ICH

BY

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ICH BACKGROUND

- The International Council for Harmonisation (ICH),is formerly the International Conference on Harmonisation (ICH).
- Unique harmonisation initiative for regulators and pharmaceutical industry.
- Originally founded in 1990.
- The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH.
- Reformed as a non profit legal entity under Swiss Law on 23 October 2015.
- The new ICH Association is a non-profit legal entity under Swiss Law with the aim to focus global pharmaceutical regulatory harmonisation work in one venue.

ICH-Need to harmonise

- The realisation that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions.
- However in many cases the realisation was driven by tragedies, such as that with thalidomide in Europe in the 1960s.
- For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products.
- The industry, at the time, was becoming more international and seeking new global markets; however the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally.
- The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of health care, escalation of the cost of R&D and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.

Purpose of ICH

- Promotion of public health through **international harmonisation** that contributes to:
  - Prevention of unnecessary duplication of clinical trials and post market clinical evaluations
  - Development and manufacturing of new medicines
  - Registration and supervision of new medicines
  - Reduction of unnecessary animal testing without compromising safety and effectiveness
- Accomplished through **Technical Guidelines** that are implemented by the regulatory authorities.

ICH Members

- **Regulatory Members**
  - European Commission (EC)
  - US Food and Drug Administration (FDA)
  - Ministry of Health, Labour and Welfare of Japan (MHLW) also represented by the Pharmaceuticals and Medical Devices Agency (PMDA)
  - Health Canada
  - Swissmedic
  - Agência Nacional de Vigilância Sanitária (ANVISA, Brazil)
  - Ministry of Food and Drug Safety (MFDS, Republic of Korea)
- **Industry Members**
  - European Federation of Pharmaceutical Industries and Associations (EFPIA)
  - Japan Pharmaceutical Manufacturers Association (JPMA)
  - Pharmaceutical Research and Manufacturers of America (PhRMA)
  - International Generic and Biosimilar Medicines Association (IGBA)
  - World Self-Medication Industry (WSMI)
  - Biotechnology Innovation Organisation (BIO)







ICH Observers

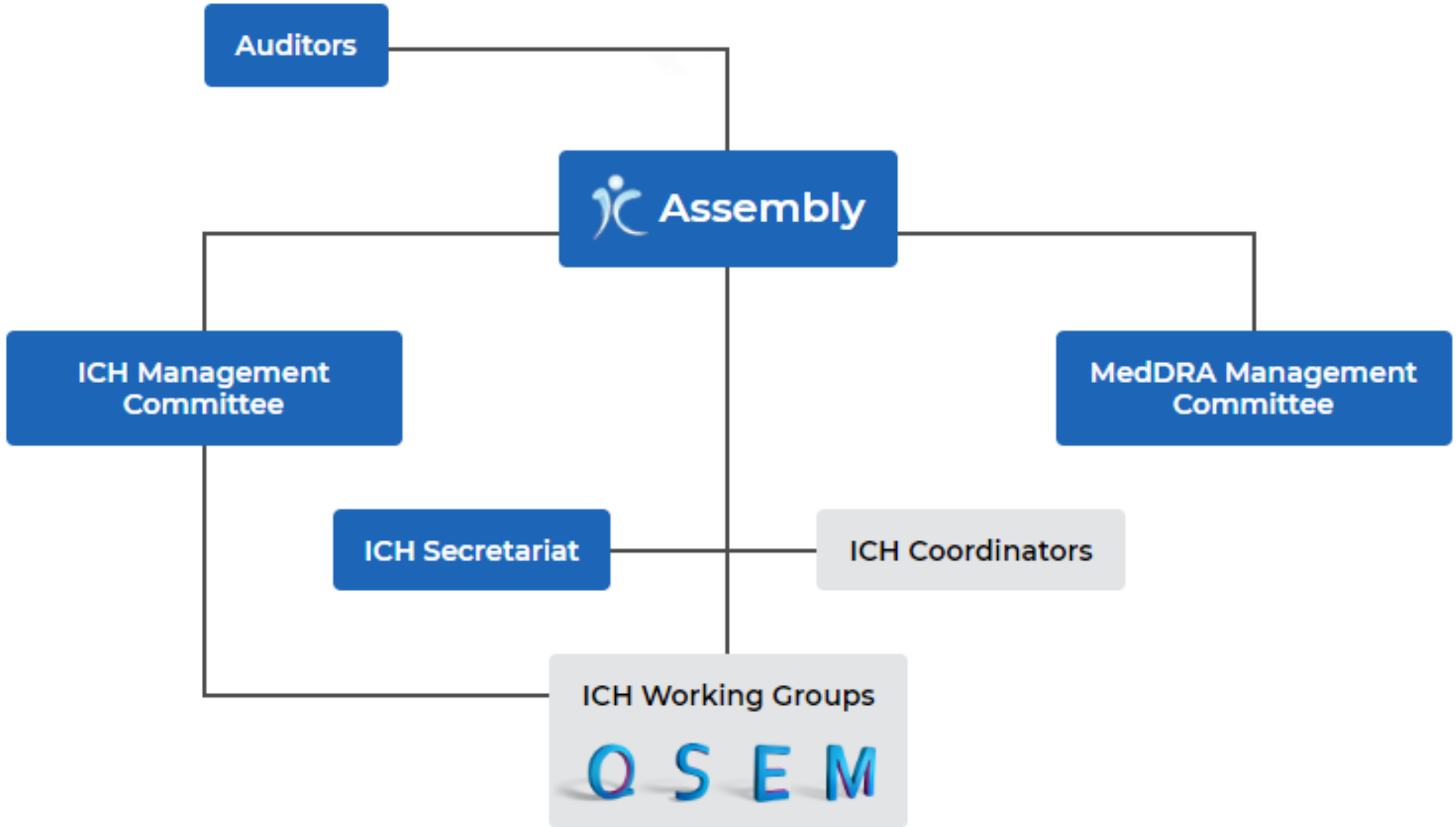
Standing Observers

- The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- The World Health Organization (WHO)

Observers

- Central Drugs Standard Control Organization (CDSCO, India)
- Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED, Cuba)
- Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
- Health Sciences Authority (HSA, Singapore)
- Medicines Control Council (MCC, South Africa)
- National Center for the Expertise of Drugs, Medical Devices and Equipment (National Center, Kazakhstan)
- Roszdravnadzor (Russia)
- Food and Drug Administration (TFDA, Chinese Taipei)
- Therapeutic Goods Administration (TGA, Australia)
- Asia-Pacific Economic Cooperation (APEC)
- Association of Southeast Asian Nations (ASEAN)
- East African Community (EAC)
- Gulf Cooperation Council (GCC)
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- Southern African Development Community (SADC)
- Active Pharmaceutical Ingredients Committee (APIC)
- Council for International Organizations of Medical Sciences (CIOMS)
- European Directorate for the Quality of Medicines & HealthCare (EDQM)
- International Pharmaceutical Excipient Council (IPEC)
- United States Pharmacopeia (USP)

Organisation of ICH



Assembly is :

The overarching body of the Association, composed of all Members that take decisions, regarding Articles of Association, Rules of Procedures, admission of new Members, Adoption of ICH Guidelines, etc.

The Assembly takes decisions by consensus.In the absence of consensus vote in accordance with the Articles of Association, where only regulatory members have the right to vote

Management Committee is:

The body that oversees operational aspects of the Association on behalf of all Members, including administrative and financial matters and oversight of the WGs.

The Management Committee provides Recommendations on the selection of new topics for harmonisation as well as on the adoption, withdrawal or amendments of ICH Guidelines.

Observers:

Limited eligibility criteria for new Observers

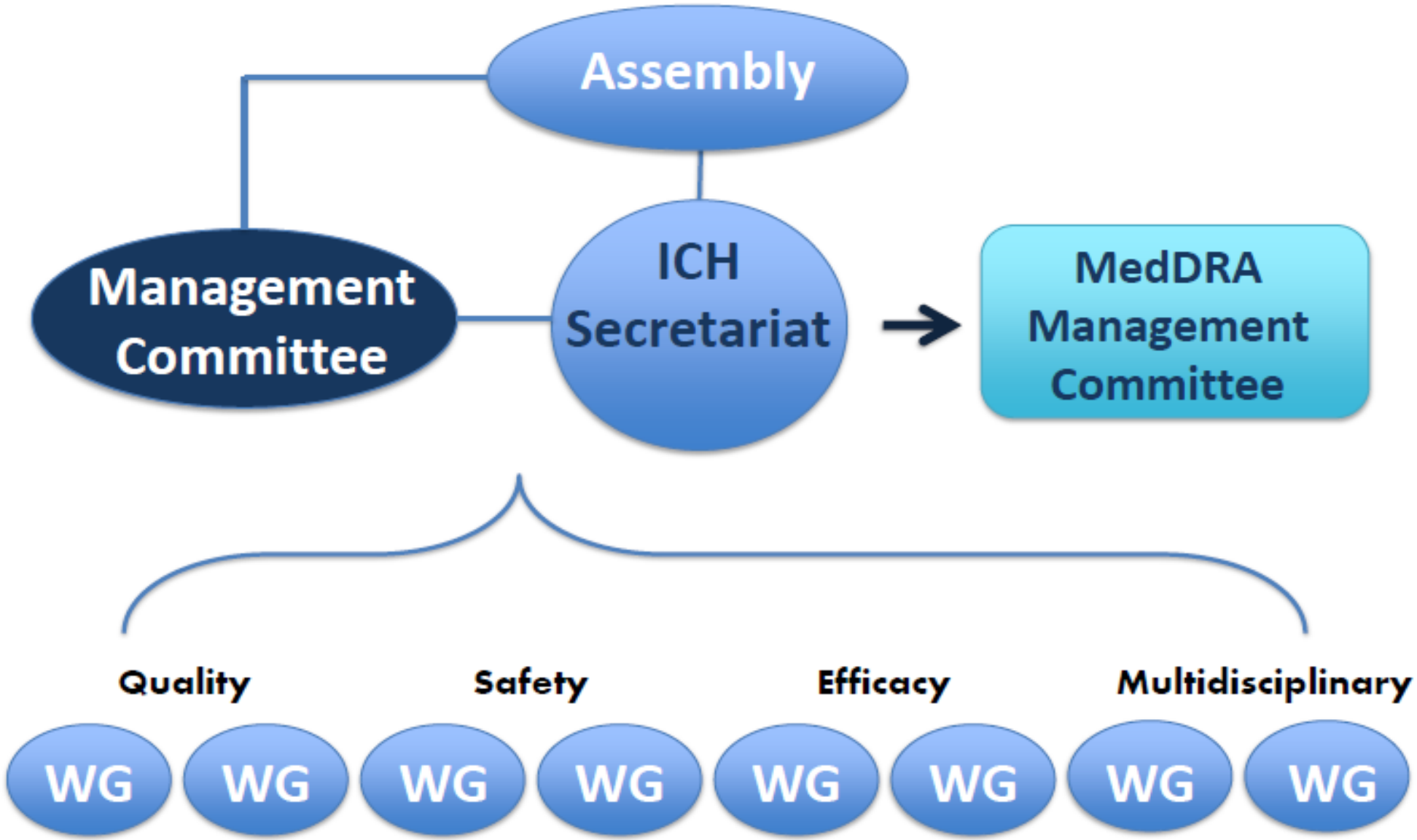
Rights of Observers:

