ICH GUIDELINES

INTRODUCTION, ORGANIZATION & GUIDELINES

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GENERAL INTRODUCTION:

- Also known as “International Conference on Harmonization of Technical requirements for Pharmaceuticals for Human Use”
- Project, that brings together regulatory authorities of Europe, Japan & US, to discuss scientific & technical aspects of pharmaceutical product registration.

OBJECTIVES OF ICH:

- Harmonization of legislative & technical requirements
- Mutual acceptance of data between Europe, Japan & US
- To reduce cost of research work duplications
- To reduce time-frame for global marketing of newer drugs after approval
- To maintain & formulate guidelines on quality, safety & efficacy-based regulations, for consumer & patient benefits.

LOCATION OF ICH:

- The ICH Secretariat is based in Geneva
- Biennial meetings & conferences of ICH Steering Committee ◊ shuffle between the European Union, Japan & the US.

ICH MEMBERS:

- ICH consists of representatives from 6 parties that represent the regulatory bodies & research-based industry in the EU, Japan & the USA
- In Japan, the members include:

a. Ministry of Health, Labour & Welfare(MHLW)

b. Japan Pharmaceutical Manufacturers Association(JPMA)

- In Europe, the members include:

a. European Union(EU)

b. European Federation of Pharmaceutical Industries and Associations(EFPIA)

ICH MEMBERS:

- In the USA, the members include:

a.Food and Drug Administration(FDA)

b.Pharmaceutical Research and Manufacturers of America(PhRMA)

- Additional members include:

a.Observers from the WHO(represent non-ICH countries & regions)

b.European Free Trade Association(EFTA)

c.Canada

ICH ORGANIZATION

ICH ORGANIZATION:

- ICH structure consists of:

a. ICH steering committee

b. ICH co-ordinators

c. ICH Secretariat

d. ICH Working Groups.

ICH STEERING COMMITTEE:

- Functions of this body include:

a.Governs ICH

b.Determines policies & procedures for ICH

c.Selects topics for harmonization

d.Monitors progress of harmonization initiatives

- Each of the 6 ICH parties ◊ – has 2 seats on the ICH Steering Committee.

ICH CO-ORDINATORS:

- Help in smooth functioning of ICH
- Co-ordinators are nominated by each of the 6 parties
- Acts as the main contact point with the ICH Secretariat.

ICH SECRETARIAT:

- Functions include:

a.Prepares for documentation of meetings of Steering Committee

b.Co-ordinates preparations for Working Group & Discussion Group meetings.

•The following information can be obtained from ICH Secretariat:

a.ICH guidelines

b.General ICH process.

ICH WORKING GROUP:

- Based on type of harmonization activity needed ◊ Steering Committee will endorse establishment of one of the 3 types of working groups, namely:

a. Expert Working Group(EWG)

b. Implementation Working Group(IWG)

c. Informal Working Group.

ICH OPERATION:

- ICH operates through the Steering Committee, with administrative support from Secretariat & Coordinators
- Steering committee meets at least twice a year
- During above meetings ◊ the following measures are adopted:

a. Discussion of new topics for adoption

b. Review of existing topics progress reports

c. Discussion of maintenance & implementation of guidelines.

- Topics identified for harmonization by Steering Committee ◊ selected from Safety, Efficacy, Quality & Multidisciplinary matters.

STEPS IN THE ICH PROCESS:

- There are 5 steps involved
- They include:

A. STEP 1:

- Drafts are prepared ◊ → circulated through many revisions ◊ → leads to assimilation of a "final harmonized draft"

B. STEP 2:

- Draft is signed by EWG ◊ → forwarded to Steering Committee for signing ◊ → signifies acceptance for consultation by each of the 6 co-sponsors

STEPS IN THE ICH PROCESS:

C. STEP 3:

- 3 regulatory sponsors ◊ → initiate their normal consultation process to receive comments.

D. STEP 4:

-Reached, when the Steering Committee agrees that there is sufficient scientific consensus on technical issues

-This endorsement is based on signatures from the 3 regulatory parties to ICH, affirming that the Guideline is recommended for adoption by the regulatory bodies of the 3 regions.

STEPS IN THE ICH PROCESS:

E. STEP 5:

- Guidelines ◊→ incorporated into national/ regional internal procedures(implementation in the 3 ICH regions).

ICH GUIDELINES

ICH GUIDELINE TOPICS:

- ICH guideline topics include:

a.QUALITY

b.EFFICACY

c.SAFETY

d.MULTIDISCIPLINARY.

ICH GUIDELINE TOPICS:

A. QUALITY(Q):

-Refer to topics related to chemical & pharmaceutical Quality Assurance

-Examples include:

i.Stability testing

ii.Impurity testing, etc

ICH GUIDELINE TOPICS:

B. EFFICACY(E):

-Refers to topics, that deal with clinical studies in human subjects

-Include:

a.Dose-Response studies

b.Good Clinical Practices, etc.

