INTRODUCTION TO ICH

ICH stands for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use".

ICH's logo has been designed with a view to representing the letters "I", "C", "H" in a manner which embodies the letters in an abstract human form. The principle colour of the logo is blue, a colour often synonymous with healthcare, and which adds an air of vitality and wellbeing to the depicted abstract figure. Purple was chosen as being complementary to blue.

1. ICH mission

ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical Guidelines and requirements for pharmaceutical product registration.

Harmonisation is achieved through the development of ICH Tripartite Guidelines.

2. History

Since ICH's inception in 1990, the ICH process has gradually evolved.

ICH's first decade saw significant progress in the development of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics. Work was also undertaken on a number of important multidisciplinary topics, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).

As the second decade the development of ICH Guidelines continued, but with more attention given to the following need to:

- Maintain already existing Guidelines as science and technology continued to evolve;
- Expand communication and dissemination of information on ICH Guidelines with non-ICH regions became a key focus;
- Facilitate the implementation of ICH Guidelines in ICH's own regions;
- Leverage with other organisations was also acknowledged, particularly for the development of electronic standards.

Entering into its third decade of activity, ICH's attention is directed towards extending the benefits of harmonisation beyond the ICH regions. Training, as well as active participation of non-ICH regions in Guideline development are seen as key in this effort.

3. Organization

a. ICH Steering Committee and its sub-groups

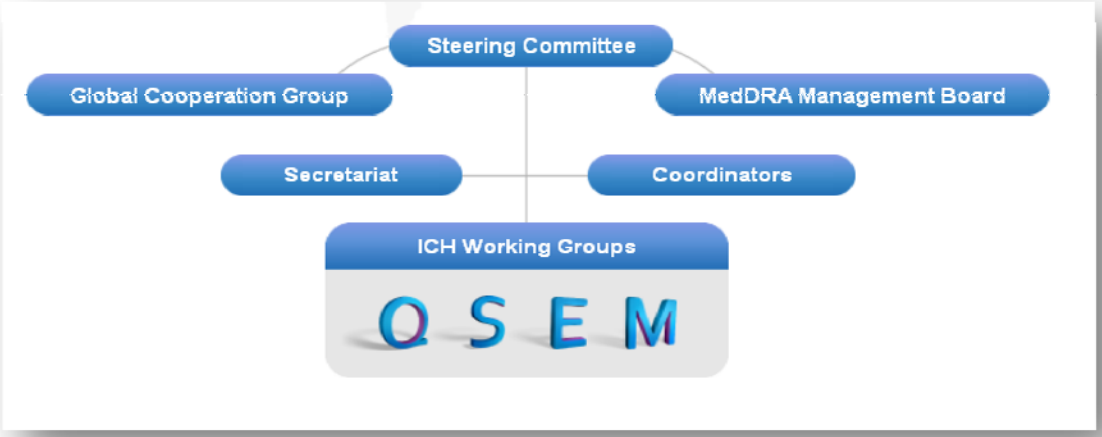

Figure 1: *ICH structure*

The ICH structure consists of the ICH Steering Committee, ICH Coordinators, ICH Secretariat and ICH Working Groups. The ICH Global Cooperation Group (GCG) and the ICH MedDRA Management Board are sub-committees of the ICH Steering Committee (Figure 1).

The ICH Steering Committee and its sub-committees are comprised of representatives from six parties that represent the regulatory bodies and research-based industry in the European Union, Japan and the USA (Table 1 and Figure 2).

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 associated with the ICH process from the beginning to act as a link with non-ICH countries and regions. These non-voting members who are part of the ICH

Steering Committee and its sub-groups include the World Health Organization (WHO), European Free Trade Association (EFTA), and Canada.

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) which has been closely involved with ICH since its inception participates as a non-voting member.

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

Each of the official 6 ICH Parties (EU, EFPIA, MHLW, JPMA, PhRMA & FDA) and the ICH Observers (WHO, EFTA & Health Canada) nominate official representatives to each ICH Working Group. The official membership of EWG/IWG shall be comprised of one *Topic Leader* and one *Deputy Topic Leader* for ICH Parties and one representative per ICH Observer (EFTA, Health Canada, WHO). Experts are nominated by the ICH regional Coordinators.

Depending on the topic under harmonisation, other experts may also be invited by the ICH Steering Committee to nominate one representative to participate to the ICH Working Groups.

If approved by the Steering Committee, one expert can be invited from: ICH Regional Pharmacopeias, ICH Interested Parties (World Self-Medication Industry - WSMI, International Generic Pharmaceutical Alliance - IGPA, Biotechnology Industry, International Pharmaceutical Excipients Council – IPEC 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 countries.