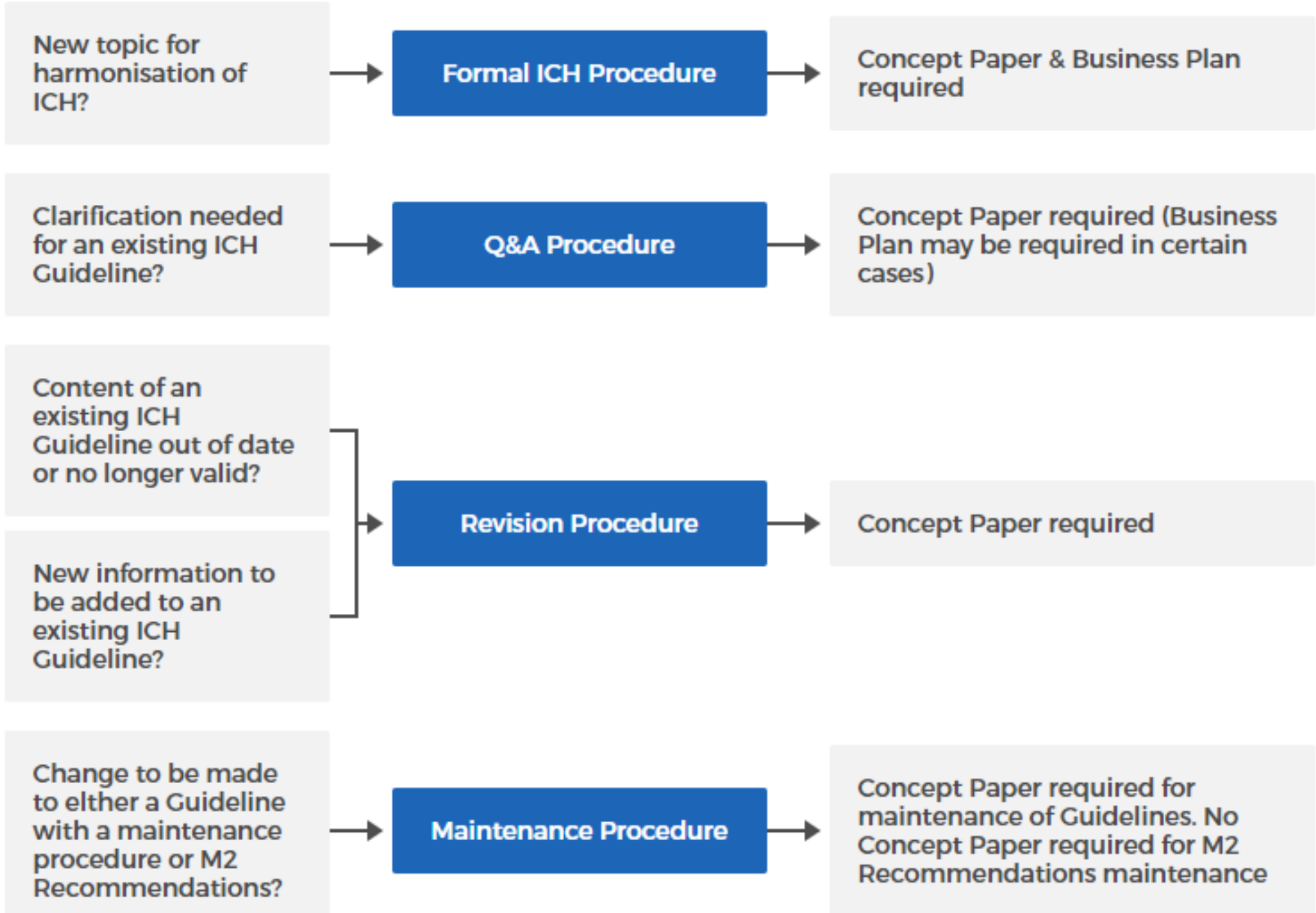
To attend ICH Assembly meetings, but no right to vote or automatically appoint experts in WGs.

Standing Observers (WHO and IFPMA) maintain their right to appoint experts in WGs

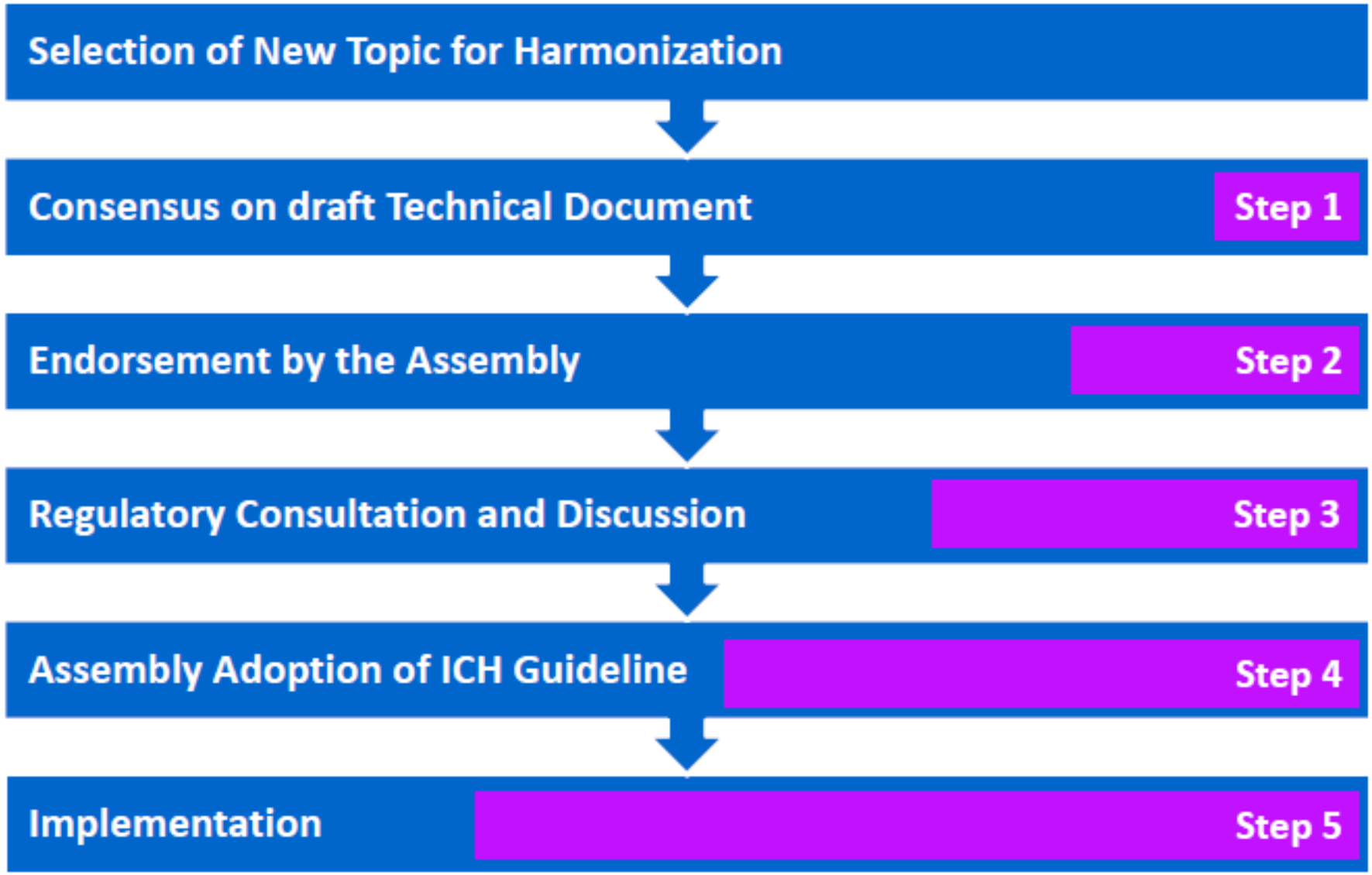
No duties are imposed on Observers

Governance of ICH Association




New topic for harmonisation of ICH?
Formal ICH Procedure
Concept Paper & Business Plan required
Clarification needed for an existing ICH Guideline?
Q&A Procedure
Concept Paper required (Business Plan may be required in certain cases)
Content of an existing ICH Guideline out of date or no longer valid?
New information to be added to an existing ICH Guideline?
Revision Procedure
Concept Paper required
Change to be made to elther a Guideline with a maintenance procedure or M2 Recommendations?
Maintenance Procedure
Concept Paper required for maintenance of Guidelines. No Concept Paper required for M2 Recommendations maintenance

ICH Harmonization Process



- Step 1:
  - The WG works to prepare a consensus draft of the technical document.
- Step2:
- Step 2a:
  - The Members of the ICH Assembly are invited to endorse the technical document
- Step 2b
  - The Regulatory Members of the ICH Assembly are invited to endorse the draft Guideline
- Step 3
  - Public consultation by the ICH Regulatory Members and ICH Secretariat All comments are considered by the WG.
  - Step 3 is finalised once consensus is reached by the regulatory experts of the WG
- Step 4
  - The Regulatory Members of the ICH Assembly adopt the final ICH harmonised Guideline
- Step 5
  - Implementation by the ICH Regulatory Members

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.

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.

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.

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).

ICH Work Products: Harmonised Regulatory Guidelines

Safety

- Carcinogenicity studies
- Genotoxicity studies
- Toxicokinetics and Pharmacokinetics
- Toxicity testing
- Reproductive toxicology
- Biotechnology products
- Pharmacology studies
- Immunotoxicology studies
- Nonclinical evaluation for anticancer pharmaceuticals
- Photosafety evaluation

Efficacy

- Clinical safety
- Clinical study reports
- Dose-response studies
- Ethnic factors
- Good clinical practice
- Clinical trials
- Clinical evaluation by therapeutic category
- Clinical evaluation
- Pharmacogenomics

Quality

- Stability
- Analytical validation
- Impurities
- Pharmacopoeias
- Quality of biotechnology products
- Specifications
- Good manufacturing practice
- Pharmaceutical development
- Quality risk management
- Pharmaceutical quality system
- Development and manufacture of drug substances

Multidisciplinary

- MedDRA terminology
- Electronic standards
- Nonclinical safety studies
- CTD and eCTD
- Data elements and standards for drug dictionaries
- Gene therapy
- Genotoxic impurities

ICH Guidelines-Quality		Status	Date
Q1(R2)	Stability Testing of New Drug Substances and Products	Step 5	2003-02-06
Q1B	Stability Testing : Photostability Testing of New Drug Substances and Products	Step 5	1996-11-06
Q1C	Stability Testing for New Dosage Forms	Step 5	1996-11-06
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	Step 5	2002-02-07
Q1E	Evaluation of Stability Data	Step 5	2003-02-06
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV	Withdrawn	
Q2(R1)	Validation of Analytical Procedures: Text and Methodology	Step 5	2005-11-01
Q2(R2)/Q14	EWG Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation	Step 1	
Q3A(R2)	Impurities in New Drug Substances	Step 5	2006-10-25
Q3B(R2)	Impurities in New Drug Products	Step 5	2006-06-02
Q3C(R6)	Maintenance of the Guideline for Residual Solvents	Step 5	2016-11-09
Q3C(R7)	Maintenance of the Guideline for Residual Solvents	Withdrawn	
Q3C(R8)	Maintenance EWG Maintenance of the Guideline for Residual Solvents	Step 3	
Q3D	Guideline for Elemental Impurities	Step 5	2014-11-12
Q3D	training Implementation of Guideline for Elemental Impurities		
Q3D(R1)	Guideline for Elemental Impurities	Step 5	2019-03-22
Q3D(R2)	Maintenance EWG Revision of Q3D(R1) for cutaneous and transdermal products	Step 1	
Q3E	informal WG Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics		
Q4A	Pharmacopoeial Harmonisation		
Q4B	Annex 1(R1) Residue on Ignition/Sulphated Ash General Chapter	Step 5	2010-09-27
Q4B	Annex 10(R1) Polyacrylamide Gel Electrophoresis General Chapter	Step 5	2010-09-27
Q4B	Annex 11 Capillary Electrophoresis General Chapter	Step 5	2010-06-09
Q4B	Annex 12 Analytical Sieving General Chapter	Step 5	2010-06-09