ICH GUIDELINE TOPICS:

C. SAFETY(S):

-Refers to topics, that deal with in-vitro & in-vivo pre-clinical studies

-Examples include:

i.Carcinogenicity testing

ii.Genotoxicity testing, etc.

ICH GUIDELINE TOPICS:

D. MULTIDISCIPLINARY(M):

-Refer to topics, that do not fit uniquely into any of the above categories

-Hence also known as “cross-cutting topics”

QUALITY GUIDELINES:

- Consists of :

a. Q1A-Q1F

b. Q2

c. Q3A-Q3D

d. Q4

e. Q5A-Q5E

f. Q6A-Q6B

g. Q7

h. Q8

i. Q9

j. Q10.

Q1A - Q1F Stability

Q2 Analytical Validation

Q3A - Q3E Impurities

Q4A - 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 GUIDELINES:

- Deals with:

a. STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS:

- The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product.

b. PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS:

- Give guidance on the basic testing protocol required to evaluate the light sensitivity and stability of new drugs and products.

Q1A-Q1F GUIDELINES:

c. STABILITY TESTING FOR NEW DOSAGE FORMS:

-Gives guidelines for new formulations of already approved medicines

-Defines the circumstances under which reduced stability data can be accepted.

d. EVALUATION OF STABILITY DATA:

-Addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products.

-Provides recommendations on establishing shelf lives for drug substances and drug products intended for storage at or below “room temperature”.

Q2 GUIDELINES:

- Deals with ANALYTICAL VALIDATIONS:

a. VALIDATION OF ANALYTICAL PROCEDURES- TEXT AND METHODOLOGY:

-The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose

-Gives validation parameters needed for a variety of analytical methods

- Discusses the characteristics that must be considered during the validation of the analytical procedures.

Q2 GUIDELINES:

- Types of Analytical Procedures to be validated include:

a. Identification tests

b. Quantitative tests for impurities content

c. Limit tests for the control of impurities

d. Quantitative tests of the active moiety in samples of drug substance or drug product or other selected components in the drug product.

Q3A-Q3D GUIDELINES:

- Deals with IMPURITIES
- Include:

a. <u>IMPURITIES IN NEW DRUG SUBSTANCES</u>:

-Guideline◊ addresses the chemistry and safety aspects of impurities, including the listing of impurities, threshold limit, identification and quantification

- Impurities are classified into 3:

a.Organic impurities (process- and drug-related)

b.Inorganic impurities

c.Residual solvents .

Q3A-Q3D GUIDELINES:

b. IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS :

- Examples include:

i. Benzene - 2ppm

ii. CCl4- 4ppm

iii. Dichloromethane- 5ppm

iv. Dichloroethane - 8ppm

v. Acetonitrile- 410ppm

vi. Chloroform - 60ppm

vii. Chlorobenzene- 360ppm

Q4 GUIDELINES:

- Deals with PHARMACOPOEIAS
- Includes:

a. EVALUATION AND RECOMMENDATION OF PHARMACOPOEIAL TEXTS FOR USE IN THE ICH REGIONS:

- This document describes a process for the evaluation and recommendations given by the Expert Working Group (EWG), for selecting pharmacopoeial texts to facilitate their recognition by regulatory authorities for use(interchangeable in the ICH regions).

Q5 GUIDELINES:

- Deals with QUALITY OF BIOTECHNOLOGICAL PRODUCTS:
- Includes:

a. <u>VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS DERIVED FROM CELL LINES OF HUMAN OR ANIMAL ORIGIN:</u>

-Concerned with testing and evaluation of viral safety of biotechnology products derived from cell lines of human or animal origin (i.e., mammalian, avian, insect)

- Objective is to provide a general framework for virus testing experiments for the evaluation of virus clearance and the design of viral tests and clearance evaluation studies.

Q5 GUIDELINES:

b. DERIVATION AND CHARACTERISATION OF CELL SUBSTRATES USED FOR PRODUCTION OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS:

- Objective of this guideline is to provide broad guidance on appropriate standards for cell substrates.

Q6 GUIDELINES:

- Deals with SPECIFICATIONS FOR NEW DRUG SUBSTANCES AND PRODUCTS
- Includes:

A. SPECIFICATIONS -TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS:

- Main objective of this guideline is to establish a single set of global specifications for new drug substances & drug products.
- This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria, which play a major role in assuring the quality of the new drug substance and new drug product during shelf life.

Q7 GUIDELINES:

- Deals with Good Manufacturing Practice Guidelines for Active Pharmaceutical Ingredients
- Main objective of this guideline is to maintain the quality of the active pharmaceutical ingredients(API).

Q8 GUIDELINES:

- Deals with PHARMACEUTICAL DEVELOPMENT
- Main objective is to provide guidance on the contents of Pharmaceutical Development of drug products
- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- The Pharmaceutical Development section also describe the type of dosage form and the formulation that are suitable for the intended use.
- Q8 guidelines give information about drug substance, excipients, container closure system, etc.

