INTERNATIONAL CONFERENCE ON HARMONISATION: AN OVERVIEW

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REVIEW ARTICLE

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ABSTRACT

The International Conference on Harmonisation (ICH) is a project that makes together the regulatory bodies of Europe, Japan and the United States and professionals from the pharmaceutical domain in the three areas to discuss scientific and technical views of medicinal product registration. The one aim of ICH is to reduce the need to repeat the testing carried out during the R &D of new Pharmaceuticals by suggesting ways to attain greater harmonisation in the interpretation and application of technical guidelines and requirements for Pharmaceuticals registration. Harmonisation would lead to a more frugal use of human, animal and material resources, and the evacuation of unnecessary time lag in the global development and availability of new Pharmaceuticals while maintaining safeguards on quality, safety, and efficacy, and regulatory duties to protect public health.

Keywords: ICH, QSEM, CTD, MHLW, JPMA, PhMRA, FDA, EU, EFPIA, Quality, Safety, Efficacy, IWG.

INTRODUCTION

ICH denotes for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human consumption".

ICH's logo has been contrived with a view to symbolizing the letters "I", "C", "H" in a manner which embodies the letters in an outline human form. The main colour of the logo is blue, a colour often used with healthcare.

ICH mission:

ICH's mission is to make suggestions towards accomplishing greater harmonisation in the interpretation and application of technical Guidelines and requirements for medicinal product registration.

History of ICH:

Since ICH's origin in 1990, the ICH process has step by step evolved. ICH's first 10 years saw substantial progress in the growth of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics (QSEM). Work was also undertaken on a number of important multidisciplinary subjects, which admitted MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).

As the second tenner the exploitation of ICH Guidelines continued, but with more care given to the following need to:

- Maintain already present Guidelines as science and technology continued to develop;
- Expand communication and spreading of information on ICH Guidelines with non-ICH regions became a key focus;
- Provide the implementation of ICH Guidelines in ICH's own regions;

Entering into its third tenner of activity, ICH's attention is directed towards continuing the benefits of harmonisation outside the ICH regions. Training, active participation of non-ICH regions in Guideline exploitation is seen as key in this effort. (1)

Organisation

a. ICH Steering Committee and its sub-groups

The ICH Steering Committee and its sub-groups are constituted of representatives from 6 parties that represent the regulatory bodies and research-based industry in the USA, Japan and the European Union. (2)

Table 1: Regulatory bodies and research-based Industry

Region	Regulatory Body	Research Based Industry
Japan	**MHLW** - Ministry of Health, Labour and Welfare	**JPMA** - Japan Pharmaceutical Manufacturers Association
Europe	**EU** - European Union	**EFPIA** - European Federation of Pharmaceutical Industries and Associations
USA	**FDA** - Food and Drug Administration	**PhRMA** - Pharmaceutical Research and Manufacturers of America

The ICH Observers have been affiliated with the ICH process from the starting to act as a link with non-ICH countries. These non voting members who are component of the ICH Steering Committee and its sub group include the European Free Trade Association (EFTA), World Health Organization (WHO), and Canada.