Q4B	Annex 13 Bulk Density and Tapped Density of Powders General Chapter	Step 5	2012-06-07
Q4B	Annex 14 Bacterial Endotoxins Test General Chapter	Step 5	2012-10-18
Q4B	Annex 2(R1) Test for Extractable Volume of Parenteral Preparations General Chapter	Step 5	2010-09-27
Q4B	Annex 3(R1) Test for Particulate Contamination: Sub-Visible Particles General Chapter	Step 5	2010-09-27
Q4B	Annex 4A(R1) Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter	Step 5	2010-09-27
Q4B	Annex 4B(R1) Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter	Step 5	2010-09-27
Q4B	Annex 4C(R1) Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter	Step 5	2010-09-27
Q4B	Annex 5(R1) Disintegration Test General Chapter	Step 5	2010-09-27
Q4B	Annex 6 Uniformity of Dosage Units General Chapter	Step 5	2013-11-13
Q4B	Annex 7(R2) Dissolution Test General Chapter	Step 5	2010-11-11
Q4B	Annex 8(R1) Sterility Test General Chapter	Step 5	2010-09-27
Q4B	Annex 9(R1) Tablet Friability General Chapter	Step 5	2010-09-27
Q4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions	Step 5	2007-11-01
Q4B	FAQs Frequently Asked Question		
Q5A(R1)	Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin	Step 5	1999-09-23
Q5A(R2)	EWG Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin	Step 1	
Q5B	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products	Step 5	1995-11-30
Q5C	Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products	Step 5	1995-11-30

Q5D	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products	Step 5	1997-07-16
Q5E	Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process	Step 5	2004-11-18
Q6A	Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	Step 5	1999-10-06
Q6B	Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	Step 5	1999-03-10
Q7	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	Step 5	2000-11-10
Q7	Q&As Questions and Answers: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	Step 5	2015-06-10
Q8(R2)	Pharmaceutical Development	Step 5	2009-08-01
Q8/9/10	Q&As (R4) Q8/Q9/Q10 - Implementation	Step 5	2010-11-11
Q9	Quality Risk Management	Step 5	2005-11-09
Q10	Pharmaceutical Quality System	Step 5	2008-06-04
Q11	Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)	Step 5	2012-05-01
Q11	Q&As Questions & Answers: Selection and Justification of Starting Materials for the Manufacture of Drug Substances	Step 5	2017-08-23
Q12	EWG Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management	Step 5	2019-11-20
Q13	EWG Continuous Manufacturing of Drug Substances and Drug Products	Step 1	

ICH Guidelines- Safety		Status	Date
S1(R1)	EWG Rodent Carcinogenicity Studies for Human Pharmaceuticals	Step 1	
S1A	Need for Carcinogenicity Studies of Pharmaceuticals	Step 5	1995-11-29
S1B	Testing for Carcinogenicity of Pharmaceuticals	Step 5	1997-07-16
S1C(R2)	Dose Selection for Carcinogenicity Studies of Pharmaceuticals	Step 5	2008-03-11
S2(R1)	Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use	Step 5	2011-11-09
S3A	Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies	Step 5	1994-10-27
S3A	Q&As Questions and Answers: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure - Focus on Microsampling	Step 5	2017-11-16
S3B	Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies	Step 5	1994-10-27
S4	Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)	Step 5	1998-09-02
S5(R2)	Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility	Step 5	2005-11-01
S5(R3)	EWG Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals	Step 5	2020-02-18
S6(R1)	Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals	Step 5	2011-06-12
S7A	Safety Pharmacology Studies for Human Pharmaceuticals	Step 5	2000-11-08
S7B	The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals	Step 5	2005-05-12
S8	Immunotoxicity Studies for Human Pharmaceuticals	Step 5	2005-09-15
S9	Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 5	2009-11-18
S9	Q&As Questions and Answers: Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 5	2018-04-27
S10	Photosafety Evaluation of Pharmaceuticals	Step 5	2013-11-13
S11	EWG Nonclinical Safety Testing in Support of Development of Paediatric Medicines	Step 5	
S12	EWG Non-clinical Biodistribution Studies for Gene Therapy Products	Step 1	

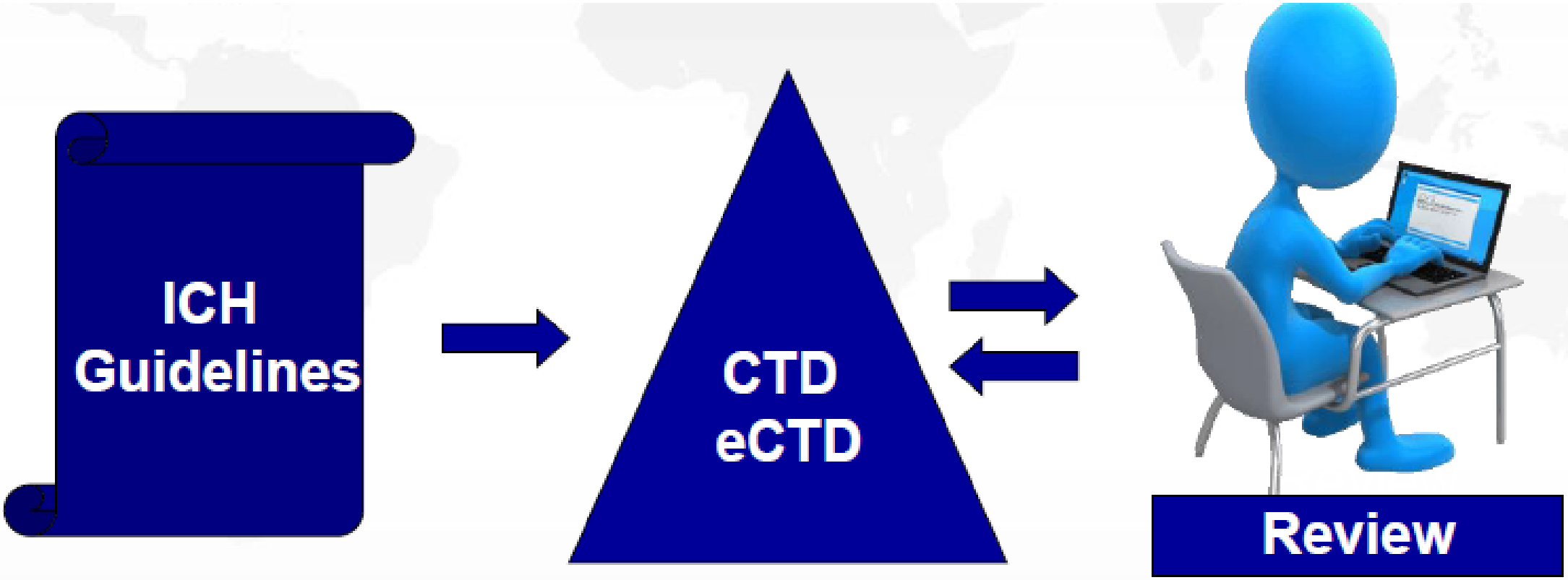
ICH Guidelines-Efficacy		Status	Date
E1	The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions	Step 5	1994-10-27
E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	Step 5	1994-10-27
E2B(R3)	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs)	Step 5	2012-11-01
E2B(R3)	EWG/IWG Electronic Transmission of Individual Case Safety Reports (ICSRs)		
E2B(R3)	Q&As Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports	Step 5	2019-06-01
E2C(R2)	Periodic Benefit-Risk Evaluation Report	Step 5	2012-12-17
E2C(R2)	Q&As Questions & Answers: Periodic Benefit-Risk Evaluation Report	Step 5	2014-03-31
E2D	Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting	Step 5	2003-11-12
E2D(R1)	EWG Post Approval Safety Data Management: Definition and Standards for Expedited Reporting	Step 1	
E2E	Pharmacovigilance Planning	Step 5	2004-11-18
E2F	Development Safety Update Report	Step 5	2010-08-17
E3	Structure and Content of Clinical Study Reports	Step 5	1995-11-30
E3	Q&As (R1) Questions & Answers: Structure and Content of Clinical Study Reports	Step 5	2012-07-06
E4	Dose-Response Information to Support Drug Registration	Step 5	1994-03-10
E5	Q&As (R1) Questions & Answers: Ethnic Factors in the Acceptability of Foreign Clinical Data	Step 5	2006-06-02
E5(R1)	Ethnic Factors in the Acceptability of Foreign Clinical Data	Step 5	1998-02-05
E6(R2)	Good Clinical Practice (GCP)	Step 5	2016-11-10
E6(R3)	EWG Good Clinical Practice (GCP)	Step 1	

E7	Studies in Support of Special Populations: Geriatrics	Step 5	1993-06-24
E7	Questions & Answers: Studies in Support of Special Populations : Geriatrics	Step 5	2010-07-16
E8	General Considerations for Clinical Trials	Step 5	1997-07-17
E8(R1)	EWG Revision on General Considerations for Clinical Studies	Step 3	2019-05-08
E9	Statistical Principles for Clinical Trials	Step 5	1998-02-05
E9(R1)	EWG Addendum: Statistical Principles for Clinical Trials	Step 5	2019-11-20
E10	Choice of Control Group and Related Issues in Clinical Trials	Step 5	2000-07-20
E11(R1)	Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population	Step 5	2017-08-18
E11A	EWG Paediatric Extrapolation	Step 1	
E12	Principles for Clinical Evaluation of New Antihypertensive Drugs		
E14	The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	Step 5	2005-05-12
E14	Q&As (R3) Questions & Answers: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	Step 5	2015-12-10
E14/S7B	IWG Questions & Answers: Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrythmic Potential	Step 1	
E15	Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories	Step 5	2007-11-01
E16	Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions	Step 5	2010-08-20
E17	General principles for planning and design of Multi-Regional Clinical Trials	Step 5	2017-11-16
E18	Genomic Sampling and Management of Genomic Data	Step 5	2017-09-06
E19	EWG Optimisation of Safety Data Collection	Step 3	2019-04-04
E20	EWG Adaptive Clinical Trials	Step 1	

ICH Guidelines-Multidisciplinary		Status	Date
M1	MedDRA - Medical Dictionary for Regulatory Activities	Step 5	1999-01-01
M1	PtC WG MedDRA Points to Consider		
M2	EWG Electronic Standards for the Transfer of Regulatory Information		
M3(R2)	Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals	Step 5	2009-06-11
M4	Q&As (R2) Questions & Answers: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals	Step 5	2011-06-15
M4	Q&As (R3) Questions & Answers: Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use	Step 5	2004-06-10
M4(R4)	Organisation Including the Granularity document that provides guidance on document location and paginations	Step 5	2016-06-15
M4E	Q&As (R4) Questions & Answers: CTD on Efficacy	Step 5	2004-06-10
M4E(R2)	CTD on Efficacy	Step 5	2016-06-15
M4Q	Q&As (R1) Questions & Answers: CTD on Quality	Step 5	2016-08-01
M4Q(R1)	CTD on Quality	Step 5	2002-09-12
M4Q(R1)	IWG Quality		
M4S	Q&As (R2) Questions & Answers: CTD on Safety	Step 5	2003-11-11
M4S(R2)	CTD on Safety	Step 5	2002-12-20
M5	Data Elements and Standards for Drug Dictionaries		
M6	Virus and Gene Therapy Vector Shedding and Transmission		
M7	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	Step 5	2014-06-05
M7(R1)	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	Step 5	2017-06-01
M7(R2)	Maintenance EWG/IWG Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	Step 1	
M8	eCTD v3.2.2 Electronic Common Technical Document (eCTD) v3.2.2	Step 5	2008-07-01
M8	eCTD v4.0 Electronic Common Technical Document (eCTD) v4.0	Step 5	2015-12-10
M8	EWG/IWG Electronic Common Technical Document (eCTD)	Step 5	2018-08-06
M9	Biopharmaceutics Classification System-based Biowaivers	Step 5	2019-11-20
M9	Q&As Q&As on Biopharmaceutics Classification System-based Biowaivers	Step 5	2019-11-20
M10	EWG Bioanalytical Method Validation	Step 3	2019-02-26
M11	EWG Clinical electronic Structured Harmonised Protocol (CeSHarP)	Step 1	
M12	EWG Drug Interaction Studies	Step 1	
M13	Informal WG Bioequivalence for Immediate-Release Solid Oral Dosage Forms		

GCP (Good Clinical Practice)

Clinical trials conducted in one ICH region can be used in other ICH regions by setting the common standards on science and ethics.



CTD brings together all Quality, Safety and Efficacy information in a common, harmonised format, accepted by regulators in all ICH regions. It has revolutionised regulatory review processes for regulators and industry.

