ICH

The International Conference on Harmonisaton of Technical Requirements for Registration of Pharmaceuticals for Human Use

Regulatory authorities

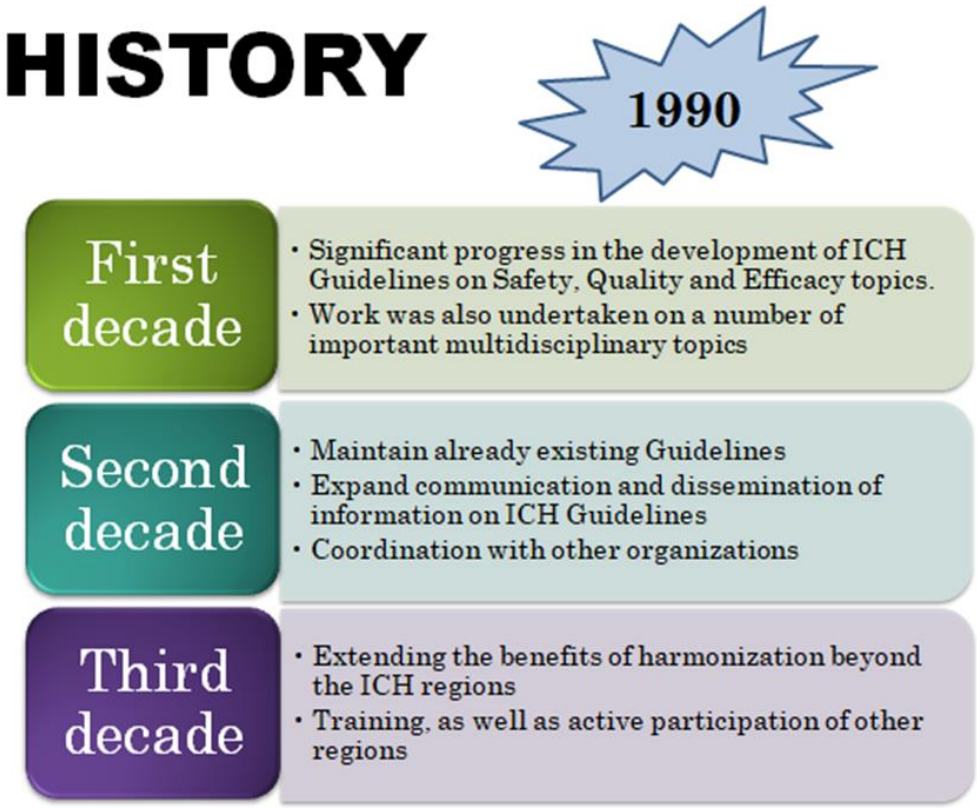
- Europe
- Japan
- United States

MISSION

Make recommendations towards achieving greater harmonization in the interpretation and application of technical Guidelines and requirements for pharmaceutical product registration.

OBJECTIVES

- Harmonisation of technical requirements
- Ensure safety, efficacy and quality of medicines are developed and registered in the most efficient and cost-effective manner.
- Prevent duplication of clinical trials in humans
- Minimize the use of animal testing without compromising safety and effectiveness.



ICH MEMBERS

Region	Regulatory ICH Parties	Industry ICH Parties
Europe	.European Commission (EC) and the European Medicines Agency (EMA)	.The European Federation of Pharmaceutical Industries and Associations(EFPIA)
Japan	.Ministry of Health, Labor and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA)	.The Japan Pharmaceutical Manufacturers Association (JPMA)
US	.Food and Drug Administration (FDA) .Health Products and Food Branch (HPFB) .Swissmedic.	. The Pharmaceutical Research and Manufacturers of America (PhRMA).