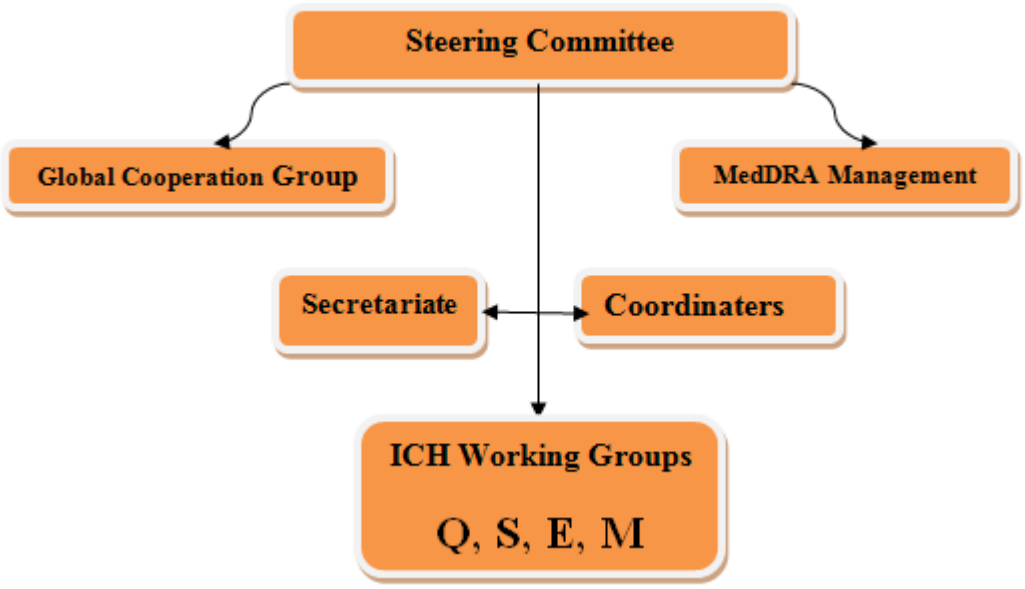

Figure 1: ICH Organizational Structure

ICH Expert Working Groups (EWGs) / Implementation Working Groups (IWGs)

Each of the official 6 ICH members (EFPIA, EU, MHLW, JPMA, PhRMA & FDA) and the ICH perceivers (WHO, EFTA & Health Canada) appoint official representatives to each ICH Working Group. The official membership of ICH Expert Working Groups shall be comprised of one Topic Leader and one Deputy Topic Leader for ICH members and one representative per ICH Observer (EFTA, Health Canada, WHO). Experts are constituted by the ICH regional Coordinators. (3)

Depending on the subject under harmonisation, other specialist may also be invited by the ICH Steering Committee to nominate one representative to take part to the ICH Working Groups.

If accepted by the Steering Committee, one expert can be called from: ICH Regional Pharmacopeias, ICH Interested members (World Self Medication Industry - WSMI, International Generic Pharmaceutical Alliance - IGPA, International Pharmaceutical Excipients Council – IPEC, Biotechnology Industry and Active Pharmaceutical Ingredient Industry - API) as well as Regional Harmonisation Initiatives (RHIs), Individual Drug Regulatory Authorities

(DRAs) and Department of Health (DoH) from non ICH member countries.

WORK PRODUCTS

Guidelines: ICH has originated over 50 harmonised Guidelines aiming at eliminating gemination in the development and registration process, so that a single set of reports can be generated to demonstrate the quality, safety and efficacy of a new pharmaceutical product.

ICH has also developed Questions and Answers (Q&A) when additional guidance and advice were considered required helping the interpretation of certain harmonised tripartite Guidelines.

CTD: The Common Technical Document (CTD) describes the common format for the formulation of a well integrated CTD for applications that will be submitted to regulatory bodies.

eCTD: The Electronic Common Technical Document (eCTD) has been prepared for the electronic submission of the Common Technical Document (CTD) from applicant to drug regulator, in order to provide international electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

MedDRA: The Medical Dictionary for Regulatory Activities (MedDRA) Terminology has also been developed under the aegis of International conference on harmonization.

PROCESS OF HARMONISATION

The ICH Steering Committee is responsible for the administration of ICH. This includes determining on the adoption of every ICH project, whether a new issue, maintenance of an existing Guideline, or a specific implementation works.

Each harmonisation action is started by a Concept Paper which is a short summary of the proposal. As per the category of harmonisation activity a Business Plan may also be needed. Any ICH member or Observer is welcomed to give a proposal for a new ICH implementation activity.

The ICH Steering Committee determines on the adoption of every ICH task and then supports the creation of a EWG/IWG. ICH harmonisation activities categorised into four types. They are Formal ICH Procedure, Questions & Answers Procedure, Revision Procedure and Maintenance Procedure.

a. Formal ICH Procedure (4):

A formal ICH procedure is started with the approval by the SC of a Concept Paper and Business Plan. An Expert Working Group (EWG) with membership as specified by the Concept Paper is afterwards established. At the same time, a Rapporteur (and co-Rapporteur) is officially assigned by the Steering committee and a Regulatory Chair is officially assigned the three regulatory parties of the Steering committee. The EWG works to develop a draft Guideline and bring it through the various steps of the procedure which end in *Step 5* and the implementation in the ICH regions of a Harmonised Tripartite Guideline.