MedDRA (Medical Dictionary for Regulatory Activities)

- Highly specific, standardised medical terminology developed by ICH to facilitate sharing of regulatory information
- It is used for registration, documentation and safety monitoring of medical products both before and after marketing authorisation

MedDRA

THANK YOU

ISO SERIES

By

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INTRODUCTION

- ISO 9000 were published by the international organization of standardization based in **Switzerland.** International standard organization is a worldwide federation of national standard bodies from 149 countries,1 from each country.
- It is an in fact an international set of quality standards documented by the members of ISO technical committee 176 and **presented in form of ISO 9000 series of standards.**
- The ISO 9000 series of standards represent the essential requirements that every enterprise needs to address to ensure the consistent production and timely delivery of its goods and services to the market place.
- The ISO 9000 series is **able to provide the quality management benefits to any organization,** with out dictating how the organization is to be run.
- The ISO 9000 series is modified periodically and the original standards were published in 1987, 1st revised in 1994 and the current versions were issued in 2000.

WHY WE NEED ISO 9000 ??

- **ISO 9000 ensures consistent quality:** It helps to maintain consistency of product quality so that criterion “fitness for use” is maintained.
- **ISO 9000 generates profits:** It generates profits by imparting customer confidence, lowering production cost and improving productivity.
- **ISO 9000 is for export:** The driving force behind ISO 9000 is its export prospects. That is it helps in company in becoming a global competitor or to penetrate the world market for example exports of product to 12 members of EEC/EFTA and countries like Singapore, Argentina, Brazil, Mexico etc requires ISO certification. In the near future for business within the country also requires ISO accreditation.

PRINCIPLES OF ISO 9000:

- To plan the means by which the quality will be achieved.
- To document these plans into operating procedures.
- To communicate procedure to every one whose work affects quality.
- To monitor success of efforts.

ELEMENTS OF ISO 9000 SYSTEM

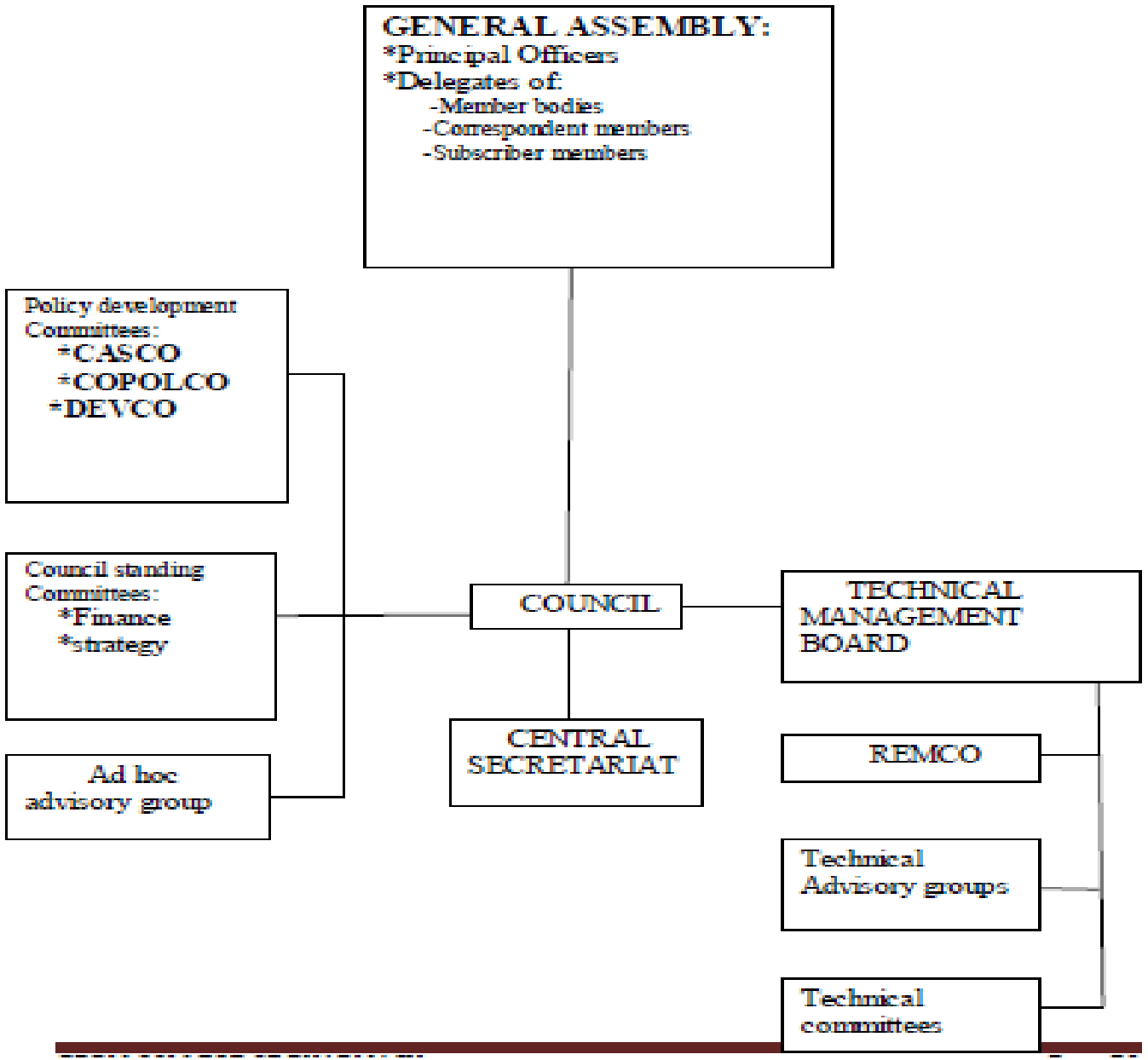
ISO 9000 system standard calls for compliance to the following elements to achieve quality in products and services.

- Management responsibility
- Quality system contract review
- Design control
- Purchasing raw material
- Process control
- Inspection and testing
- Corrective actions
- Handling storage packaging delivery
- Quality records , Training
- Servicing and Statistical techniques

HOW ISO 9000 STANDARDS BENEFIT THE SOCIETY

- **For business:** The wide spread adoption of International Standards means that suppliers can base the development of their products and services on specifications that have wide acceptance in their sectors. This in turn means that business using International Standards are increasingly free to compete on many more markets around the world.
- **For customers:** The worldwide compatibility of technology which is achieved when products are based on International Standards brings them an increasingly wide choice of offers and they also benefit from the effects of competition among suppliers.
- **For governments:** International Standards provide the technological and scientific bases underpinning health, safety and environmental legislation.
- **For developing countries:** International Standards that represent an international consensus on the state of the art constitute an important source of technological know-how. By defining the characteristics that products and services will be expected to meet on export markets, International Standards give developing countries a basis for making the right decisions when investing their scarce resources and thus avoiding squandering them.
- **For consumers:** Conformity of products and services to International Standards provides assurance about their quality, safety, and reliability.
- **For everyone:** International Standards can contribute to the quality of life in general by ensuring that the transport, machinery and tools we use are safe.
- **For the planet**: We inhabit, International Standards on air, water and soil quality, and on emissions of gases and radiation, can contribute to efforts to preserve the environment.

STRUCTURE OF ISO



- All strategic decisions are referred to the ISO members, who meet for an annual General Assembly.
- The proposals put to the members are developed by the ISO council, drawn from the membership as a whole which resembles the board of directors of a business organization.
- ISO council meets two times a year and its membership is rated to ensure that it is representative of ISO's membership. Operations are managed by a secretary – General, which is a permanent appointment.
- The secretary general reports to the ISO council the latter being chaired by the president who is a prominent figure in standardization or in business, elected for 2 years.
- The Secretary –General is based at ISO Central Secretariat in Geneva, Switzerland with a compact staff which provides administrative and technical support to ISO members.

CONSTITUENTS OF ISO 9000 SERIES QUALITY SYSTEM

Quality system	Title	What it contains
ISO 9000	Quality management and Quality assurance standards	Guidelines for selection and use of standards.
ISO 9001	Quality systems	Model for quality assurance in design, development, production, installation, and servicing.
ISO 9002	Quality systems	Model for Quality Assurance in production, installation, and servicing
ISO 9003	Quality systems	Model for Quality Assurance in final inspection and testing.
ISO 9004	Quality Management and Quality system	Guidelines for designing quality system and its management.

1. ISO 9000: “Quality Management and quality assurance standards

ISO 9000 defines terms and provides overall guidance on the selection and application of these three main standards (ISO 9001, ISO 9002, ISO 9003) it is a descriptive document and is not part of the registration/ certification process.

ISO 9000 consists of 4 parts (subclasses).

Sub class	What it deals
ISO 9000-1	Guidelines for selection and use
ISO 9000-2	Generic guidelines for the application of ISO 90001-ISO 9003
ISO 9000-3	Guidelines for the application of ISO 90001 to the development supply and maintenance of software.
ISO 9000-4	Guidelines to the dependability programmed management.

2. ISO 9001: Quality systems-“Model for Quality Assurance in Design, Development, Production, Installation, Servicing”

The emphasis is on product design and the main application is to those contractual arrangements that involve product design and development in addition to production, installation, or servicing; it applies also where product requirements are defined in functionality or performance. The design and production of customized packing and production of OTC medicines could be addressed by this standard.

Management Responsibility” : The involvement and commitment of top management is required in defining quality policy and objectives.

“Purchasing” : This section, defines how to assure the quality of materials purchased by suppliers; it goes one step further back in the contract/ supply chain. It refers to definitions of specifications, selection of subcontracts, respective evaluation to be performed by the supplier and discuss about on retention of records.

“Product identification” This requires traceability of the product by the supplier through the various stages of the production, delivery, and installation.

Process control” This requires that production should be planned and implemented via approved process , during which should be appropriate control.

“Inspection and Testing” The supplier is responsible for assuring the quality of purchased materials/components from subcontractors.

“Corrective and Preventive action “ This expands with respective to the section required to correct and prevent future occurrences.

“Quality system” A documented quality system is too implemented and maintained, usually in the format of a quality manual.

“Contract review” A contract should exist that clearly defines the quality requirements and assures that supplier has the capability of meeting these requirements.

“Design control” : This section along with ISO 9004-1, provides the extensive guidance with respect to design control.

“Control of quality records” This requires the retention of records relating to product quality for an agreed period of time.

“Internal Quality Audits” Documented internal audits are to be performed, in accordance with a defined plan to provide assurance of ongoing compliance

Training” Training is required for all personal engaged in quality related activities, and records are to be maintained.

“Servicing” This brief section requires that where service is part of a contractual arrangement there shall be procedures to evaluate and report on performance

“Statistical techniques” Statistical techniques are to be applied to verify process capability and product characteristics. ISO 9004-1 defines possible areas of application market analysis, product design, stability, process control and capability, sampling, and data analysis.

3. ISO 9002: Quality systems- “Model for quality assurance in production, installation and servicing”

- This standard applies to more routine production where product quality requirements can be adequately expressed in terms of specifications. In these situations design criteria are either unimportant or have been previously resolved. Confidence in supplier processing capability is required.
- The production and supply of recipients and bulk pharmaceutical chemicals could fit into this standard, which is probably the most extensively applied ISO9000 standard in the pharmaceutical industry. ISO 9002 is identical to ISO 9001 with the conclusion of the section on design control.

