

ICH- GUIDELINES OF ICH-Q S E M

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Outline

- ICH
- Mission
- Need to Harmonize
- Structure
- Observers
- Process of Harmonization
- Guidelines Q S E M
- Regulatory Requirements of Following countries:
 - EU
 - MHRA
 - TGA
 - ROW

What is ICH?

- The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry **to discuss scientific and technical aspects of drug registration**. ICH was created in April 1990.

ICH Guidelines

- The ICH topics are divided into **four** categories and ICH topic codes are assigned according to these categories.
 - Quality Guidelines
 - Safety Guidelines
 - Efficacy Guidelines
 - Multi Disciplinary Guidelines

International Conference on Harmonization

- It is a joint initiative involving regulators & industry as equal partners in the scientific & technical discussion of the testing procedure which are required to ensure and assess the Quality, Safety, & efficacy of medicines.

Mission

- To make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, there by reducing duplicating of testing carries out during the research and development of new Human Medicines.

- Harmonization 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.
- 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 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 pharmaco-genetics/genomics techniques to produce better targeted medicines.
- 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).

Need to Harmonize

- Realization was driven by tragedies, such as that with thalidomide in Europe in the 1960s.
- The 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on Quality, Safety and Efficacy of new Medicinal products.
- Divergence in technical requirements from country to country.
- Structure Regulatory Body Industry European union
Ministry of Health, Labor & welfare, Japan an (MHLW) US
Food & Drug Association (USFDA) European Federation of
Pharmaceutical Industries Association s (EFPIA) Japan
Pharmaceutical Association (JPMA) Pharmaceutical
Research & Manufacturers of America (PhRMA).

Observers

- WHO, EFTA (European Free Trade Association), Canada, Australia – Non voting members
- IFPMA (International federations of Pharmaceutical Manufacturers Association) representative

Process of Harmonization

- ICH harmonization activities fall into 4 categories:
 1. Formal ICH procedure: New topic for Harmonization
 2. Q&A Procedure: Clarification on existing guideline
 3. Revision Procedure
 4. Maintenance Procedure

The Guidelines – Q S E M

- Quality (Q1-Q11)
- Chemical & Pharmaceutical QA
- Safety (S1-S10, M3)
- Dealing with in-vitro & in-vivo preclinical testing
- Efficacy (E1-E16 Except E13)
- Clinical study in human beings
- Multidisciplinary (M1-M8)
- Terminology, electronic standards, common documents

Quality

- Q1- Stability
- Q2- Analytical Validation
- Q3- Impurities
- Q4- Pharmacopoeias
- Q5- Quality of Biotechnological Products
- Q6- Specification
- Q7- Good Manufacturing Practice
- Q8- Pharmaceutical Development
- Q9- Quality Risk Management
- Q10- Pharmaceutical Quality System

Safety

- S1- Carcinogenicity Studies
- S2- Geno-toxicity Studies
- S3- Toxicokinetics and Pharmacokinetics
- S4- Toxicity Testing
- S5- Reproductive toxicology
- S6- Biotechnological Product
- S7- pharmacology Studies
- S8- Immunotoxicology Studies
- S9- Nonclinical evaluation for anticancer Pharmaceutical
- S10- Photo safety Evaluation

Efficacy

- E1&E2- Clinical Safety
- E3- Clinical Study Reports
- E4- Dose-response Studies
- E5- Ethnic Factors
- E6- Good Clinical Practice
- E7,E8,E9,E10,E11- Clinical Trials
- E12- Guidelines for Clinical Evaluation by therapeutic Category
- E14- Clinical Evaluation
- E15&E16- Pharmacogenomics

Multidisciplinary

- M1- Med DRA Terminology
- M2- Electronic Standards
- M3- Non-clinical Safety Studies
- M4- CTD
- M5- Data elements & Standards for Drug dictionaries
- M6- Gene Therapy
- M7- Genotoxic impurities
- M8- eCTD

Regulatory Requirements Of Different Countries

European Union

- Intergovernmental political and economic union of 28 European countries having internal single market through the standardized system of laws.
- Established under the name in 1992 by the treaty on European Union.
- European Medicine Agency (EMA) is a decentralized agency of the European Union.
- EMA protects public and animal health by ensuring that all medicines available on the EU market are safe, effective of high quality.
- The agency is responsible for the scientific evaluation, supervision and safety monitoring of the medicines developed by pharmaceutical companies for the use in EU.
- EMA and the member state cooperate share expertise in the assessment of new medicines and of new safety information.

The Role of EMA:

- EMA plays an important role in the regulation of medicines in the EU.
- On the basis of scientific assessments carried out. It grants and refuses, changes and suspends marketing authorizations for medicine that have been submitted via the centralized procedure.
- The European commission can also take action concerning other aspects of medicine regulations:
- **Right of Initiative-** It can propose new legislation for pharmaceutical sector;
- **Implementation-** it can adopt implementing measures as well as oversee the correct application of EU law on pharmaceuticals;
- **Global outreach:** it ensure appropriate collaboration with relevant international partners and promotes the EU regulatory system globally.