Step 1: Consensus building

The process of unanimity starts when the Steering Committee acquires a Concept Paper as a new topic. *Step 1* is started when the EWG begin the preparation of a unanimity draft of the technical document, depending on the objectives set out in the Concept Paper. Work is conducted via e-mail, telephonic conferences and web conferences. If supported by the Steering committee, the EWG will also meet face to face at the 2 years SC meetings. Meanwhile reports on the progress of the draft technical document are made to the SC on a regular interval.

When consensus is reached among all six party EWG members, the EWG will sign the *Step 1* Experts sheet. The *Step 1* Technical Document with EWG signatures is then presented to the Steering Committee to request acceptance under *Step 2a* of the ICH process.

Step 2a: Confirmation of six-party unanimity on the technical document:

Step 2a is reached when the Steering Committee accepts based on the report of the EWG, that there is enough scientific consensuses on the technical issues for the Technical Document to proceed to the next stage of regulatory

consultation. The unanimity text approved by the Steering Committee is signed-off by the Steering Committee as the *Step 2a* Final Technical Document.

Step 2b: Espousal of the draft Guideline: Based on the technical document, the three ICH regulatory members will take the actions they deem essential to develop the "draft Guideline". The unanimity text approved by the three regulatory ICH members is signed-off by the three regulatory ICH members as *Step 2b* Draft Guideline.

Step 3: Regulatory consultation and Discussion: *Step 3* occurs in three separate stages:

Stage I: Regional regulatory consultation: The Guideline being the scientific unanimity leaves the ICH process and becomes the subject of normal varied regulatory consultation in the three regions. In the European union it is published as a draft Committee for Medicinal Products for Human Use (CHMP) Guideline, in Japan it is interpreted and issued by MHLW for internal and external consultation and in the USA it is issued as draft guidance in the Federal Register.

Regulatory authorities and industry associations in non ICH areas may also annotate on the draft consultation documents by furnishing their comments to the ICH Secretariat.

Stage II: Discussion of regional consultation comments: After receiving all comments from the consultation process, the EWG works to handle the comments received and reach unanimity on what is called the *Step 3* Experts Draft Guideline. If the Rapporteur was from an industry member, until *Step 2b* a new Rapporteur from a regulatory party is appointed, preferably from the same area as the previous Rapporteur. The same procedure depicted in Step 1 is used to address the consultation results. The draft document to be formulated as a result of the Step 3 phase is called Step 3 Experts Draft Guideline.

Stage III: Finalisation of Step 3 Experts Draft Guideline

After due consideration of the consultation results by the EWG, unanimity is reached amongst the experts from the three regulatory ICH members on a revised version of the *Step 2b* Final Draft Guideline, the *Step 3* Experts Draft Guideline is signed by the EWG experts of the three regulatory ICH members. The *Step 3* Document with regulatory EWG signatures is presented to the Steering Committee to request acceptance as *Step 4* of the ICH process.

Step 4: Acceptance of an ICH Harmonised Tripartite Guideline: *Step 4* is completed when the Steering Committee accepts, on the basis of the report from the Regulatory Chair and the regulatory Rapporteur of the EWG, that there is sufficient unanimity on the draft guideline. *Step 4* is reached when the *Step 4* Final Document is signed-off by the SC signatories for the regulatory members of ICH as an ICH Harmonised Tripartite Guideline at *Step 4* of the ICH procedure.

Step 5: Implementation: After completing *Step 4*, the harmonised tripartite Guideline moves immediately to the final step of the process that is the regulatory execution or *Step 5*. *Step 5* is accomplished according to the same national/regional procedures that apply to other regional regulatory requirements, in the, USA, Japan and the European Union.

b. The Questions & Answers Procedure (5):

The Q&As procedure is followed when additional guidance is considered required to help the interpretation of certain ICH Guidelines and ensure a smooth and uniform implementation in the ICH regions and outside.

The Implementation working group works to reach unanimity on a draft Q&A document and makes a recommendation to the Steering committee on whether the document should be a *Step 2b* or a *Step 4*. This recommendation is based on the level of data provided by the answers.

The document then follows the normal way of a *Step 2b/Step 4* Document as per the Formal ICH Process.

c. The Revision Procedure

The Revision Procedure is complied either in cases where the scientific/technical content of an existing ICH Guideline is no longer valid, or in

cases where there is new data to be added with no amendments to the existing ICH Guideline needed. In the case of the latter, the new data can be added in the form of an Addendum or an Annexure to the Guideline in question.