4. ISO 9003: Quality systems- “Model for quality assurance in final inspection and test”

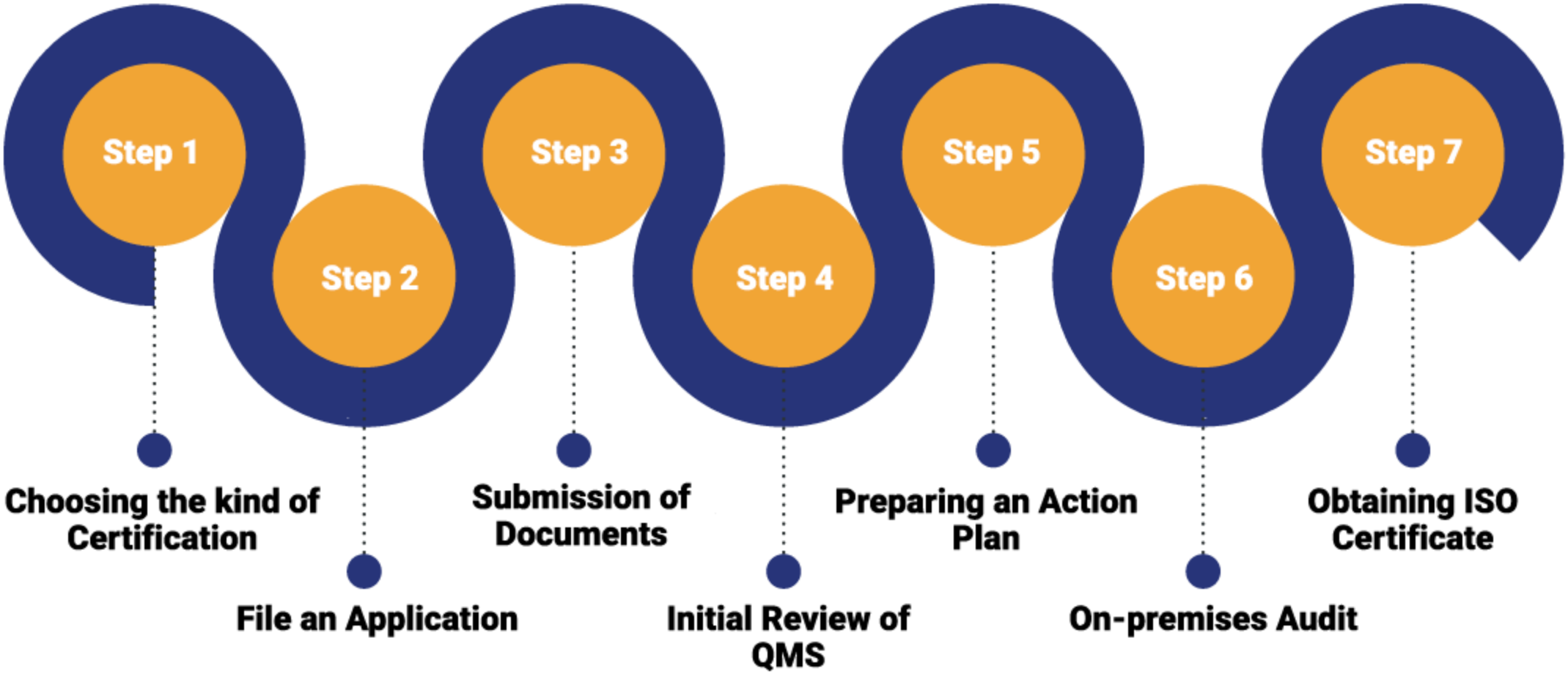
- This standard applies to contractual arrangements that rely on a supplier’s ability to perceive a situation where this would apply within the pharmaceutical industry where quality must be built into the design and production of the possible situation could be for the evaluation of production with the low level defectives where inspection is used to cull out the defectives.
- The standard is a condensed version of ISO 9002 with exclusion of specific sections which do not apply; purchasing, process control, servicing.

5) ISO 9004: “Quality management and quality system elements”

This descriptive standard, currently in eight parts, provides more detailed guidance on the quality elements included in the registration / certification standards ISO 9001, 9002 and 9003. The eight parts are entitled:

1. Guidelines
2. Guidelines for servicing
3. guidelines for processed materials
4. Guidelines for quality improvement
5. Guidelines for quality plans
6. Guidelines on quality assurance for project management
7. Guidelines for configuration management and
8. Guidelines on quality principles and their application to management practices.

ISO APPLICATION & APPROVAL PROCESS



Step-1-Choosing The Kind Of Certification

•The very first step is to choose the kind of certification the organization wants.

Step-2-File An Application

•Once the entrepreneur selects the ISO standard; it shall make an application in a respective form based on the ISO registrar. The application shall include the power and responsibilities of the entrepreneur and certification body.

Step-3-Submission Of Documents

•Application shall be filed along with the requisite documents and the same shall be reviewed by the ISO certification body. ISO Certification body will review all the quality manuals and documents related to various policies being followed in the organization.

Step-4-Initial Review Of The Quality Management System

•To identify any significant weakness in the Organization, the Pre-assessment (Initial review) of the Quality Management System in an organization is reviewed by the registrar and will also provide an opportunity to correct the deficiencies before the regular registration assessment is conducted.

Step-5-Preparing An Action Plan

•Once the initial review of the Quality management system is reviewed, the ISO registrar notifies the existing gaps in the organization, and to eliminate these gaps the applicant has to prepare an action plan. The action plan should contain the list of the requisite work to be performed to meet the Quality Management System.

Step -6-On-Premises Audit By The Registrar

•The registrar will conduct a non-premises inspection to audit the changes made in the organization. However, if the registrar finds that the requisite changes do not meet the requirements of the ISO standards, the registrar will categorize the organization into two categories depending on severity.

•1. Minor Non-compliances

•2. Major Non-compliances

•Note-The ISO registration cannot precede until all significant non-compliances are closed by the Registrar while doing a re-audit.

Step-7-Obtaining ISO Certificate

•The registrar will issue the ISO certification when all the non-conformities are resolved and are updated in the ISO audit report.

ISO 14000

WHAT DOES IT DO AND WHO IS IT FOR?

- ISO 14000 is a series of international standards designed to help organizations operate with sustainability, adhere to environmental regulations, and continuously improve processes.
- The ISO 14000 standard contains ISO 14001:2015 which specifies the requirements for an effective Environmental Management System (EMS).
- ISO 14000 is considered as a generic management system and it is applicable for the following:
  - Any organization (single-site to large MNCs, high risk to low-risk companies).
  - The manufacturing industries (equipment manufacturers and suppliers), process industries, and service industries.
  - All industries of local government, public and private sectors.

History of ISO 14000

- According to history, the first environmental management system, BS 7750 was published in 1992 by the BSI group.
- The International Organization for Standardization (ISO) created the ISO 14000 family of standards in 1996.
- In 2004, ISO 14001 underwent to revision and the current revision of ISO 14001 was published in September 2015.

ISO 14000 Environmental Management System

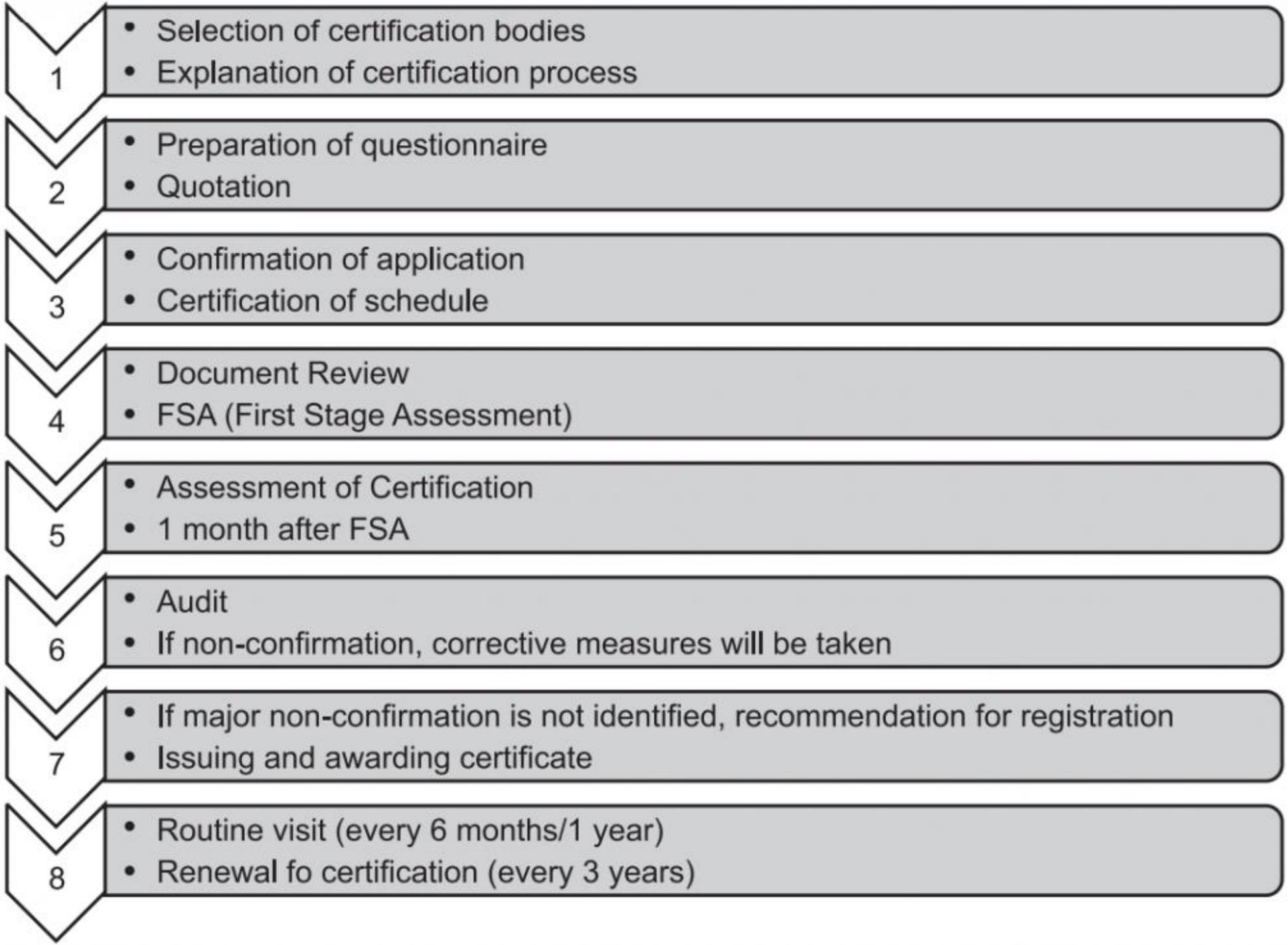
iAuditor
by SafetyCulture

Benefits of ISO 14000

- Better marketability.
- Better utilization of resources.
- Environmental responsibilities.
- Better quality of finished goods and products.
- Customers’ satisfaction.
- Enhancement of the reputation and reliability of the organization.
- Improvement of the relationship among management, employees, customers, and investors.
- Cost reduction.

ISO 14000 Series

- **ISO 14001 (2015) :** EMS: Requirements with guidance for use
- **ISO 14004 (2016) :** EMS: General guidelines on implementation
- **ISO 14006 (2011) :** EMS: Guidelines for incur : prorating eco-design
- **ISO 14015 (2001) :** EM: Environmental assessment of sites and organizations (EASO)
- **ISO 14020 to 14025 (2000) :** EM: Environmental labels and declarations
- **ISO 14031 (2013) :** EM: Guidelines for environmental performance evaluation
- **ISO 14040 (2001) :** EM: Life cycle assessment, environment goal setting
- **ISO 14050 (2009):** EM: Vocabulary (terms and definitions)
- **ISO 14063 (2006):** EM: Guidelines and examples of environmental communication
- **ISO 14064 (2006):** Quantification of emitted Greenhouse gases and their reduction


1
Selection of certification bodies
Explanation of certification process
2
Preparation of questionnaire
Quotation
3
Confirmation of application
Certification of schedule
4
Document Review
FSA (First Stage Assessment)
5
Assessment of Certification
1 month after FSA
6
Audit
If non-confirmation, corrective measures will be taken
7
If major non-confirmation is not identified, recommendation for registration
Issuing and awarding certificate
8
Routine visit (every 6 months/1 year)
Renewal fo certification (every 3 years)


परीक्षण और अंशशोधन प्रयोगशाला प्रत्यायन बोर्ड
NATIONAL ACCREDITATION BOARD FOR TESTING & CALIBRATION LABORATORIES
INDIA
भारत

NABL

What is NABL?

- NABL stands for **National Accreditation Board for Testing and Calibration Laboratories.**
- This institution is an autonomous body which is a part of the Quality Council of India.
- The main aim of this institution is to provide an impartial assessment of the quality standards for institutions, government bodies, and primary institutions.
- The type of testing conducted for NABL approval will include proficiency testing, lab testing, medical testing, and testing for referenced medical producers.
- This would also include testing for various food industries on the quality standards.