MHRA

- Medicine and Healthcare Products Regulatory Agency is an Executive agency of the Department of the Health of United Kingdom.
- MHRA was set up in April, 2003 bringing together the function of medicine Control agency (MCA) and the Medical Device Agency (MDA).
- MHRA is responsible for ensuring that medicines and medical devices work, and are acceptably safe.
- MHRA functions when the company wants to start clinical trials in patients.

Role of MHRA

- Licensing
- Safety and efficacy monitoring
- Enforcement of laws
- Regulations of clinical trials
- Providing information to public and Health Professionals
- MHRA does not regulate dietary supplements, veterinary products and cosmetics.

TGA

- Therapeutic Goods Administration is the regulatory body for therapeutic good in Australia.
- TGA is responsible for conducting assessment and monitoring activities to ensure that therapeutic goods available in Australia are an acceptable standard.
- The objectives of Therapeutic Goods Act 1989, Which came into effect on 15th Feb 1991 is to provide a national framework for the regulation of therapeutic goods in Australia to ensure quality, safety and efficacy of the medicines and ensure quality, safety and performances of medical devices.

- Essentially TG must be entered on Australian Register of Therapeutics goods (ARTG) before supplied in Australia.
- ARTG is computer database of information of TG
- Australia Manufacture all medicines licensed under part 4 of the TG act 1989.
- Once approval for marketing in Australia, ARTG can be identified by AUST R (for registered Medicines) or AUST L (for listed medicine) that appears on packaging of the medicines.
- ROW (Rest of the world): divided the world in 5 regions (ASIA, Emerging Europe/Turkey/Israel, Latin America, Middle East/Africa, Russia/CIS)
- Key functions:
 - 1. Product registration
 - 2. Regulation of drug manufacturing, importation and distribution
 - 3. Adverse drug reaction monitoring
 - 4. Licensing of premises, person and practices.
 - 5. Main goal of the agency is to guarantee the safety, efficacy, and quality of the available drug product.

QUALITY GUIDELINES (Q)

- Harmonization 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

QUALITY GUIDELINES (Q)

- Q1A - Q1F (Stability)
- Q2 (Analytical Validation)
- Q3A - Q3D (Impurities)
- Q4 - Q4B (Pharmacopoeias)
- Q5A - Q5E (Quality of Biotechnological Products)
- Q6A- Q6B (Specifications)
- Q7 (Good Manufacturing Practice)
- Q8 (Pharmaceutical Development)
- Q9 (Quality Risk Management)
- Q10 (Pharmaceutical Quality System)
- Q11 (Development and Manufacture of Drug Substances)
- Q12 (Lifecycle Management)
- Q13 (Continuous Manufacturing of Drug Substances and Drug Products)
- Q14 (ANALYTICAL PROCEDURE DEVELOPMENT)

Q1A -- Q1F (STABILITY)

- Q1A(R2)- Stability Testing of New Drug Substances and Products
- Q1B- Stability Testing : Photo stability 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

Q2 (ANALYTICAL VALIDATION)

- Q2(R1)- Validation of Analytical Procedures: Text and Methodology
- Q2(R2)/Q14- Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

Q3A - Q3D (IMPURITIES)

- Q3A(R2)- Impurities in New Drug Substances
- Q3B(R2)- Impurities in New Drug Products
- Q3C(R7)- Impurities: Guideline for Residual Solvents
- Q3C(R8)- Impurities: Guideline for Residual Solvents
- Q3D(R1)- Guideline for Elemental Impurities
- Q3D(R2)- Revision of Q3D(R1) for cutaneous and transdermal products
- Q3D- Training Implementation of Guideline for Elemental Impurities

SAFETY GUIDELINES (S)

- 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)

SAFETY GUIDELINES (S)

- 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)
- S11 (Nonclinical Paediatric Safety)

S1A - S1C (CARCINOGENICITY STUDIES)

- S1(R1)- Rodent Carcinogenicity Studies for Human Pharmaceuticals
- S1A- Need for Carcinogenicity Studies of Pharmaceuticals
- S1B- Testing for Carcinogenicity of Pharmaceuticals
- S1C(R2)- Dose Selection for Carcinogenicity Studies of Pharmaceuticals
- S2(R1)- Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use S2 (Genotoxicity Studies)

S3A - S3B (TOXICOKINETICS AND PHARMACOKINETICS)

- S3A- Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies.
- S3A Q&As- Questions and Answers: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure - Focus on Micro sampling
- S3B- Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

S4- Duration of Chronic Toxicity Testing in Animals

- S4 (Toxicity Testing) (Rodent and Non Rodent Toxicity Testing)

S5 (REPRODUCTIVE TOXICOLOGY)

- S5(R2)- Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
- S5(R3)- Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals

- S6(R1)- Preclinical Safety Evaluation of Biotechnology- Derived Pharmaceuticals S6 (Biotechnological Products)

S7A - S7B (PHARMACOLOGY STUDIES)

- S7A- Safety Pharmacology Studies for Human Pharmaceuticals
- S7B- The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.
- S8- Immunotoxicity Studies for Human Pharmaceuticals S8 (Immunotoxicology Studies)

S9 (NON-CLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS)

- S9- Non-clinical Evaluation for Anticancer Pharmaceuticals
- S9 Q&As- Questions and Answers: Nonclinical Evaluation for Anticancer Pharmaceuticals
- S10- Photosafety Evaluation of Pharmaceuticals
- S11 (NON-CLINICAL PAEDIATRIC SAFETY)
- S11- Non-clinical Safety Testing in Support of Development of Pediatric Medicines

EFFICACY GUIDELINES (E)

- 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.