The procedure is started with the endorsement by the Steering committee of a Concept Paper. For revisions a Business Plan is not required. An Expert Working Group (EWG) with membership as specified by the Concept Paper is later established.

The revision process is almost similar to the formal ICH Procedure i.e. 5 ICH Steps. The only change is that the final result is a revised version of a present Guideline, than a new guideline.

The revision of a guideline is contrived by the letter R1 after the usual denomination of the Guideline. When a Guideline is revised more than one time, the document will be named as R2, R3, R4, etc at each new change. In cases where an Addendum or Annexure has been developed, upon reaching *Step 4* the Addendum or Annexure is normally added to the already present guideline resulting in a revised Guideline.

d. The Maintenance Procedure

The maintenance procedure is currently applicable only for alterations to the Q3C Guideline on Impurities: Residual Solvents. In each case the process is used when there is new information to be added or the technical content is no longer valid.

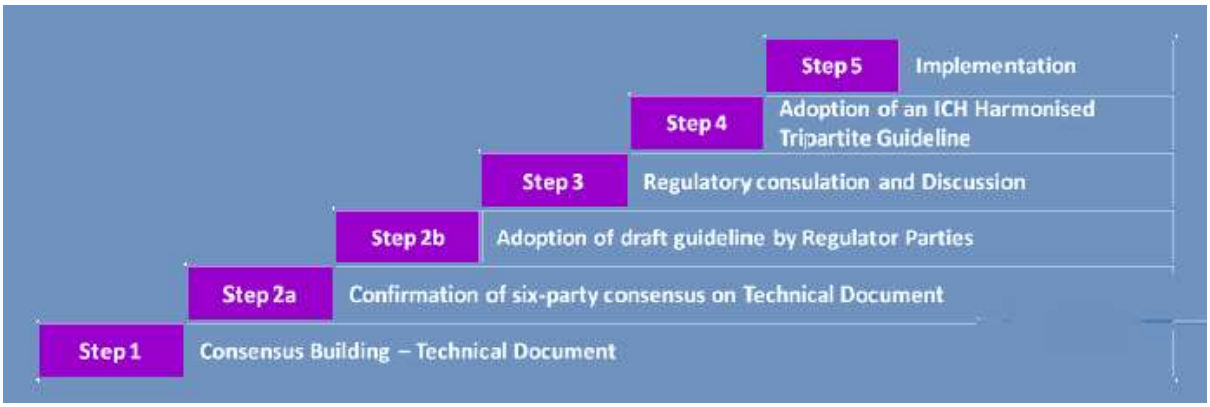

Figure 2: ICH Formal Procedure

ICH guidelines (6): ICH guidelines are mainly categorised into four types they are

1. Quality guidelines
2. Safety guidelines
3. Efficacy guidelines
4. *Multidisciplinary Guidelines*

1. Quality guidelines

Harmonisation attainment in the Quality area include important milestones such as the carrying of stability studies, determining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Table 2: Quality Guidelines

S.No.	Guidelines
1	**Q1A-Q1F Stability:** Q1A: Stability testing of new drug substances and products Q1B: Stability testing: photostability testing of new drug substances and products Q1C Stability testing for new dosage forms Q1D Bracketing and matrixing designs for stability testing of new drug substances and products Q1E Evaluation of stability data Q1F Stability data package for registration applications in climatic zones III and

	IV
2	**Q2 Analytical validation:** Validation of analytical procedures
3	**Q3A-Q3D Impurities:** Q3A Impurities in new drug substances Q3B Impurities in new drug products Q3C Impurities: Guidelines for residual solvents Q3D Impurities: Guidelines for elemental impunities
4	**Q4A-Q4B Pharmacopeias:** Q4A: Pharmacopeial Harmonization Q4B Evaluation and recommendation of pharmacopeial texts for use In the ICH regions
5	**Q5A-Q5E Quality of biotechnological products:** Q5A Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5B Analysis of expression construct in cells used for production of r-DNA derived protein products Q5C Stability testing of biotechnological/ biological products Q5D Derivation and characterization of cell substrates used for production of biotechnological/ biological products Q5E comparability of biotechnlogical / biological products subject to changes in their manufacturing process
6	**Q6A-Q6B Specifications:** Q6A Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances Q6B Test procedures and acceptance criteria for biotechnological/ biological products
7	Q7 Good manufacturing practices for Active pharmaceutical ingredients
8	Q8 Pharmaceutical development
9	Q9 Quality risk management
10	Q10 Pharmaceutical quality system
11	Q11 Development and manufacture of drug substances (Chemical entities and biological entities)

2. Safety guidelines:

ICH has prepared a comprehensive set of safety guidelines to reveal potential risks like carcinogenicity, reprotoxicity and genotoxicity. A recent finding has been a non-clinical testing schema for determining the QT interval prolongation liability.