- Laboratory compliance and testing have to be according to specific standards.
- These standards have to be under the ISO/ IEC 17025: 2005 - which provides the quality standards for testing and calibration laboratories.
- Laboratories have to also satisfy the standards for competence and quality, which is under ISO 15189: 2012.
- Apart from this, the labs have to be in accordance with quality standards as required by the ISO/IEC 17043/2010, which relates to proficiency testing in medical labs.
- Hence NABL approval is required for any form of institution that gets into medical research, bioengineering, **pharmacy**, food processing and materialistic research and development (R & D).

History of NABL

- In 1982, The laboratory accreditation program in India - DST -"National Coordination of Testing & Calibration Facilities (NCTCF)"
- In 1993, NCTCF was renamed as "National Accreditation Board for Testing and Calibration Laboratories (NABL)".
- In 1996, The National Accreditation Board for Testing and calibration laboratories to be set up as a society under the Societies Registration Act.
- In 1998, NABL became autonomous body under DST, GoI.
- In 2016, transferred to the Department of Industrial Policy and Promotion (DIPP), subsequently transferred to QCI (Quality Council of India) as one of its Board.
- In the year 2017, NABL society regn. no. S/33451 has been merged with QCI society regn. no. S/30832.
- NABL maintains linkages with the international bodies like International Laboratory Accreditation Co-operation (ILAC) and Asia Pacific Accreditation Co-operation (APAC).

Why is NABL Approval Required?

- NABL approval is required for a Conformity Assessment Body (CAB) to prove that the products developed come with the quality that meets consumers' needs. All CABs have to ensure to take NABL approval to meet the requirements of quality standards.
- Hence NABL approval would provide formal recognition related to a product that is produced in a CAB. This would not only be important for domestic products but also required when products and devices are exported outside India. In the accreditation process, a third-party assessment is conducted on quality standards. These quality standards should confirm with the international requirements.
- NABL approval is thus a quality assessment that provides technical standard approval when it comes to products that are produced by the CABs.

Objectives of NABL Approval

- This form of approval would provide a license to the individual CABs to operate in the domestic markets.
- CABs complying with the requirements of the NABL will ensure that compliance is followed regularly.
- NABL approval would increase the standards of quality of CAB products, especially in medical testing, food testing, and forensic testing. This will improve the quality of products developed and manufactured in India.
- NABL has entered into MOUs (Memorandum of Understandings) with different international institutions on enhancing training and access to technical R & D. Any CAB with NABL approval would get the benefits of international training.
- NABL approval will promote confidence and increase the production in medical and calibration labs.
- Quality Assurance standards would be provided through NABL.
- This approval will improve the long term performance of the CAB.

BENEFITS OF ACCREDITATION

- Formal recognition of competence of a conformity assessment body by NABL in accordance with international standard has many advantages:

❖ International recognition/ equivalence,

❖ Access to Global market,

❖ Time and money efficient,

❖ Enhanced customer confidence and satisfaction,

❖ Robust Quality Management System,

❖ Continual improvements,

❖ Better operational control,

❖ Assurance of accurate and reliable results,

❖ Cost Reduction,

❖ Prevent loss due to defects

Which Conformity Assessment Bodies (CABs) require NABL Approval?

Services provided by NABL

NABL provides accreditation to:

✓ Testing laboratories as per ISO/IEC 17025

✓ Calibration laboratories as per ISO/IEC 17025

✓ Medical testing laboratories as per ISO 15189

✓ Proficiency Testing Providers (PTP) as per ISO/IEC 17043

✓ Reference Material Producers (RMP) as per ISO 17034

Laboratories Testing Equipment

NABL approval is required for laboratories that test different products and equipment. Such laboratories will include:

- Chemical
- Biological
- Mechanical
- Electrical
- Electronics
- Fluid Flow
- Forensic
- Non-Destructive (NDT)
- Photometry
- Radiological
- Diagnostic Radiology QA Testing
- Software & IT System

Calibration Laboratories

Calibration laboratories will also require NABL approval. The following laboratories would require NABL approval:

- Mechanical
- Electro Technical
- Fluid Flow
- Thermal
- Optical
- Medical Devices
- Radiological

Medical Laboratories

All forms of pharmaceutical and medical companies would require NABL approval to test different medications. This approval is crucial for the medical industry. The following laboratories require this approval:

- Clinical Biochemistry
- Clinical Pathology
- Haematology
- Microbiology & Infectious disease serology
- Histopathology
- Cytopathology
- Flow Cytometry
- Cytogenetics
- Molecular Testing

Proficiency Laboratories

Different laboratories that test the proficiency of products will require this form of approval. The following proficiency laboratories will require this approval:

- Testing
- Calibration
- Medical
- Inspection

Reference Material Laboratories

Laboratories that analyze different materials' reactions would also require approval from the NABL. The following reference material laboratories require this approval:

- Chemical Composition
- Biological & Clinical Properties
- Physical Properties
- Engineering Properties
- Miscellaneous Properties

Medical Imaging- Conformity Assessment Bodies (MI-CAB)

- Projectional Radiography & Fluoroscopy
  a. X-Ray, Bone Densitometry (DEXA), Dental X-Ray-OPG, Mammography etc.
  b. Fluoroscopy
- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Ultrasound and Colour Doppler
- Nuclear Medicine
  a. SPECT
  b. PET CT
  c. PET MRI
- Basic Diagnostic Interventional Radiology Procedures

Approach to Accreditation

- **Awareness Training**
  - Separate training sessions for top management, middle management and junior level management.
  - Creates a motivating environment throughout the organization for ISO 17025 implementation.
- **Quality Policy & Objectives Finalization**
  - Work shop with top management on development of quality policy.
  - Work shop with top management and middle level functional management on development of quality objectives.
- **Gap Analysis**
  - Understanding of all the operations of the organization.
  - Development of process map for the activities of the organization.
  - Comparing existing operations with requirements of ISO 17025:2005 standard.
- **Documentation / Process Design**
  - Quality Manual, Functional Procedures, Work Instructions, System Procedures, Formats
- **Documentation / Process Implementation**
  - Work–shop on process / document implementation as per ISO 17025 requirements..
  - Departmental / Individual assistance in implementing the new processes / documents..

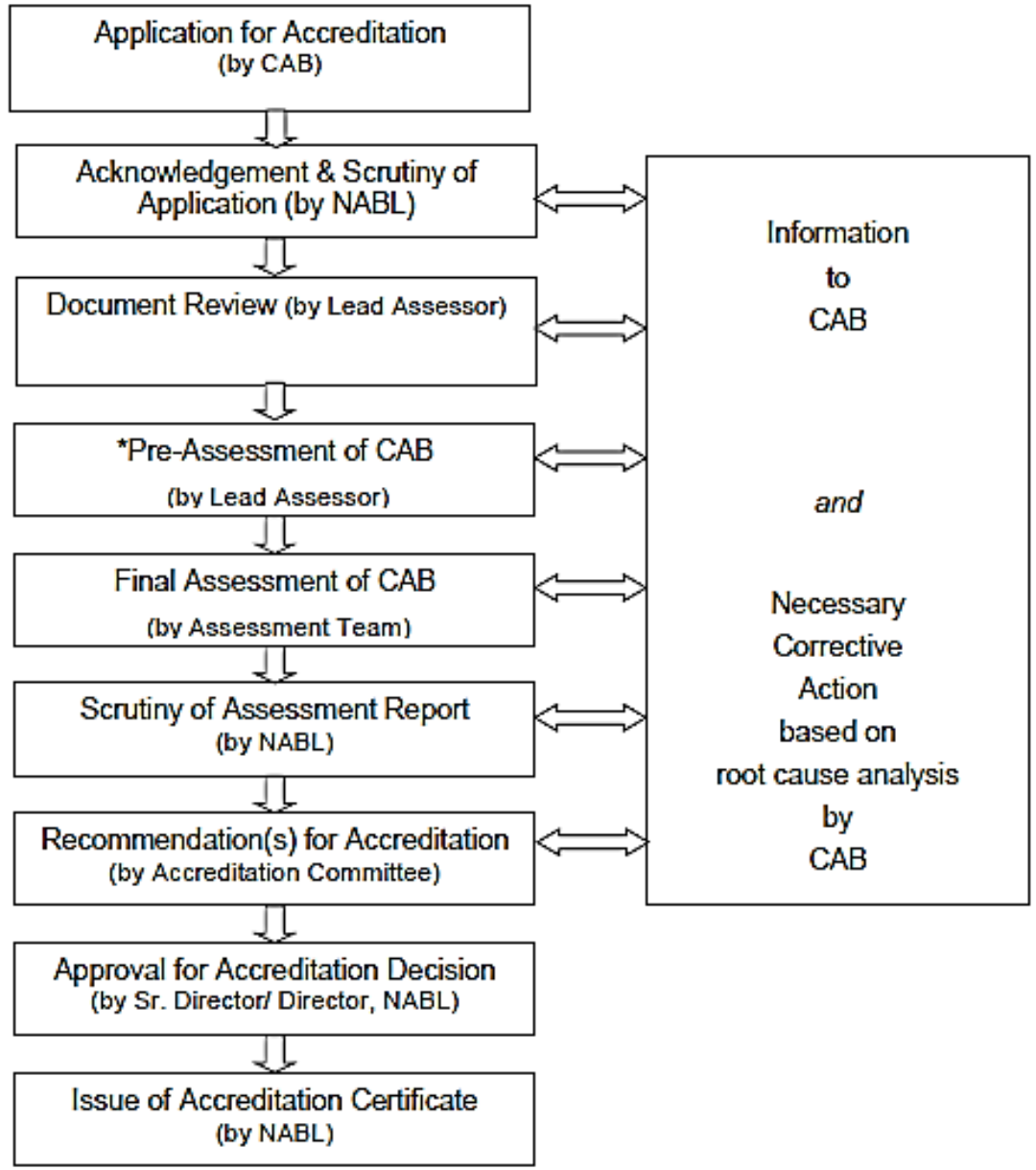
- **Internal Audit**
  - Internal Audit Training & Examination (Optional).
  - Successful employees / we carry out internal audit of the organization covering all the departments and operations.
  - Suggest corrective and preventive actions for improvements in each of the audited departments.
- **Management Review Meeting**
  - Quality Policy & Objectives
  - Results of internal audit
  - Results of supplier evaluation
  - Results of customer complaints
  - Results of customer feedback etc.
- **Shadow Audit**

  A replica of final certification audit.

  Finds degree of compliance with ISO 17025 standard.

  Gives an idea to the employees about the conduct of the final certification audit.
- **Corrective –Preventive Actions**
  - On the basis of shadow audit conducted in the last step, all the non-conformities will be assigned corrective and preventive actions.
  - A check will ensure that all the NCs are closed and the organization is ready for the final certification audit.
- **Final Certification Audit**
  - Upon completion of various stages of accreditation audit, the audit, your organization will be awarded accreditation.

ACCREDITATION PROCESS



*Optional for laboratories (Testing/ Calibration/ Medical Testing)

NABL Symbol for Testing Laboratories	*NABL Symbol for Calibration Laboratories*	*NABL Symbol for Medical Testing Laboratories*
TC- XXXX	CC- XXXX	MC- XXXX

NABL Symbol for Proficiency Testing Providers	*NABL Symbol for Reference Material Producers*
PC- XXXX	RC- XXXX

The validity of the NABL Approval

- When an applicant has received the certificate, it will be valid for **two years**. Annual surveillance is carried out by the NABL.
- The CAB has to apply for the renewal of license before the expiry.
- This must be carried out six months before the expiry of the license.

Documents Required for NABL Approval

- NABL 112- Criteria for medical laboratories.
- NABL 120: Guidance for Classification of Product Groups in Testing & Calibration Field.
- NABL 126- Specific Criteria for Medical Devices Calibration.
- NABL 151 for testing laboratories.
- NABL 152 for calibration laboratories.
- NABL 153 for medical laboratories.
- NABL 155 (Application form and Check List for NABL medical).
- NABL 160 Information related to the management of the quality system manual.
- NABL 180 for Proficiency Testing Providers (PTP) and.
- NABL 190 for Reference Material Producers (RMP)..
- NABL 100 General Information of NABL.
- NABL 219- Assessment forms and checklist for NABL (ISO/IEC 17025:2017).