Q9 GUIDELINES:

- Deals with QUALITY RISK MANAGEMENT
- The purpose of this document is to offer a systematic approach to quality risk management.
- The primary principles of quality risk management include:

a. Evaluation of the risk to quality ◊should be based on scientific knowledge and ultimately link to the protection of the patient

b. Level of effort and documentation of the quality risk management process should commensurate with the level of risk.

Q10 GUIDELINES:

- Deals with PHARMACEUTICAL QUALITY SYSTEM
- Guideline ◊→ provides a comprehensive model for an effective pharmaceutical quality system, with reference to International Standards Organization (ISO) quality concepts
- Also includes applicable Good Manufacturing Practice (GMP) regulations.

SAFETY GUIDELINES:

- Include S1-S9 guidelines
- Mainly deal with in-vivo & in-vitro pre-clinical studies

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

S12 Non-clinical Biodistribution Considerations for Gene Therapy Products

S1A-S1C GUIDELINES:

- Based on CARCINOGENICITY STUDIES
- Includes:

a. GUIDELINES ON THE NEED FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS:

•Provides a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs.

- These recommendations take into account the known risk factors as well as the intended indications and duration of exposure.
- The objectives of carcinogenicity studies are to identify a tumorigenic potential in animals and to assess the relevant risk in humans.

S2 GUIDELINES:

- Mainly based on GENOTOXICITY studies
- Includes:

a. GUIDANCE ON SPECIFIC ASPECTS OF REGULATORY GENOTOXICITY TESTS FOR PHARMACEUTICALS:

-Provides specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results.

- Includes terms related to genotoxicity tests to improve consistency in applications.

S3 GUIDELINES:

- Based on pharmacokinetic & toxicokinetic studies
- Includes:

a. NOTE FOR GUIDANCE ON TOXICOKINETICS- THE ASSESSMENT OF SYSTEMIC EXPOSURE IN TOXICITY STUDIES:

- The primary objective of toxicokinetics is to describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study.
- This document gives guidance on developing test strategies in toxicokinetics and the need to integrate these pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and their relevance to clinical safety issues.

S4 GUIDELINES:

- Deals with “Duration of Chronic Toxicity Testing in Animals”(Rodent and Non-Rodent Toxicity Testing)
- The objective of this guidance is to set out the considerations that apply to chronic toxicity testing in rodents and non rodents as part of the safety evaluation of a medicinal product, that includes:

a.Rodents(a study of 6 months duration)

b.Non-rodents(a study of nine months duration)

S5 GUIDELINES:

- Deals with “Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility”
- This document provides guidance on tests for reproductive toxicity.
- It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.

S6 GUIDELINES:

- Deals with “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”
- This document covers the pre-clinical safety testing requirements for biotechnological products.
- It addresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed, and the impact of antibody formation on duration of toxicology studies.

S7 GUIDELINES:

- Deals with :

A.SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS

B.THE NONCLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS

S8 GUIDELINES:

- Deals with :

a. <u>IMMUNOTOXICITY STUDIES FOR HUMAN PHARMACEUTICALS:</u>

- This guideline addresses the recommendations on nonclinical testing for immunosuppressant.
- The guideline might also apply to drugs in which clinical signs of immunosuppressant are observed during clinical trials and following approval to market.
- The term immunotoxicity in this guideline will primarily refer to immunosuppression, i.e. a state of increased susceptibility to infections or the development of tumors.

S9 GUIDELINES:

- Includes “Nonclinical Evaluation for Anticancer Pharmaceuticals”.

EFFICACY GUIDELINES:

- Refer to topics that deal with clinical studies in human subjects
- Examples include:

a. Dose Response Studies

b. Good Clinical Practices, etc.

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

E21 Inclusion of Pregnant and Breastfeeding Individuals in Cli

EFFICACY GUIDELINES:

- Guidelines mainly deal with:

1. Clinical safety
2. Structure & content of clinical safety reports
3. Dose-Response Information to Support Drug Registration
4. Ethnic Factors in the Acceptability of Foreign Clinical Data
5. Good Clinical Practice : Consolidated Guidelines
6. Guidelines for Clinical Trials
7. Guidelines for Clinical Evaluation by Therapeutic Category
8. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions, etc.

MULTIDISPLINARY GUIDELINES:

- Include:

a. M1 (MedDRA terminology)

b. Electronic Standards for Transmission of Regulatory Information (ESTRI)

c. Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

d. The Common Technical Document .

- 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 and Study Sample Analysis
- M11 Clinical electronic Structured Harmonised Protocol (CeSHarP)
- M12 Drug Interaction Studies
- M13 Bioequivalence for Immediate-Release Solid Oral Dosage Forms
- M14 Use of real-world data for safety assessment of medicines
- M15 General Principles for Model-Informed Drug Development

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THANK YOU!!!!!