4. Work products

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

ICH has also developed **Questions and Answers** (Q&As) when additional guidance and advice were considered necessary to help the interpretation of certain harmonized tripartite Guidelines.

CTD: The Common Technical Document (CTD) describes the common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities.

eCTD: The Electronic Common Technical Document (eCTD) has been developed for the electronic submission of the Common Technical Document (CTD) from applicant to regulator, in order to facilitate 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 auspices of ICH.

Consideration documents: The Consideration documents have been developed by discussion groups i.e., Gene Therapy Discussion Group (GTDG), and ICH & Women Discussion Group to report specific scientific considerations.

5. Strategy on Training and Capacity Building

The ICH Steering Committee recognises the importance of training in helping to facilitate the implementation of ICH Guidelines both in its own regions and beyond.

ICH regions: The need for oversight on training with respect to ICH Guidelines is generally left to each region's discretion, except for MedDRA, where the ICH MedDRA Management Board oversees the provision of training to MedDRA subscribers worldwide. The Steering Committee acknowledges that from time to time there is benefit in coordinating training activities so as to ensure consistency in the manner in which Guidelines are implemented, particularly where new and complex concepts are introduced.

Non-ICH regions: There is an increasing interest from non-ICH regions in the utilisation of ICH Guidelines, and as a consequence, training and capacity-building have become a key focus of the ICH Global Cooperation Group (GCG).

6. Process of harmonisation

The ICH Steering Committee is responsible for the governance of ICH. This includes deciding on the adoption of every ICH project, whether a new topic, maintenance of an existing Guideline, or a specific implementation work.

Each harmonisation activity is initiated by a Concept Paper which is a short summary of the proposal. Depending on the category of harmonisation activity a Business Plan may also be required.

Any ICH Party or Observer is welcomed to submit a proposal for a new ICH activity.
The ICH Steering Committee decides on the adoption of every ICH project and then endorses the creation of an EWG/IWG.

ICH harmonisation activities fall into 4 categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure.

a. Formal ICH Procedure

A formal ICH procedure is initiated with the endorsement by the SC of a Concept Paper and Business Plan. An Expert Working Group (EWG) with membership as specified by the Concept Paper is subsequently established. The EWG works to develop a draft Guideline and bring it through the various steps of the procedure which culminate in *Step 5* and the implementation in the ICH regions of a Harmonised Tripartite Guideline.

Figure 3: *Various Steps of a formal ICH procedure*

Consensus building: *Step 1* is initiated when the EWG begin the preparation of a consensus draft of the Guideline, based on the objectives set out in the Concept Paper. Work is conducted via e-mail, teleconferences and web conferences. If endorsed by the SC, the EWG will also meet face-to-face at the biannual SC meetings. Interim reports on the progress of the draft are made to the SC on a regular basis.
When consensus on the draft is reached among all six party EWG members, the EWG will sign the *Step 2* Experts sign-off sheet. The *Step 2* Experts Document with EWG signatures is then submitted to the Steering Committee to request adoption under *Step 2* of the ICH process.

Confirmation of six-party consensus*:* *Step 2* is reached when the Steering Committee agrees, based on the report of the EWG, that there is sufficient scientific consensus on the technical issues for the draft Guideline to proceed to the next stage of regulatory consultation. This agreement is confirmed by at least one of the SC members for each of the six ICH parties signing their assent. The consensus text approved by the Steering Committee is signed-off by the Steering Committee as the *Step 2* Final Document.

Regulatory consultation and Discussion: *Step 3* occurs in two distinct stages:

> **Stage I: Regional regulatory consultation**: The Guideline embodying the scientific consensus leaves the ICH process and becomes the subject of normal wide-ranging regulatory consultation in the three regions. In the EU it is published as a draft CHMP Guideline, in Japan it is translated and issued by MHLW for internal and external consultation and in the USA it is published as draft guidance in the Federal Register. Regulatory authorities and industry associations in non-ICH regions may also comment on the draft consultation documents by providing their comments to the ICH Secretariat.
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> **Stage II: Discussion of regional consultation comments**: After obtaining all comments from the consultation process, the EWG works to address the comments received and reach consensus on what is called the *Step 4* Experts Document.

If the Rapporteur was from an industry party, following *Step 2* a new Rapporteur from a regulatory party is appointed, preferably from the same region as the previous Rapporteur.
If both regulatory and industry parties of the EWG are satisfied that the consensus achieved at *Step 2* is not substantially altered as a result of the consultation, or consensus is reached on any alterations, the *Step 4* Experts Document is signed by the EWG regulatory experts.
The *Step 4* Document with regulatory EWG signatures is submitted to the Steering Committee to request adoption as *Step 4* of the ICH process.

Adoption of an ICH Harmonised Tripartite Guideline: *Step 4* is reached when the *Step 4* Final Document is signed-off by the SC signatories for the regulatory parties of ICH as an ICH Harmonised Tripartite Guideline at *Step 4* of the ICH process.

