ISSN: 0976-7126
Latif *et al.*, 15(2):15-20, 2024

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

A review on ICH Guidelines

Md Shahzad Latif[1]*, Tanya Sharma[2], Himani Tiwari[3] and Kaushal Kishor Chandrul[4]

1, Student of B. Pharm. 4th Year; 2, Assistant Professor; 3, HOD; 4, Principal

Department of Pharmacy, Mewar University, Gangrar Chittorgarh, (R.J.) - India

Article info

Received: 05/01/2024

Revised: 13/02/2024

Accepted: 25/02/2024

© IJPLS

www.ijplsjournal.com

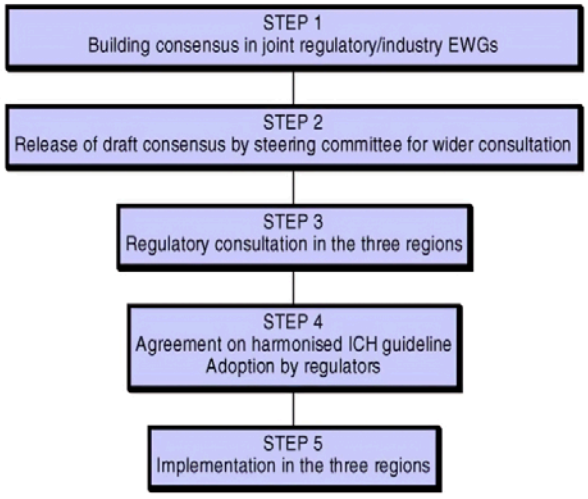
Abstract

This article discusses the development of global guidance for registering technical dossiers for medicinal product applications. It highlights the relevance of NMR spectroscopy in drug development and control. The pharmaceutical industry's globalization has led to efforts to harmonize registration requirements across different regions, reducing costs while ensuring safe and effective medications. In the 1980s, discussions on harmonization began between Europe, Japan, and the United States, resulting in the establishment of the International Conference on Harmonisation (ICH) in 1991. ICH is a tripartite body consisting of regulators and industry representatives from the US, EU, and Japan. The ICH Steering Committee, supported by the IFPMA, identifies, and develops harmonized guidelines in areas such as efficacy, safety, quality, and multidisciplinary topics. More information can be found on the ICH website.

Key-words: ICH, Good clinical practices guidelines, Quality, Safety, Efficacy, Multidisciplinary, Pharmaceutical development, Quality by design, Real time release, Control strategy.

Introduction

The ICH process for new guidelines involves five stages, starting with topic consideration and consensus development by the Expert Working Group. The draft consensus is then released for wider consultation in the three regions, with comments received through IFPMA and WHO contacts. The final guideline is issued for adoption in the three regions, with formal adoption in Europe by CHMP. Existing guideline revisions go through a simplified process. Initially, ICH focused on technical aspects of drug registration, but has now expanded to include guidance on the Common Technical Document.

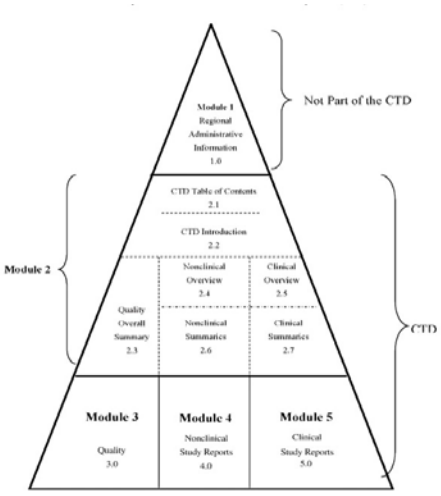


***Corresponding Author**

ISSN: 0976-7126
Latif *et al.,* 15(2):15-20, 2024

The Common Technical Document

The ICH Topic M4 aims to establish a single set of registration documents for marketing authorization across the three ICH regions. It is linked to Topic M2, which sets standards for data interchange. The final Common Technical Document (CTD) was completed in 2000 and implemented in 2003. The CTD provides instructions for registration dossier format, but regional requirements may vary. The CTD has a modular structure and guidelines for new drug registrations. Module 3 focuses on product quality and analytical techniques. Deviations from guidelines should be explained and justified to the regulatory authorities. Quantitative NMR techniques are included in Module 3.