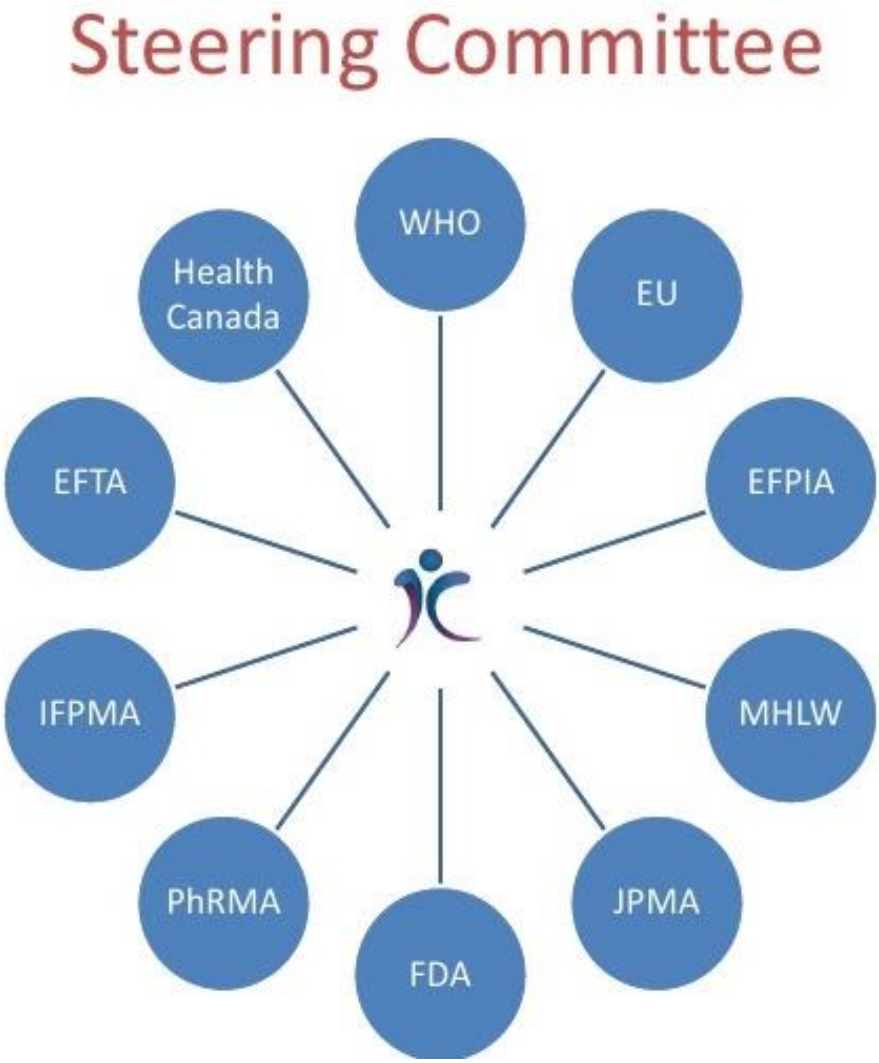
ORGANISATION

The ICH structure consists of

- ICH Steering Committee
- ICH Coordinators
- ICH Secretariat and
- ICH Working Groups.

- **ICH Steering Committee**

The Steering Committee is the body that governs the ICH, determines the policies and procedures for ICH, selects topics for harmonization and monitors the progress of harmonization initiatives. Each of the six ICH parties has two seats on the ICH Steering Committee