5. Main goal of the agency is to guarantee the safety, efficacy, and quality of the available drug product.

Quality-by-Design In Pharmaceutical Development

Quality by design (QbD) is a systematic approach to product development that begins with predefined objectives and emphasizes product and process understanding and controls based on sound science and quality risk management (ICH Q8). Quality by Design is a concept first outlined by **Joseph M. Juran** in various publication

Objective of QbD

- The main objective of QbD is to achieve the quality products.
- To achieve positive performance testing

- Ensures combination of product and process knowledge gained during development.
- From knowledge of data process desired attributes may be constructed.

Benefits of QBD for Industry

- Eliminate batch failures.
- Minimize deviations and costly investigations.
- Empowerment of technical staff.
- Increase manufacturing efficiency, reduce costs and Project rejections and waste.
- Better understanding of the process.
- Continuous improvement.
- Ensure better design of product with less problem

Benefits FDA

- Provide better consistency.

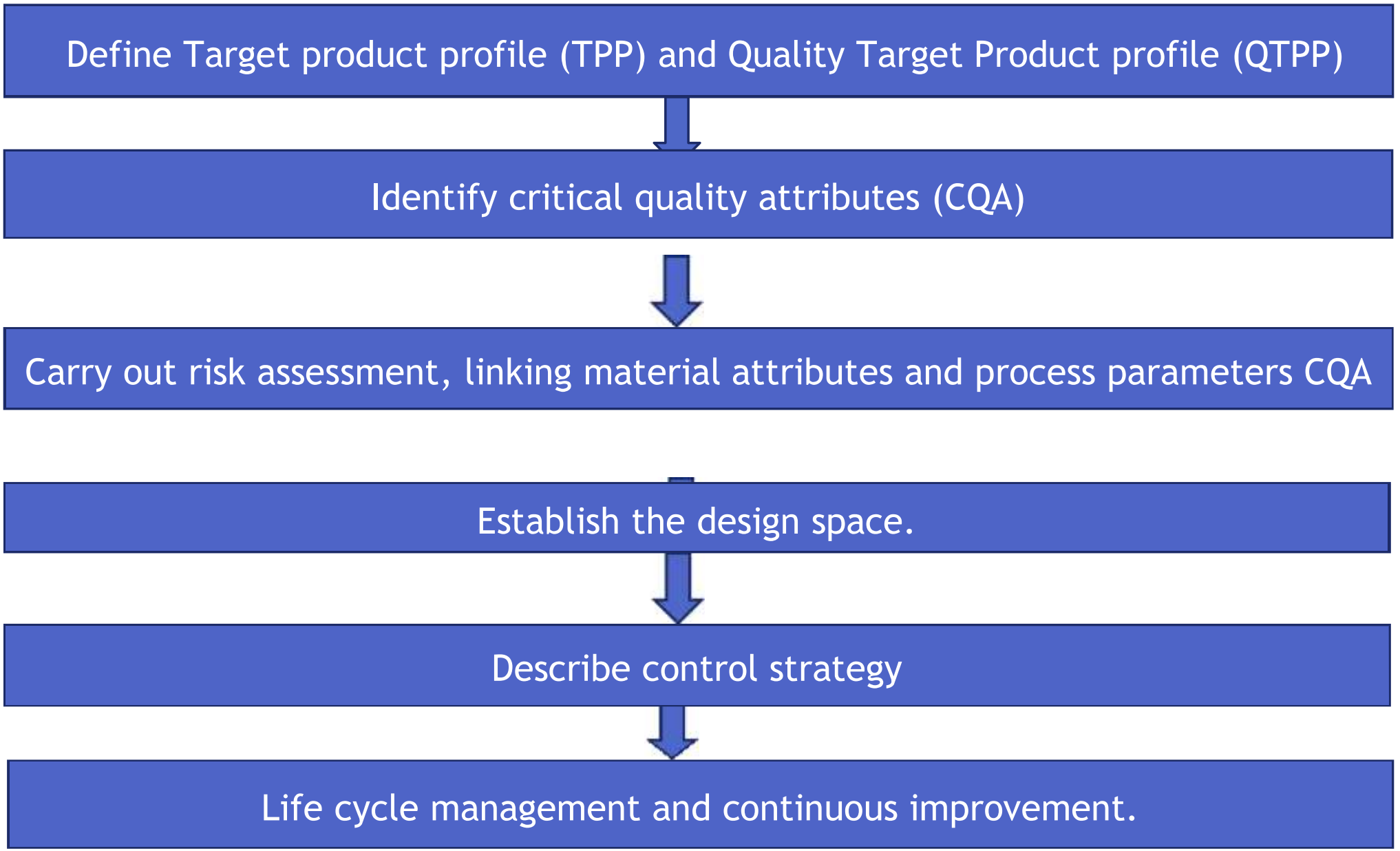
- More flexibility in decision making.
- Ensure scientific base of analysis.
- Ensures decisions made on science and not on
- empirical information.
- Improves quality of review.

Approaches to pharmaceutical Development

Aspects	Traditional	QbD
Pharmaceutical development	Empirical	Systematic and multivariate experiments.
Manufacturing process	fixed	Adjustable with experiment design space.
Process control	Offline and has wide or slow response	PAT (process analytical technique) utilized for feedback.
Product specification	Based on batch data	Based on the desired product performance.

Control strategy	By end product testing	Risk based, controlled shifted up stream, real time release.
Life cycle management	Post approval changes needed	Continual improvement enable within design space.

Flow of QbD


Define Target product profile (TPP) and Quality Target Product profile (QTPP)
Identify critical quality attributes (CQA)
Carry out risk assessment, linking material attributes and process parameters CQA
Establish the design space.
Describe control strategy
Life cycle management and continuous improvement.

Target Product Profile (TPP)

A prospective summary of the quality characteristics of drug product that ideally will be achieved to ensure the desired quality, taking in to account safety & efficacy of drug product."(ICH Q8) Target product profile should includes-

- Dosage form
- Route of administration
- Dosage strength
- Pharmacokinetics
- Stability

The TPP is a patient & labeling centered concepts, because it identifies the desired performance characteristics of the product, related to the patient's need & it is organized according to the key section in the drug labeling.

Quality Target Product Profile (QTPP)

- QTPP is a quantitative substitute for aspects of scientific safety & efficacy that can be used to design and optimize a formulation and mfg. process.
- QTPP should only include patient relevant product performance.
- The Quality Target product profile is a term that is an ordinary addition of TPP for product quality
- QTPP is related to identity, assay, dosage form, purity, stability in the label.

Critical Quality Attributes (CQAs)

- A CQA has been defined as “a physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

- Critical Quality Attributes are generally associated with the drug substance, excipients, intermediates and drug product.
- The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release, moisture content, microbial limits.
- Physical attributes such as color, shape, size, odor, score configuration, and friability. These attributes can be critical or not critical

Critical Material Attributes (CMA)

- A CMA of a drug substance, excipient, and in-process materials is a physical, chemical, biological, or microbiological characteristic of an input material that should be consistently within an appropriate limit to ensure the desired quality of that drug substance, excipient, or in-process material.
- The CMA is likely to have an impact on CQA of the drug product.

- A material attributes can be an excipients raw material, drug substances, reagents, solvents, packaging & labeling materials.

Critical Process Parameters (CPP)

A CPP of manufacturing process are the parameters which, when changed, can potentially impact product CQA and may result in failure to meet the limit of the CQA

Operations during tableting	Critical Process Parameters
Wet granulation	Mixing time impeller speed Binder fluid addition rate & time Method of binder addition Temperature
Drying	Drying time Inlet air flow Exhaust air temperature & flow
Milling	Milling speed Screen size Feeding rate
Mixing	Mixer type Mixing time Order of addition
Compression	Pre compression force Main compression force Dwell time Hopper design Punch penetration depth Roller type Auger screw rate Ejection force
Coating	inlet air flow Time Temperature Spray pattern & rate

Risk Assessment

Risk assessment is the linkages between material attributes & process parameters. It is performed during the lifecycle of the product to identify the critical material attributes (CMA) & critical process parameters (CPP).

Design Space

As per ICH Q8-

This is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

A design space may be built for a single unit operation or for the ensure process.

Name of Design	Application
Screening Design [S.D]	Screening designs are effective way to identified significant main effects. The term "Screening design" refers to an experimental plan i.e. indented to find a few significan factors from a list of many potential ones. It is used to estimate a linear model
Response Screening Design	Response screening design involves just the main effects and interactions or they may also have quadratic and possibly cubic terms to account for curvature model which ma be appropriate to described a response
General Factorial Design	Design for 1 to 12 factors where each factor may have a different number of levels
Fractional Factorial Design	Full factorial experiments can require many runs. The solution to this problem is to use only a fraction of the runs specified by the full factorial design. In general, we pick a fraction such ½, ¼ etc. of the runs called for by the full factorial.
2 – level factorial design	Design for 2 to 21 factors where each factor is varied over 2 levels. It is used for estimating main effects and interactions. It may be used for screening many factors to find the significant few
Placket – Burmam Design	These designs have run numbers that are in multiple of 4.placket Burmam [PB] design are used for screening experiments because in PB designs, main effects are, heavenly confounded with two – factor interactions. It is a design for 2 to 31 factors where each factor is varied over 2 levels. It is useful for ruggedness testing where one can hope to find little effect on response due to interaction of any of the factors
Box- Behnken Design	The Box- Behnken Design is an independent quadratic design which does not contain an embedded factorial or fractional factorial design. These designs are rotatable [or nea rotatable] & requires 3 levels of each factors. Each factor is varied over 3 levels. If categorical factors are added, the Box – Behnken Design will be duplicated for every combination of the categorical fractional levels
D – Optimal Design	A design for categorical factors that is created based on the model which is specified. The design is a subset of all possible combination of factors. It is generated to minimiz the error associated with the model coefficients
Taguchi OA Design	These are orthogonal array designs from Taguchi's textbook. In these design, all main effects and no interactions are considered

TOOLS APPLIED IN QBD APPROACH

Design of Experiment (DoE):

This is a systematic approach applied to conduct experiments to obtain maximum output. We have capability and expertize to perform DoE in product development using software like Minitab and Statistica.

