidelines • Creating overall structure of these guidelines (i.e. the relationships between the different guidelines)	• Priority list and overall structure of all guidelines	2020.Q3 -2021.Q1
3rd Stage	• Creating opportunity proposal for high priority topics to propose a form of expert working group • Opportunity proposal for the other topic will be created in order of priority	• Opportunity proposal	2021.Q2 -2021.Q3
4th Stage	• Following regular ICH process; New Topic proposal, adoption and Steps 1-4	• ICH Guideline	2021.Q4 -20XX.QX

*Note: The timing will be optimized by the discussion group; some opportunity proposals may be reported in shorter term, whereas other topics may need a long-term discussion.

Pharmacoepidemiology Discussion Group

It is recommended to establish an informal pharmacoepidemiology discussion group (PEpi-DG) to accomplish this work. The PEpi-DG will serve for a two-year period.

Roles of the PEpi-DG

- In the Stages 1 and 2, the PEpi-DG will support the advancement of strategic approaches to realize international technical scientific harmonization by considering overall structure and sequencing to avoid any overlap between proposed and current ICH Guidelines.
- The PEpi-DG will consider topics based on the need and concerns of both regulators and members of industry in relation to this topic.
- A step by step approach will be taken in the PEpi-DG for finding a way for international harmonization in this emerging area.
- The PEpi-DG will generally work via e-mail and web/teleconference, however, the ICH Management Committee may consider granting a face-to-face meeting of the PEpi-DG during a biannual ICH Meeting upon approval of a specific work plan in line with current practice for other ICH Working Groups.

Members of the PEpi-DG

- The PEpi-DG consists of highly experienced experts in pharmacoepidemiology with strong expertise for safety assessment.
- ICH Members and Observers with interest in this topic may appoint experts to the PEpi-DG in accordance with the applicable ICH Standard Operating Procedures.

Interaction between the MC and Assembly and PEpi-DG

- The PEpi-DG will report its outcomes to the MC and the Assembly at regular intervals (e.g. every 6 months)
- The MC will perform an annual milestone review to consider outcome of the discussion and provide feedback to the PEpi-DG.
- At the end of its mandate the PEpi-DG will report on its outcomes to the MC and the Assembly, and highlight future areas related to RWD on which further harmonization work might bring benefits.

Expected outcome

- During Stage 3, the PEpi-DG will create opportunity proposal(s) based on the discussion at stages 1 and 2.
- After completing the work for Stage 3, an interested party shall submit a new topic proposal based on the outcome from this DG to follow the regular ICH process (stage 4).

Conclusion

As discussed above, it is necessary to consider a long-term plan in order to more effectively progress towards harmonization in the pharmacoepidemiology space. Timely creation of guidelines while ensuring holistic consideration of the structures most necessary for the ICH region will promote a globally-harmonized approach in post-marketing safety-related regulatory actions and facilitate more effective utilization of RWD based on the most current scientific evidence.