- **ICH Coordinators**

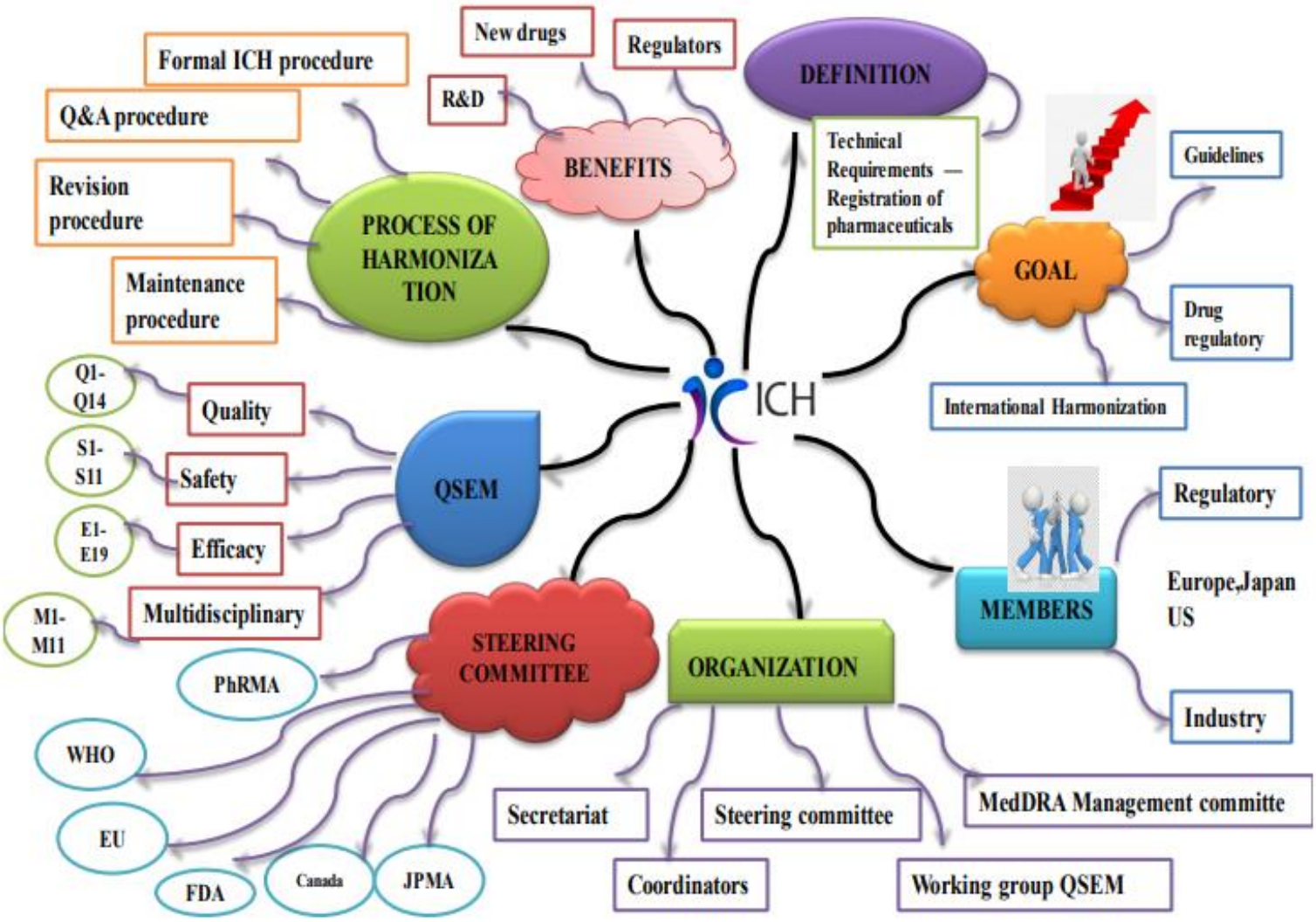
The Co-ordinators are fundamental to the smooth running of the ICH and are nominated by each of the six parties. An ICH Coordinator acts as the main contact point with the ICH Secretariat.

- **ICH Secretariat**

The Secretariat is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Working Group and Discussion Group meetings. Information on ICH Guidelines and the general ICH process can be obtained from the ICH Secretariat.

- **ICH Working Group**

Depending on the type of harmonization activity needed, the Steering Committee will endorse the establishment of one of three types of working group i.e., Expert Working Group (EWG), Implementation Working Group (IWG) or Informal Working Group