Industry Perspectives on ICH Guidelines

The International Conference on Harmonization (ICH) was initiated in 1990 to standardize the drug registration and approval process. This was driven by the need to reduce healthcare costs, speed up the availability of new treatments, and improve communication between regulatory agencies and sponsor companies. The ICH is a collaboration between regulators and industry to develop guidelines for testing the safety and efficacy of medicines. While progress has been made, the implementation and maintenance of the guidelines are still in early stages. This paper focuses on the guidelines relevant to clinical trials and their use in the drug registration process.

United States

The modern era of drug review and approval began in 1962 with the Food, Drug and Cosmetic Act. Sponsors were required to provide proof of efficacy for the first time, leading to changes in the pharmaceutical industry and the FDA's approach. The FDA's review process slowed from the 1960s to the 1980s due to increased regulation. In contrast, Europe had a quicker process. In 1988, the FDA implemented new guidelines, and in the 1990s, acts were enacted to improve the review process and modernize drug registration. The FDA's performance has improved, with a decrease in review time over the years.

European Union

The European approval process, initially based on individual country approvals, was centralized in the mid-1990s by the Committee for Proprietary Medicinal Products (CPMP). This led to harmonized guidelines and a mutual recognition process, allowing pharmaceutical companies to submit applications to two European countries for review. This centralized procedure requires a majority of 15 member states, requiring a demonstration of relative advantage to currently marketed therapies. Cost is a significant issue in approval.

Japan

The most successful pharmaceutical products in Japan are manufactured by Japanese companies. While this may be due in part priorities, many companies from other countries have difficulty in Japan because of questions about exchangeability of data and regulatory process due to deference's in medical practice. The Japanese review system was difficult for the 'foreign' pharmaceutical companies to negotiate. This is comprehensively reviewed by Colby [3].

Differing roles of Industry Trade Associations Pharma versus EFPIA versus JPMA

The Pharmaceutical Research Manufacturers Association (PhRMA), European Federation of Pharmaceutical Industry Associations (EFPIA), and Japanese Pharmaceutical Manufacturers Association (JPMA) represent industry interests in the US, Europe, and Japan. However, with globalization of drug development, individual trade group roles have become unclear. The pharmaceutical industry is not harmonized in their

scientific and advocacy efforts towards regulatory agencies on an international basis, making it difficult for representatives to identify issues specific to the FDA.

Rest of World (Row)

The rest of the world is even less consistent in approaches to drug development. However, the World Health Organization (WHO) Conference of Drug Regulatory Authorities and the International Federation of Pharmaceutical Manufacturer Associations and other smaller groups do have some co-ordination and advocacy efforts on behalf of the pharmaceutical industry. Those groups have not been successful in transforming the regulatory procedures in other regions.

Drive to Harmonize

The pharmaceutical industry is focusing on harmonization to reduce the time required to market products and establish common understanding among diverse countries. This consistency helps regulators save resources during the review and approval process, ensuring faster approval of safe and effective medicines. Harmonization also saves resources in regulatory and industrial settings by allowing simultaneous submission, review, and approval of pharmaceuticals worldwide. This benefits regulators by providing consistency in information for review and allowing companies to have a single development and regulatory strategy worldwide. Globalization is essential for maximizing product value and hastening product development in high-profile markets worldwide.

The Basic Principles of the ICH are to

The International Committee for Harmonization of Medicinal Products (ICH) is a global organization that develops scientific consensus through discussions between regulatory and industry experts. It provides wide consultation on draft consensus documents, produces a harmonized text, and gains commitment from regulatory authorities to implement harmonized texts. The ICH also ensures a process for updating and supplementing current guidelines and monitoring their use to maintain harmonization benefits. Each ICH topic is addressed by an Expert Working Group (EWG) with members from six co-sponsors: the EU, Japan, the US, and the US FDA. The EWG follows a vet-step process of consensus building and consultation, with comments from all interested parties being widely sought. The consensus text is then submitted to the Steering Committee, which accepts it. The guideline is then treated as a regulatory draft for consultation in the EU, the US, and Japan. The final text is then recommended for regulatory implementation by the authorities in each region.

Key ICH Guidelines description and current status e1 And E2

Guidelines E1 and E2 set minimum standards for patient exposure in clinical trials, based on the assumption that most new adverse events are detected within the first 6 months. These guidelines are being tested as they are implemented. E2 outlines a safety reporting approach, potentially reducing the burden on the industry.