Design of experiments done by 2 method-

Screening: Designs applied to screen large number of factors in minimal number of experiments to identify the significant ones. Main purpose of these designs is to identify main effects and not the interaction effects. For such studies common designs used are-

Placket-Burman and

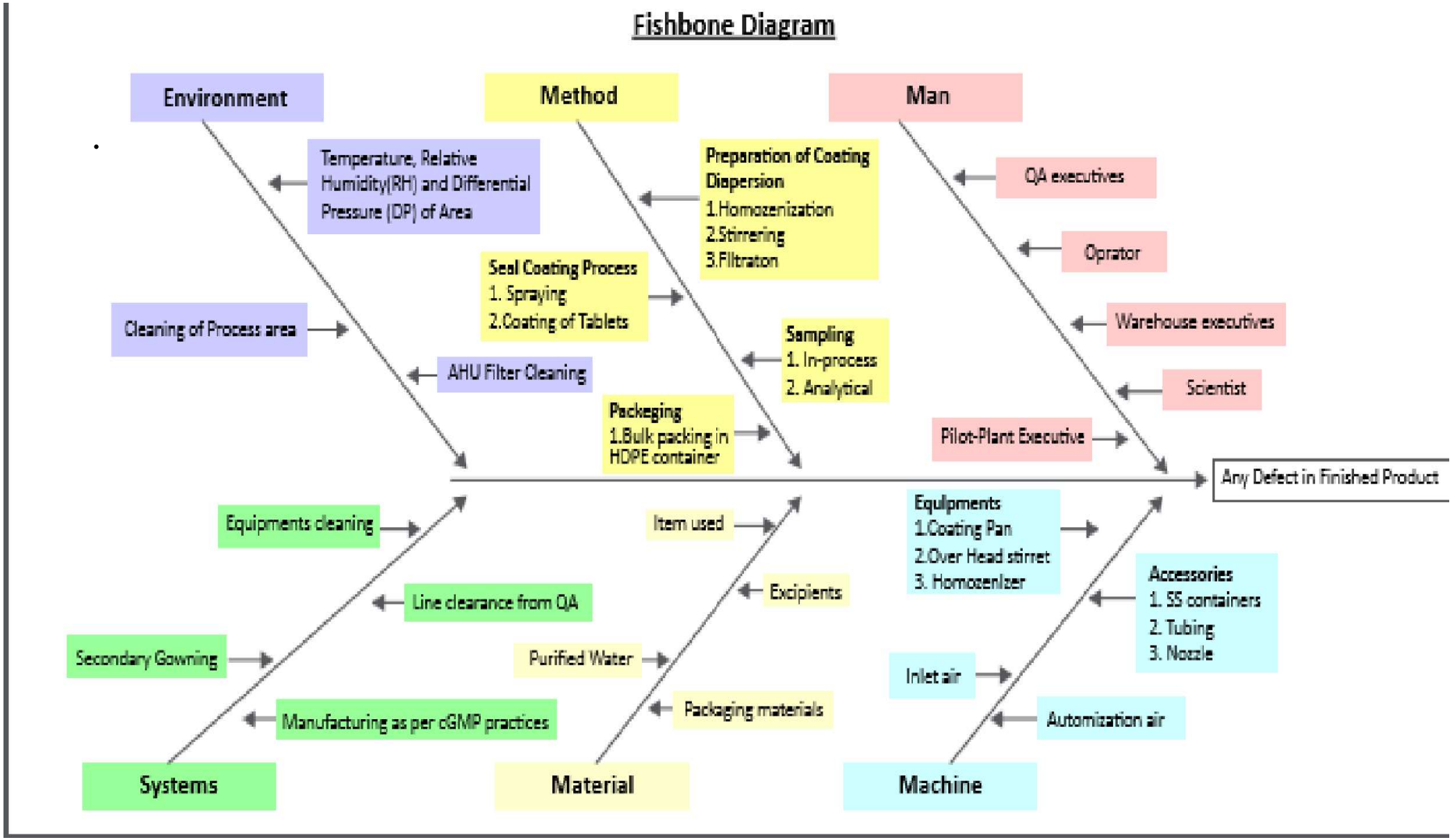
Fractional factorial design.

Optimization: Experimental designs considered to carry out optimization are

mainly full factorial design, surface response methodology (e.g. Central composite, Box-Behnken), and mixture designs. These designs include main effects and interactions and may also have quadratic and cubic terms require to obtain curvature. These designs are only applied once selected factors are identified, which seem to be contributing in process or formulation.

Risk assessment methodology

1- Cause and Effect Diagrams (fish bone/Ishikawa): This is very basic methodology to identify multiple possible factors for a single effect. Various cause associated with single effect like man, machine, material, method, system, and environment need to be considered to identify root cause



2- Failure Mode Effect Analysis (FMEA): This is an important tool to

evaluate potential failure modes in any process. Quantification of risk by interaction of probability functions of severity, occurrence, and detectability of any event can be done. FMEA can be effectively performed with good understandingof process.

3- PAT (Process Analytical Technology) : Assurance of product quality during intermittent steps using Process Analytical Technology (PAT) is recommended by regulatory authorities, which is yet to be extensively accepted by the pharmaceutical industry over conservative methodologies. It involves advanced online monitoring systems like NIR (Near IR), Handheld Raman Spectrometer, Online Particle Size Analyzer etc. We are experienced in application of NIR and Raman Spectrometer to monitor processes viz. blending and wet granulation. These technologies further make assurance of continuous improvement in

process and product quality through its life cycle.

Control strategy

Based on process and product understanding, during product development sources of variability are identified.

Understanding the sources of variability and their impact on processes, in-process materials, and drug product quality can enable appropriate controls to ensure consistent quality of the drug product during the product life cycle.

Elements of a Control Strategy

- Procedural controls
- In-process controls
- batch release testing
- Process monitoring

- Characterization testing
- Comparability testing
- Consistency testing

Application of Qb D

Application of QbD to Influenza Vaccines

Influenza vaccine: Influenza (flu) is caused by influenza viruses & is spread mainly by coughing, sneezing, & close contact with infected person. Flu is communicable disease that spreads around the US every winter in Oct.

Symptoms:

- Fever/chills
- Sore throat
- Muscle aches
- Fatigue

- Cough
- Headache

Vaccination : Vaccination is the phenomenon of protective immunization. In modern concept vaccination involves the administration (injection or oral) of an antigen to obtain an antibody response that will protect the organism against future infections.

People should not take this vaccine-

- If they have any severe, life-threatening allergies. E.g: Allergy to gelatin, antibiotics or eggs, you may be not to get vaccinated.
- If you are not feeling well, then also not to get vaccinated.

By using QbD the following parameters should be controlled during vaccine production process

1) Cell propagation: In this step, limiting concentration of nutrients may be helpful for optimal cell growth. If high nutrient

concentration then it inhibit cell growth. For that to do on line monitoring of the nutrients concentration.

2) Virus prorogation: The following variable parameters controlled during fermentation process.

- **pH:** for maximum effectiveness of fermentation can be achieved by continuous monitoring pH i.e. It required most favorable pH.
- **Temperature:** Temperature control is important for good fermentation process. If temperature is lower then it causes reduced product formation & if it is higher then it affects the growth of organisms. For avoiding this, bioreactors equipped with heating & cooling system as per the requirement to maintain the reaction vessel at optimal temperature.
- **Dissolved oxygen:** Optimal supply of nutrients & oxygen, due to this it prevents the growth of toxic metabolic byproducts.

- **Agitation:** Good mixing also creates a favorable environment for growth & good product formation. If agitation is excessive then it damages the cells & increase temperature of medium.
- **Foam formation:** Avoiding this parameter antifoam chemicals are used such as mineral oils, vegetable oils which lowers the surface tension of the medium & causes foam bubbles to collapse. Also mechanical foam control devices fitted at top of fermenter.

3) Purication: in this step check the purity by using ion exchange chromatography & remove the impurity.

4) Inactivation: Optimum concentration of formaldehyde is used for inactivation of viruses.

PHARMACEUTICAL QUALITY ASSURANCE

UNIT I

By

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Subject Name: Quality Assurance Module -1

Subject Code: BP 606T

Objectives of the course

- Understand the cGMP aspects in a pharmaceutical industry.
- Understand the responsibilities of QA & QC departments.

Learning outcomes

1) Students learnt about the quality assurance and quality control parameters which affects academics as well as pharmaceutical industry.
2) Students learnt ICH guidelines which governs pharmaceutical quality management and process of harmonization brief overview of QSEM
3) Students learnt about ISO guidelines, NABL accreditation and knowledge how to implement design expert software to optimize the formulations.

Structure/contents of UNIT I

- **Quality Assurance and Quality Management concepts:** Definition and concept of Quality control, Quality assurance and GMP
- **Total Quality Management (TQM):** Definition, elements, philosophies
- **ICH Guidelines:** purpose, participants, process of harmonization, Brief overview of QSEM, with special emphasis on Q-series guidelines, ICH stability testing guidelines
- **QbD:** Definition, overview, elements of QbD program, tools
- **ISO 9000 & ISO 14000:** Overview, Benefits, Elements, steps for registration
- **NABL accreditation :** Principles and procedures

History and Evolution

Definitions of Quality

- There is no lack of definitions of quality. Here are some general ones:
  - Delivering to a customer a product or service that meets the specification agreed on with the customer, and delivering it on time
  - Satisfying customer requirements
  - Fitness for purpose
  - Getting it right the first time
- The International Organization for Standardization (ISO) definitions of quality are:

  The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs

Importance of Quality in Pharma industry

- Within the pharmaceutical industry, quality is the key issue that has to be addressed above all others.
- It is the reason that so many regulations, guidelines and controls are important.
- Quality Assurance, Quality Control (QC) and Good Manufacturing Practices (GMP) are the prime consideration for the manufacturing, distribution and marketing of pharmaceutical products for the ensuring of its identify, strength, purity, pharmacological safety, and efficacy & effectivity.


Quality
Management
Quality
Assurance
GMP
Quality
Control

- Quality management, with the overall policy of the organization towards quality, comes above everything else.
- Next comes quality assurance, which is the unit that ensures the policy is achieved.
- GMP is a part of quality assurance; it deals with the risks that cannot be tested and builds quality into the product.
- Quality control is a part of GMP: the part that is focused on testing of the environment and facilities, as well as the testing of the materials, components and product in accordance with the standard.

Definition of quality assurance

WHO definition

- Quality Assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objects of ensuring that pharmaceutical products are of the expected quality required for their intended use. Quality Assurance, therefore, incorporates GMP (Good Manufacturing Practices), GLP (Good Laboratory Practice), and Original Product Design and Development.

EU guidelines,

- QA is defined as ‘a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product.

- It is the process that gives assurance that quality will be achieved.
- It is about putting things in place in advance so that everything goes according to plan and there are no problems with the quality of the final product.
- It is therefore about preventative measures.
- Inside an organization, quality assurance provides a management tool.
- In contractual situations, quality assurance provides confidence for the customer (whether that is a pharmacist, doctor or patient) in the quality of the drug being supplied.

Responsibilities of QA

- Product design and development
- Specification for production and control
- Managerial responsibilities
- Control of starting and packaging materials
- Control of intermediate materials
- Control of finished products
- Batch release
- Control of storage and distribution
- Self-inspection programme

Definition of quality control

- Quality control is defined in the EU guidelines as:
- that part of GMP that is concerned with sampling, specifications, testing and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.
- QC is an historical process in which proof is obtained that the appropriate level of quality has been achieved.
- Of itself, QC can have no effect on the quality of the product.
- It is merely a measuring process.

- The quality control process is therefore primarily confined to laboratory operations, testing and/or inspecting samples of raw materials, packaging materials, in-process materials and finished products.
- QC staff will also monitor aspects of the environment that have an effect on product quality. However, in many companies, the QC department also has responsibility for many of the areas that relate to quality assurance.

Responsibilities of QC

- Adequate resources
- Sampling
- Validated or verified test methods
- Adequate records
- Correct active ingredients and correctly labelled containers
- Assessment of results
- Product release
- Reference samples
- Control of components and drug product containers and closures.
- Sampling and testing of in-process materials and drug products.
- Laboratory controls
- Records and reports

Summary of quality control requirements

Resources	Tasks	Objects
Adequate facilities	Sampling	Starting materials
Trained personnel	Inspecting	Packaging materials
Approved procedures	Testing	Intermediates
	Monitoring	Bulk products
	Releasing/rejecting	Finished products
		Environmental conditions

QA

- Proactive : It aims to prevent defects before they occur through process design.
- Process:QA is process-oriented, and it focuses on preventing quality issues.
- Actions: QA involves the actions which create the product.
- System: Quality assurance control systems are the methods and procedures which are used to safeguard quality standards.
- Creation: The result of QA activities is a roadmap for creating high-quality products. It involves defining standards for product design, manufacture, packaging, distribution, marketing, and sales.
- Entire Team: Quality assurance activities involve the entire team. Every member of a life sciences organization is responsible for QA activities by following SOPs. While the quality management system (QMS) is generally the responsibility of the quality unit and the leadership team, QA activities involve standards for training, documentation, and review across the workforce.

QC

- Reactive : QC is reactive and exists to identify defects after they have happened.
- Product:QC is product-oriented and focused on identifying quality issues in manufactured products.
- Results: QC is focused on the resulting product.
- Parts: Quality control systems measure parts, including the outputs of the system.
- Verification: QC involves verification of products post-manufacture and before distribution, or confirming safety and efficacy.
- Dedicated Personnel: QC is generally the responsibility of certain personnel within the organization whose duties include following SOPs for product testing. QC staff follow SOPs for quality control and document their findings based on standardized procedures for product testing and process validation.

THANK YOU