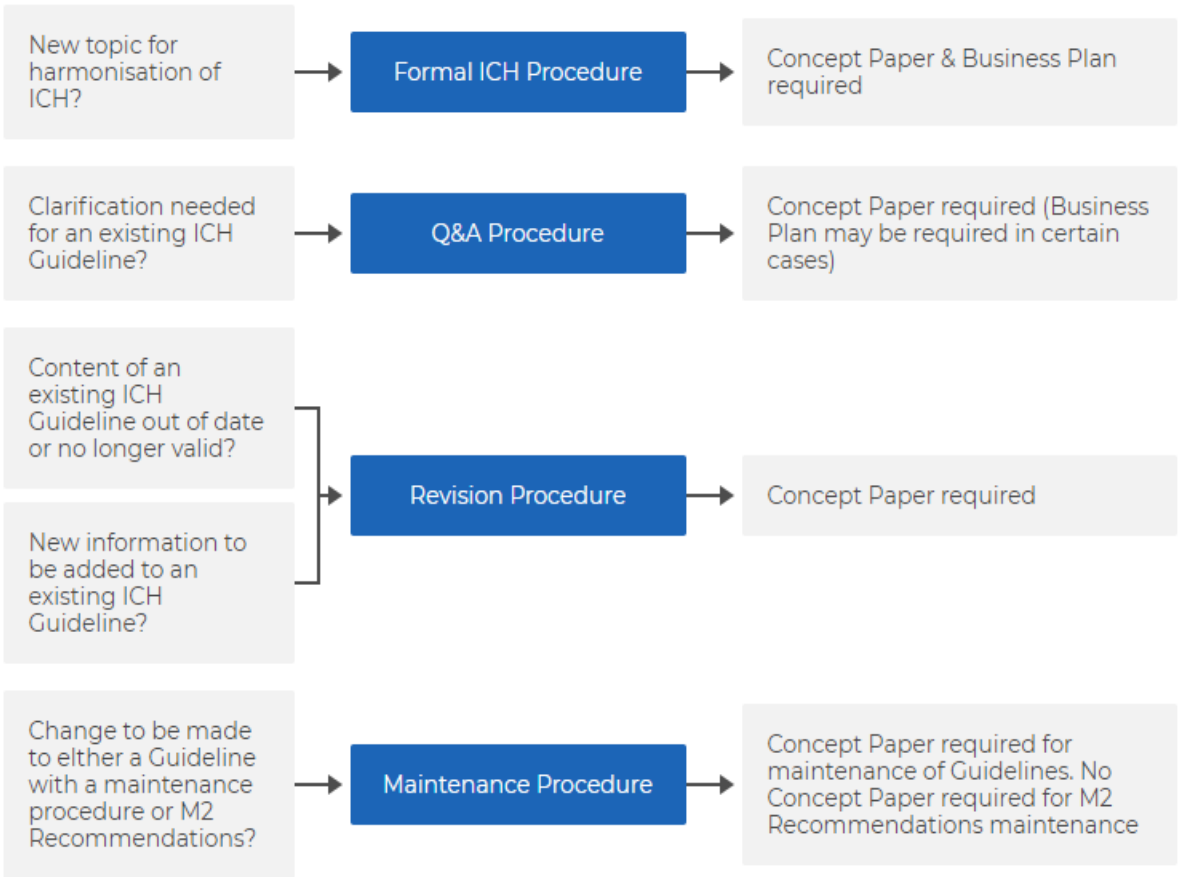


PROCESS OF HARMONIZATION

ICH harmonisation activities fall into 4 categories:

- Formal ICH Procedure
- Q&A Procedure
- Revision Procedure
- Maintenance Procedure

- **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.**
- **The Business Plan outlines the costs and benefits of harmonising the topic proposed by the Concept Paper.**



FORMAL ICH PROCEDURE

The Formal ICH Procedure is a step-wise procedure consisting of 5 steps.

The procedure is initiated with the endorsement by the ICH Assembly of a Concept Paper and Business Plan. An Expert Working Group (EWG) 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 Guideline.

Step 1: Consensus building

The EWG works to prepare a consensus draft of the Technical Document, based on the objectives set out in the Concept Paper. Work is conducted via e-mail, teleconferences and web conferences.

If endorsed by the ICH Management Committee, the EWG will also meet face-to-face at the time of the biannual Assembly meetings. Interim reports on the progress of the draft are made to the Assembly on a regular basis.