E5: Ethnic Factors in The Acceptability of Foreign Clinical Data

The E5 document outlines guidelines for using data from one region for regulatory filing in another, primarily affecting Japan and Pan-Asia. The guideline aims to modify Western trials and data for product approval in Japan, but the transition will be slower due to changes in clinical practice and the new concept of site-based audits by Western regulatory authorities. The document took years to draft and has been applied to only a few drugs due to political and complexity issues.

E6: Good Clinical Practice: Consolidated Guideline

The Global Clinical Practice (GCP) is a set of standards for clinical trial conduct, similar to European and U.S. regulations. It outlines standards for source document maintenance, Institutional Review Boards (IRBs), and study performance documentation. The guideline has significantly impacted the clinical trial environment in Japan, shifting focus in regions without GCP-like requirements. It covers ethics committee responsibilities, investigator responsibilities, study protocol principles, investigator brochures, and essential documents for clinical trial documentation.

E9: Statistical Principles For Clinical Trials

The E9 guideline is a set of guidelines for clinical development, primarily focusing on late phase or confirmatory trials. It covers study design, bias reduction, data analysis, safety evaluation, and

reporting of results. The guideline's impact is primarily on sponsor design and analysis of clinical trials used as evidence to support claims and regulatory advice. It aims to maximize the quality and utility of clinical studies in later phases of drug development, focusing on planning, protocol considerations, and bias reduction.

E10: Choice Of Control Group In Clinical Trials

The guideline, developed over four years, addresses complex issues related to the use of placebos in certain areas and diseases, as well as the nature of hypotheses. It focuses on design and interpretation of active control trials and provides a review of clinical trial conduct issues. The guideline emphasizes 'proof of efficacy' in positive controlled trials without a placebo group, addressing this by developing 'assay sensitivity' based on historical evidence of drug effects and appropriate trial conduct. This allows regulators and sponsors to make decisions based on trial objectives.

Discussion of Impacts on Clinical Research and Drug Development

The International Committee on Harmonization (ICH) has made significant gains in drug development by facilitating regional exchange of information and addressing concerns on all sides. Guidelines E5, E6, and E9 have provided structure to key areas in global drug development, particularly in Japan. However, there are concerns that if the guidelines are not implemented quickly enough across all regions, regional practices may diverge, increasing the number of issues in drug development. Implementation is difficult, particularly in the U.S., where sponsors continue to work with FDA staff instead of relying on ICH guidelines. The ICH has a profound impact on new pharmaceutical product development, allowing regulatory authorities and industry to streamline development and set a common quality standard. Collaboration between industry and government is needed to successfully implement a global drug development process, and academic research interests must be coordinated to ensure state-of-the-art science.

APPENDIX

ICH topic number	Guideline title	Status in ICH regions (As of June 2000)
E1	Extent of Population Exposure to Assess Clinical Safety	Adopted 1995
E2A/B/C	Clinical Safety Reporting	Adopted 1995–1998
E3	Structure and Content of Clinical Study Reports	Adopted 1995–1996
E4	Dose Response Information to Support Drug Registration	Adopted 1994
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data	Adopted 1998
E6	Good Clinical Practice	Adopted 1996–1997
E7	Clinical Trials in Special Populations: Geriatrics	Adopted 1993–1994
E8	General Considerations for Clinical Trials	Adopted 1997–1998
E9	Statistical Principles for Clinical Trials	Adopted 1998
E10	Choice of Control Group in Clinical Trials	Step 4
E11	Clinical Investigation of Medicinal Products in the Paediatric Population	Step 3 (Consultation)
E12A	Clinical Evaluation of Drugs by Therapeutic Categories: Antihypertensives	Step 1 (Consensus Building)

Conclusion

The International Harmonization of Clinical Trials (ICH) has achieved success through scientific consensus and regulatory authorities' commitment to harmonised guidelines. The ICH has a focused program for implementation and maintenance, focusing on risk management in post-marketing. The work on efficacy has significantly impacted industry, particularly in clinical trials. ICH quality guidelines have reduced duplicate testing in pharmaceutical development, impacting post-authorisation changes in manufacturing and packaging. The ICH has set up a Global Cooperation Group to disseminate information beyond its three regions, with participation from other regional harmonisation initiatives.

References

1. FDA. FDA Guidelines for the Format and Content of the Clinical and Statistical Sections of a New Drug
Application. FDA, Rockville, MD, U.S.A., 1988.
2. Kaitin KI, Healy EM. The new drug approvals of 1996, 1997, and 1998: drug development trends in the user
fee era. Drug Information Journal 2000; 34:1–14.
3. Colby MA, Birt MP. Negotiating the gray maze: the business of medicine in Japan, 1997.