EFFICACY GUIDELINES (E)

- 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)
- E19 (Safety Data Collection)
- E20 (Adaptive Clinical Trials)

E1 (CLINICAL SAFETY FOR DRUGS USED IN LONG-TERM TREATMENT)

- E1- The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions

E2A - E2F (PHARMACOVIGILANCE)

- E2A- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
- E2B(R3)- Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports.
- E2B(R3) Q&As- Implementation: Electronic Transmission of Individual Case Safety Reports.
- E2C(R2)- Periodic Benefit-Risk Evaluation Report.
- E2C(R2) Q&As- Questions & Answers: Periodic Benefit-Risk Evaluation Report.
- E2D- Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.
- E2E- Pharmacovigilance Planning.
- E2F- Development Safety Update Report.

E3 (CLINICAL STUDY REPORTS)

- E3- Structure and Content of Clinical Study Reports.
- E3 Q&As R1- Questions & Answers: Structure and Content of Clinical Study Reports.
- E4- Dose-Response Information to Support Drug Registration

E4 (Dose-Response Studies)

E5 (ETHNIC FACTORS)

- E5(R1)- Ethnic Factors in the Acceptability of Foreign Clinical Data
- E5 Q&As (R1)- Questions & Answers: Ethnic Factors in the Acceptability of Foreign Clinical Data

E6(R2)- Good Clinical Practice (GCP)

- E6 (Good Clinical Practice)

E7 (CLINICAL TRIALS IN GERIATRIC POPULATION)

- E7- Studies in Support of Special Populations: Geriatrics.
- E7 Q&As- Questions & Answers: Studies in Support of Special Populations : Geriatrics.

E8- General Considerations for Clinical Trials

- E8(R1)- Revision on General Considerations for Clinical Trials.
- E8 (General Considerations for Clinical Trials)

E9 (STATISTICAL PRINCIPLES FOR CLINICAL TRIALS)

- E9- Statistical Principles for Clinical Trials
- E9(R1)- Addendum: Statistical Principles for Clinical Trials

E10- Choice of Control Group and Related Issues in Clinical Trials

E11 - E11A (CLINICAL TRIALS IN PEDIATRIC POPULATION)

- E11(R1)- Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population
- E11A- Pediatric Extrapolation

E12- Principles for Clinical Evaluation of New Antihypertensive Drugs

- E12 (Clinical Evaluation by Therapeutic Category)

- [36.](#) E14 (CLINICAL EVALUATION OF QT) 36 Ashwini K. Bawankule [?] E14- The Clinical Evaluation of QT/ QTc Interval Prolongation and Proarrhythmic Potential for Non- Antiarrhythmic Drugs [?] E14 Q&As (R3)- Questions & Answers: The Clinical Evaluation of QT/ QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs [?] E14/S7B Q&As- Questions & Answers: Clinical and non-Clinical Evaluation of QT/ QTc Interval Prolongation and Proarrhythmic Potential [?] E15- Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories E15 (Definitions in Pharmacogenetics / Pharmacogenomics)

E16 (QUALIFICATION OF GENOMIC BIOMARKERS)

- E16- Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions.
- **E17- General principles for planning and design of Multi-Regional Clinical Trials.**
- **E18- Genomic Sampling and Management of Genomic Data.**

E19 (SAFETY DATA COLLECTION)

- E19- Optimization of Safety Data Collection
- **E20 (Adaptive Clinical Trials)**

MULTIDISCIPLINARY GUIDELINES (M)

- 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).

- MULTIDISCIPLINARY GUIDELINES (M)
- 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 i.e., eCTD)
- M9 (Biopharmaceutics Classification System-based Bio-waivers)
- M10 (Bio-analytical Method Validation)
- M11 (Clinical electronic Structured Harmonized Protocol i.e., CeSHarP)
- M12 (Drug Interaction Studies)

- M1 (MedDRA TERMINOLOGY)
- MedDRA: Medical Dictionary for Regulatory Activities
- ESTRI: Electronic Standards for the Transfer of Regulatory Information
- M3(R2)- Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.
- M3(R2) Q&As R2- Questions & Answers: Guidance on Non- Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.
- M2 (Electronic Standards)
- M3 (Non-clinical Safety Studies)

- M4 (COMMON TECHNICAL DOCUMENT)
 - CTD: The Common Technical Document
- M5 (Data Elements and Standards for Drug Dictionaries)
- M6- Virus and Gene Therapy Vector Shedding and Transmission
- M7 (MUTAGENIC IMPURITIES)
 - M7(R1)- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
 - M7(R2)- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.
 - Electronic Common Technical Document (eCTD)
- M8 (Electronic Common Technical Document)