When consensus on the draft is reached within the EWG, the technical experts of the EWG will sign the Step 1 Experts sign-off sheet. The Step 1 Experts Technical Document with EWG signatures is then submitted to the Assembly to request adoption under Step 2 of the ICH process.

Step 2a: Confirmation of consensus on the Technical Document

Step 2a is reached when the Assembly agrees, based on the report of the EWG, that there is sufficient scientific consensus on the technical issues for the Technical Document to proceed to the next stage of regulatory consultation.

Step 2b: Adoption of draft Guideline by Regulatory Members

On the basis of the Technical Document, the ICH Regulatory Members will take the actions they deem necessary to develop the draft Guideline.

Step 2b is reached when the Regulatory Members endorse the draft Guideline.

Step 3: Regulatory consultation and Discussion

Step 3 occurs in three distinct stages: regulatory consultation, discussion and finalisation of the Step 3 Expert Draft Guideline.

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 ICH regions. Regulatory authorities and industry associations in other regions may also comment on the draft consultation documents by providing their comments to the ICH Secretariat.

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 3 Experts Draft Guideline.

Stage III - Finalisation of Step 3 Experts Draft Guideline:
If, after due consideration of the consultation results by the EWG, consensus is reached amongst the experts on a revised version of the Step 2b draft Guideline, the Step 3 Expert Draft Guideline is signed by the experts of the ICH Regulatory Members. The Step 3 Expert Draft Guideline with regulatory EWG signatures is submitted to the Regulatory Members of the Assembly to request adoption as Step 4 of the ICH process.

Step 4: Adoption of an ICH Harmonised Guideline

Step 4 is reached when the Assembly agrees that there is sufficient consensus on the draft Guideline.
The Step 4 Final Document is adopted by the ICH Regulatory Members of the ICH Assembly as an ICH Harmonised Guideline at Step 4 of the ICH process.

Step 5: Implementation

Having reached Step 4, the harmonised Guideline moves immediately to the final step of the process that is the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the ICH regions.

QUESTIONS & ANSWERS PROCEDURE

The Q&A Procedure is followed when additional guidance is considered necessary to help the interpretation of certain ICH harmonised Guidelines and ensure a smooth and consistent implementation in the ICH regions and beyond. The additional guidance is usually developed in the form of Questions and Answers "Q&As".

The Q&A Procedure is driven by questions/issues raised by stakeholders, which serve as the basis for the development of model questions for which standard answers are developed. To assist the process, stakeholders are often invited via the ICH website to submit their questions on a specific Guideline.

The procedure is initiated with the endorsement by the ICH Assembly of a Concept Paper. In the case of major implementation activities, the Assembly may also consider the need for Business Plan. An Implementation Working Group (IWG) is subsequently established. The IWG works to reach consensus on a draft Q&A document and makes a recommendation to the Assembly on whether the document should be a Step 2b draft Document published for consultation or a Step 4 final Document published as final without consultation. 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.

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 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 procedure is initiated with the endorsement by the ICH Assembly of a Concept Paper. For revisions, a Business Plan is not necessary. An Expert Working Group (EWG) is subsequently established.

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.

MAINTENANCE PROCEDURE

The Maintenance Procedure is currently applicable for changes to the Q3C, Q3D and M7, Q4B (Annexes) and S5 (Annexes 1 & 2) Guidelines 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.

Maintenance Procedure for Q3C Guideline on Impurities: Residual Solvents and Q3D Guideline for Elemental Impurities

The Maintenance Procedure for Q3C/Q3D is followed when there is a proposal of a Permitted Daily Exposure (PDE) for a new solvent/elemental impurity or a revised PDE for an already classified solvent/elemental impurity.

Maintenance Procedure for M7 Guideline for the Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

The Maintenance Procedure for M7 is followed when there is a proposal of a Acceptale Intakes (AIs) or PDE for a new DNA reactive (mutagenic) impurity or a revised AIs/PDE for an already classified DNA reactive (mutagenic) impurity.