4. D'Arcy PF, Harron DWG (eds). Proceedings of the First International Conference on Harmonisation. Queen's
University of Belfast, 1992.
5. Nutley C. The value and benefits of ICH to industry. International Conference on Harmonisation for Registration
of Pharmaceuticals for Human Use, IFPMA, PhRMA, 2000.
6. Juillet Y. Thematic Session. International Conferences on Harmonization (ICH): Risks and Bene———————————fits. Special
Session Dedicated to the Harmonization of Studies for the Purpose of the International Registration of Drugs.
The Rationale and Organization of International Conferences on Harmonization, 1997.
7. Showalter J. International Conference on Harmonization. How the United States Food and Drug Administration
will proceed. Journal of Biolaw & Business 1997; 1(2):90 – 93.
8. Barton BL. International Conference on Harmonization – good clinical practices update. Drug Information
Journal 1988; 32:1143–1147.
9. Increased clinical trial sizes could allow earlier detection of AEs, Woodcock says. Health News Daily
1999; 11/8.
10. Brown JS, Kaitin KI, McAuslane N, Thomas KE, Walker SR. Population exposure required to assess clinical
safety: report to the International Conference on Harmonization Working Group. Drug Information Journal
1996; 30:17–27.
11. Goldsmith DI. The impact of the International Conference on Harmonization (ICH) on pharmacoepidemiology
and pharmacovigilance. Pharmacoepidemiology and Drug Safety 1998; 7:289 – 291.
12. Electronic ADR implementation may require more than four years, rms say. The Pink Sheet 1999; 61/8.
13. Dixon JR. The International Conference on Harmonization good clinical practice guideline. Quality Assurance
1998; 6:65–74.
14. CPMP Working Party on Ecacy of Medicinal Products. Biostatistical methodology in clinical trials in
applications for marketing authorizations for medicinal products. Statistics in Medicine 1995; 14:1659 – 1682.
15. CPMP. Draft revision of Note for Guidance on Bioavailability=Bioequivalence.
CPMP/EWP/QWP/1401/98, 1999.
16. Day S, Talbot DJ. Editorial: Statistical guidelines for clinical trials. Journal of the Royal Statistical Society,
Series A 2000; 163:1–3.
17. EFSPI Working Group. Qualified statisticians in the European pharmaceutical industry: report of a European
Federation of Statisticians in the Pharmaceutical Industry (EFSPI) Working Group. Drug Information Journal
1999; 33:407– 415.
18. ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonised Tripartite Guideline.
Statistics in Medicine 1999; 18:1905–1942.
19. Lewis JA. Statistical Principles for Clinical Trials: an introductory note on an international guideline. Statistics
in Medicine 1999; 18:1903–1904.
20. Lewis JA, Jones DR, Roehmel J. Biostatistical methodology in clinical trials – a European guideline. Statistics
in Medicine 1995; 14:1655–1682.
21. Lewis J, Louv W, Rockhold F, Sato T. The impact of the guideline entitled Statistical Principles for Clinical
Trials (ICH E9). Statistics in Medicine 2001; 22:2549 – 2560.
22. MHW. Guideline for the statistical analysis of clinical trials. Ministry of Health and Welfare, Pharmaceutical
Aairs Bureau, Tokyo, Japan, 1992.
23. Phillips A, Ebbutt A, France L, Morgan D. The International Conference on Harmonization Guideline 'Statistical
Principles for Clinical Trials': issues in applying the guideline in practice. Drug Information Journal 2000.
34:337 – 348.

24. JPMA emphasizes importance of biological statisticians. Comline – Emerging Markets of Japan and Eastern
Asia: Health Care & Biotechnology 1998: 1:17.
25. ICH unlikely to lead to Pharma innovation. Market letter 1998, pNA.
26. ICH aims to boost industry support for drug harmonization. Europe Drug & Device Report 2000; 10/4.
27. D'Arcy PF, Harron DWG. Proceedings of The Fourth International Conference on Harmonisation, Brussels 1997.
28. Cone M. Proceedings of The Fifth International Conference on Harmonisation, San Diego 2000.

Cite this article as:
Latif S. Md., Sharma T., Tiwari H. and Chandrul K. K. (2024). A Review on ICH Guidelines. *Int. J. of Pharm. & Life Sci.*, 15(2): 15-20.

Source of Support: Nil
Conflict of Interest: Not declared
For reprints contact: ijplsjournal@gmail.com