Implementation: Having reached *Step 4*, the harmonised tripartite Guideline moves immediately to the final step of the process that is the regulatory implementation or *Step 5*. *Step 5* is carried out according to the same national/regional procedures that apply to other regional regulatory Guidelines and requirements, in the European Union, Japan and the US.

b. The Q&As Procedure

The Q&As procedure is followed when additional guidance is considered necessary to help the interpretation of certain ICH harmonised tripartite Guidelines and ensure a smooth and consistent implementation in the ICH regions and beyond.

The IWG works to reach consensus on a draft Q&A document and makes a recommendation to the SC on whether the document should be a *Step 2* or a *Step 4*. This recommendation is based on the level of information provided by the answers.
The document then follows the normal path of a *Step 2/Step 4* Document as per the Formal ICH Procedure.

c. The Revision Procedure

The Revision Procedure is followed either in cases where the scientific/technical content of an existing ICH Guideline is no longer up-to-date or valid, or in cases where there is new information to be added with no amendments to the existing ICH Guideline necessary. In the case of the latter, the new information can be added in the form of an Addendum or an Annex to the Guideline in question.
The procedure is initiated with the endorsement by the SC of a Concept Paper. For revisions a Business Plan is not necessary. An Expert Working Group (EWG) with membership as specified by the Concept Paper is subsequently established.
The Revision Procedure is almost identical to the Formal ICH Procedure i.e. 5 ICH Steps. The only difference is that the final outcome is a revised version of an existing Guideline, rather than a new Guideline.
The revision of a Guideline is designated by the letter R1 after the usual denomination of the Guideline. When a Guideline is revised more than once, the document will be named R2, R3, R4, etc at each new revision. In cases where an Addendum or Annex has been developed, upon reaching *Step 4* the Addendum or Annex is normally added to the existing Guideline resulting in a revised Guideline.

d. The Maintenance Procedure

The Maintenance Procedure is currently applicable only for changes to the Q3C Guideline on *Impurities: Residual Solvents* and M2 Recommendations. In each case the procedure is used when there is new information to be added or the scientific/technical content is out-of-date or no longer valid.

7. ICH meetings

The ICH Steering Committee meets on a biannual basis during a week which also includes meetings of the ICH MedDRA Management Board and ICH Global Cooperation Group (GCG). Also occurring on the ICH week is the Regulators Forum, which has participation from both ICH regulators and non-ICH regulatory members of the GCG. These meetings run in parallel of meetings of ICH technical working groups.

Any ICH technical working group face-to-face meeting is subject to decision by the ICH Steering Committee. With a view to keeping down organizational and logistical costs of the ICH Process, EWGs should meet face-to-face only when necessary and justified in the work plan and when sufficient discussion materials are available.

In order for a face-to-face meeting to be considered official, all six ICH parties need to be represented, at least by one delegate.

Figure 4: *ICH week normally adheres to the same schedule of meetings, commencing on Saturday with the ICH MedDRA Management Board meeting and finishing on Thursday with the Steering Committee meeting. These meetings run in parallel of meetings of ICH technical working groups*

Onsite, the ICH Secretariat and the Host organizer provide administrative support to all participants to ensure the smooth running of all meetings (e.g., daily update of meeting schedule, document sign-off, presentation printing).

8. In between meetings

ICH Steering Committee: Ahead of the ICH week, the Secretariat organizes teleconferences

with the Steering Committee, Coordinators, MedDRA Management Board and Global Cooperation Group to prepare for their respective meetings and raise any issues to be addressed at the meetings. At its teleconference, the Steering Committee should reach agreement on which Working Groups will meet at the face-to-face meeting.

Between face-to-face meetings **ICH EWGs/IWGs** are encouraged to make use of modern communication technologies (e-mail, web-conferences, teleconferences, etc.) to progress draft Guidelines. **In order for a teleconference/web-conference to be considered official, all six ICH parties need to be represented, at least by one delegate.**

Working groups could also meet outside the regular ICH SC weeks. These Interim face-to-face meetings should be exceptional, endorsed by the Steering Committee and only when there is an absolute necessity in order for the topic to meet its assigned objectives in time.

ICH Coordinators designated by each of the six co-sponsors and **Focal Points** nominated by RHI/DRA/DoH representatives on the GCG, play a fundamental role in smooth running of ICH. Their roles include to act as the main contact point with the ICH Secretariat and to ensure that any ICH documents are distributed to the appropriate persons within the area of their responsibility (e.g., meeting announcement, registration forms)

In addition to providing support to the ICH Steering Committee, the ICH Secretariat is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Working Group (EWG, IWG, Informal WG) meetings.