Table 3: Safety Guidelines

S.No.	Guidelines
1	**S1A-S1C Carcinogenicity studies:** S1: Rodent carcinogenicity studies for human Pharmaceuticals S1A: Need for carcinogenicity studies of Pharmaceuticals S1B: Testing for carcinogenicity of Pharmaceuticals
2	**S2 Genotoxicity studies** S2 (R1) Guidance on genotoxicity testing and data interpretation for Pharmaceuticals intended for human use

3	**S3A-S3B Toxicokinetics and pharmacokinetics:** S3A note for guidance on toxicokinetics: The assessment of systemic exposure in toxicity studies S3B Pharmacokinetics: Guidance for repeated dose tissue distribution studies
4	**S4 Toxicity testing:** S4 Duration of chronic testing in animals (Rodent and non rodent toxicity testing)
5	**S5 Reproductive toxicology:** S5 Detection of toxicity to reproduction for medicinal products and toxicity to male fertility
6	**S6 Biotechnological products:** S6 Preclinical safety Evaluation of biotechnology derived Pharmaceuticals
7	**S7-S7B Pharmacology studies:** S7A Safety pharmacology studies for human Pharmaceuticals S7B The non clinical evaluation of the potential for delayed ventricular repolarization by human Pharmaceuticals
8	**S8 Immunological Studies:** S8 Immunotoxicity studies for human Pharmaceuticals.
9	**S9 Nonclinical evaluation for anti cancer Pharmaceuticals**
10	**S10 Photosafety evaluation of Pharmaceuticals**

3. Efficacy guidelines:

The Efficacy guidelines are concerned with the design, carrying, and safety and reporting of clinical trials. It also gives information related to novel types of medicines derived from biotechnological methods and the use of pharmacogenomics techniques to produce better targeted drug.

Table 4: Efficacy Guidelines

S.No	Guidelines
1	E1 Clinical safety for drugs used in long term treatment
2	E2A-E2F Pharmacovigilance
3	E3 Clinical study reports
4	E4 Dose response studies
5	E5 Ethnic factors
6	E6 Good clinical practice
7	E7 Clinical trials in geriatric population
8	E8 General Consideration for clinical trials
9	E9 Statistical principles for clinical trials
10	E10 choice of control group in clinical trials
11	E11 Clinical trials in paediatric population
12	E12 Clinical evaluation by therapeutic category
13	E14 Clinical evaluation
14	E15 Definitions in pharmacogenetics/ Pharmacogenomics
15	E16 Qualification of genomic biomarkers
16	E17 Multi regional clinical trails
17	E18 Genomic sampling methodologies

4. Multidisciplinary Guidelines*:*

These guidelines contains topics which are unique, and do not fit into one of the Quality, Safety and Efficacy guidelines category. *Multidisciplinary Guidelines* describes about Common Technical Document (CTD), medical terminology (MedDRA), and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

Table 5: Multidisciplinary Guidelines

S.No.	Guidelines
1	M1-MedDRA terminology :(Medical dictionery for regulatory activities)
2	M2 Electronic standerds
3	M3 Non clinical safety studies
4	M4 Common technical document
5	M5 Data elements and standers for drug dictionaries
6	M6 Gene therapy
7	M7 Genotoxic impurities
8	M8 Electronic common technical document (eCTD)

CONCLUSION: As the pharmaceutical industry growing globally day by day, there is a great need of developing guidelines those will create harmonization. ICH is formed to develop and implement harmonised guidelines that will reduce the time required for registration of a pharmaceutical product. ICH guidelines are mainly categorised into four types (Quality, Safety, Efficacy, and *Multidisciplinary*) which will cover almost all areas required for registration of a pharmaceutical product.

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CONFLICT OF INTEREST

Author declares that there are no conflict of interest.

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