Maintenance Procedure for Annexes of the Q4B Guideline Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

In November 2018, ICH and the Pharmacopoeial Discussion Group (PDG) agreed to collaborate in the maintenance of the current ICH Q4B Annexes. The Maintenance Procedure for Q4B Annexes is triggered by the PDG's sign-off of a revised text which is the subject of an existing Q4B Annex.

Maintenance Procedure for Annexes 1 and 2 of the S5 Guideline on Detection of Toxicity to Reproduction and Development for Human Pharmaceuticals

The Maintenance Procedure for S5 is followed when there is a proposal of a revision to either Annex 1 concerning the recognition and implementation of modifications of in vivo studies resulting from advances in understanding of strengths and weaknesses of these studies in predicting human reproductive risk associated with exposure to pharmaceuticals, and or Annex 2 concerning the reference compound list (integration of new data or compounds), the qualification of alternative assays (improvement of approaches to qualify an alternative assay using the reference compounds list based on gained experience) and/or scenarios of use (inclusion of new scenarios and harmonization of the use of scenarios across regions). The procedure is similar to the Formal ICH Procedure in that it follows the 5 ICH steps.

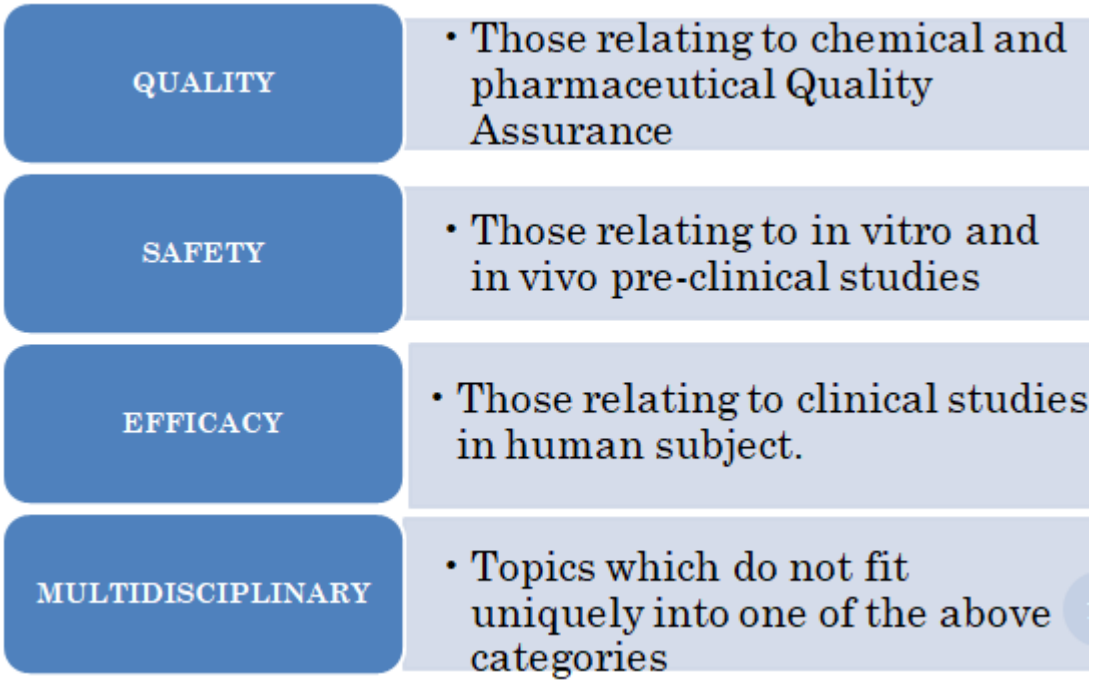
Maintenance Procedure for M2 Recommendations

Due to the Information Technology (IT) nature of the M2 EWG's work on Electronic Standards for the Transfer of Regulatory Information (ESTRI), some of their activities result in Recommendations. These Recommendations do not undergo the formal ICH step process, so as to allow for flexible change as both science, and technologies evolve. They are agreed in the EWG, signed by all Members of the EWG, and are approved by the ICH Assembly.

Each new version of the M2 Recommendations is designated by a different version number.

OVERVIEW OF QSEM

- **Q-Quality**
- **S – Safety**
- **E – Efficacy**
- **M - Multidisciplinary**



QUALITY GUIDELINES

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

- **Q1A- Q1F Stability**
  - Q1A: Stability Testing of New Drug Substances and Products
  - Q1B: 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 & IV
- **Q2 Analytical Validation**
- **Q3A - Q3D Impurities**
  - Q3A: Impurities in New Drug Substances
  - Q3B: Impurities in New Drug Products
  - Q3C: Impurities: Guideline for Residual Solvents
  - Q3D: Guideline for Elemental Impurities
- **Q4 - Q4B Pharmacopoeias**
  - Q4A: Pharmacopoeial Harmonisation
  - Q4B: Evaluation and Recommendation of Pharmacopoeial texts for use in the ICH regions
- **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 the 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 Biotechnological/Biological Products Subject to Changes in their Manufacturing Process.

- **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.
- **Q7 Good Manufacturing Practices for active pharmaceutical ingredients.**
- **Q8 Pharmaceutical Development**
- **Q9 Quality Risk Management**
- **Q10 Pharmaceutical Quality Systems**
- **Q11 Development and Manufacture of Drug Substances (chemical and biological entities)**
- **Q12 Lifecycle Management**
- **Q13 Continuous Manufacturing of Drug Substances and Drug Products**
- **Q14 Analytical Procedure Development**

SAFETY GUIDELINES

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years

- **S1A - S1C Carcinogenicity Studies**
- **S2 Genotoxicity Studies**
- **S3A - S3B Toxicokinetics and Pharmacokinetics**
- **S4 Toxicity Testing**
- **S5 Reproductive Toxicology**
- **S6 Biotechnological Products**

- **S7A - S7B Pharmacology Studies**
- **S8 Immunotoxicology Studies**
- **S9 Nonclinical Evaluation for Anticancer Pharmaceuticals**
- **S10 Photosafety Evaluation of pharmaceuticals**
- **S11 Nonclinical Paediatric Safety**
- **S12 Non clinical biodistribution considerations for gene therapy products.**

EFFICACY GUIDELINES

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

- **E1 Clinical Safety for Drugs used in Long-Term Treatment**
- **E2A - E2F Pharmacovigilance**
- **E3 Clinical Study Reports**
- **E4 Dose-Response Studies**
- **E5 Ethnic Factors**
- **E6 Good Clinical Practice**
- **E7 Clinical Trials in Geriatric Population**
- **E8 General Considerations for Clinical Trials**
- **E9 Statistical Principles for Clinical Trials**
- **E10 Choice of Control Group in Clinical Trials**
- **E11 - E11A Clinical Trials in Pediatric Population**
- **E12 Clinical Evaluation by Therapeutic Category**
- **E14 Clinical Evaluation of QT**
- **E15 Definitions in Pharmacogenetics / Pharmacogenomics**
- **E16 Qualification of Genomic Biomarkers**

- **E17 Multi-Regional Clinical Trials**
- **E18 Genomic Sampling methodologies**
- **E19 Safety Data Collection**
- **E20 Adaptive clinical trials**
- **E21 Inclusion of pregnant and breast-feeding individuals in clinical trials**

MULTIDISCIPLINARY GUIDELINES

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

- **M1 MedDRA Terminology**
- **M2 Electronic Standards**
- **M3 Nonclinical Safety Studies**
- **M4 Common Technical Document**
- **M5 Data Elements and Standards for Drug Dictionaries**
- **M6 Gene Therapy**
- **M7 Mutagenic impurities**
- **M8 Electronic Common Technical Document (eCTD)**
- **M9 Biopharmaceutics Classification System-based Biowaivers**
- **M10 Bioanalytical Method Validation**
- **M11 Clinical electronic Structured Harmonised Protocol**
- **M12 Drug interaction studies**
- **M13 Bioequivalence for immediate release solid dosage forms**
- **M14 Use of real-world data for safety assessment of medicines**
- **M15 General principles for model informed drug development**