Quality Assurance and Quality Management M01 (BP 606T)

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 of Module -1 BP 606T Learning Material

1. Quality Assurance and Quality Management Concepts-Definition and concept of Quality control, Quality assurance and GMP.
2. Total Quality Management (TQM)-Definition, elements, and philosophies.
3. ICH Guidelines- Purpose, participants, process of harmonization, Brief overview of QSEM, with special emphasis on Q-series guidelines, ICH stability testing guidelines.
4. Quality By Design (QbD)-Definition, overview, elements of QbD program, tools.
5. ISO 9000 & ISO14000-Overview, Benefits, Elements, steps for registration.
6. NABL Accreditation-Principles and procedures.

Quality Assurance

According to WHO, quality assurance is a wide- ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into major areas: development, quality control, production, distribution, and inspections.

ISO 9000 defines as "part of quality management focused on providing confidence that quality requirements will be fulfilled"

Quality Control

ISO 9000 defines quality control as "A part of quality management focused on fulfilling quality requirements". It is that part of GMP concerned with sampling, specification & testing, documentation & release procedures which ensure that the necessary & relevant tests are performed & the product is released for use only after ascertaining it’s quality.

Difference between QA and QC

Definition

- QA is a set of activities for ensuring quality in the processes by which products are developed.
- QA is a managerial tool

- QC is a set of activities for ensuring quality in products. The activities focus on identifying defects in the actual products produced.
- QC is a corrective tool

What are its goals and on what does it focus?

- QA aims to prevent defects with a focus on the process used to make the product. It is a proactive quality process.
- The goal of QA is to improve development and test processes so that defects do not arise when the product is being developed.

- QC aims to identify (and correct) defects in the finished product.
  Quality control, therefore, is a reactive process.
- The goal of QC is to identify defects after a product is developed and before it's released.

What and how does it work?

- Prevention of quality problems through planned and systematic activities including documentation.
- Establish a good quality management system and the assessment of its adequacy. Periodic conformance audits of the operations of the system.
- The activities or techniques used to achieve and maintain the product quality, process and service.
- Finding & eliminating sources of quality problems through tools & equipment so that customer's requirements are continually met.

Whose responsibility is it and what is the example of it?

- Everyone on the team involved in developing the product is responsible for quality assurance.
- Verification is an example of QA.
- Quality control is usually the responsibility of a specific team that tests the product for defects.
- Validation is an example of QC.

Responsibilities of QA

- The QA department is responsible for ensuring that the quality policies adopted by a company are followed.
- It helps to identify and prepare the necessary SOPs relative to the control of quality.
- It must determine that the product meets all the applicable specifications and that it was manufactured according to the internal standards of GMP.
- QA also holds responsible for quality monitoring or audit function. QA functions to assess operations continually and to advise and guide them towards full compliance with all applicable internal and external regulations.

Responsibilities of QC

- QC is responsible for the day-to-day control of quality within the company.
- This department is responsible for analytical testing of incoming raw materials and inspection of packaging components, including labelling.
- They conduct in-process testing when required, perform environmental monitoring, and inspect operations for compliance.
- They also conduct the required tests on finished dosage form.
- QC plays a major role in the selection of qualified vendors from whom raw materials are purchased. Testing of representative samples is required, and in many cases, an audit of vendor's operations is necessary to determine their suitability and degree

of compliance with GMPs prior to their being approved.

- The environmental areas for manufacturing of various dosage forms are tested and inspected by QC department.

Sources of Quality Variation

Because of the increasing complexity of modern pharmaceutical manufacture arising from a variety of unique drugs and dosage forms, complex ethical, legal, and economic responsibilities have been placed on those concerned with the manufacture of modern pharmaceuticals. An awareness of these factors is the responsibility of all those involved in the development, manufacture, control, and marketing of quality products.

Following variables may affect ultimate quality of product

- Raw material
- In process variations

- Packaging material
- Labeling
- Finish product
- Manual Error

Control of Quality Variation

Raw material control

- Good raw material specifications must be written in precise terminology, must be complete, must provide specific details of test methods, type of instruments, and manner of sampling must be properly identified.
- Each raw material is sampled according to standard sampling procedures and is sent to the quality control laboratory for testing according to written procedures. If acceptable, it is moved to the release storage area, after being properly stickered to indicate the item no., material name, lot

no., release date, reassay date and sign of QA inspector.

- QA personnel should keep preservation samples of active raw materials that consists of atleast twice the necessary quantity to perform all tests required, to determine whether the material meets the established specifications. These preservation samples should be retained for atleast 7 years. Approved material should be rotated so that the oldest stock is used first.

Raw materials may be classified into 2 groups:

- Active or therapeutic
- Inactive or inert

TABLE 27-1. *Raw Material Quality Assurance Monograph*

A. (Raw Material Name)
   1. Structural formula, molecular weight
   2. Chemical name(s)
   3. Item number
   4. Date of issue
   5. Date of superseded, if any, or new material
   6. Signature of writer
   7. Signature of approval

B. Samples
   1. Safety requirement
   2. Sample plan and procedure
   3. Sample size and sample container to be used
   4. Preservation sample required

C. Retest Program
   1. Retesting schedule
   2. Reanalysis to be performed to assure identity, strength, quality, and purity

D. Specifications (wherever applicable)
   1. Description
   2. Solubility
   3. Identity
      a. Specific chemical tests such as related alkaloids, organic nitrogen basis, acid moiety, or inorganic salt tests; sulfate, chloride, phosphate, sodium, and potassium tests; or other spot organic and inorganic chemical tests as needed.
      b. Infrared absorption
      c. Ultraviolet absorption
      d. Melting range
      e. Congealing point
      f. Boiling point or range
      g. Thin-layer, paper, liquid, or gas chromatography
   4. Purity and quality
      a. General completeness of solutions, pH, specific rotation, nonvolatile residue, ash, acid-insoluble ash, residue on ignition, loss on drying, water content, heavy metals, arsenic, lead, mercury, selenium, sulfate, chloride, carbonates, acid value, iodine value, saponification value.
      b. Special quality tests, particle size, crystallinity characteristics, and polymorphic forms
      c. Special purity tests, ferric in ferrous salts, peroxides and aldehydes in ether and related degradation products
   5. Assay, calculated either on anhydrous or hydrous basis
   6. Microbial limits, especially for raw materials from natural sources

E. Test Procedures
   1. Compendial, USP, or NF references
   2. Noncompendial, detailed analytical procedure, weights; dilutions; extractions; normality; reagents; instrumentation used and procedure, if any; calculations

F. Approved Suppliers
   1. List of prime suppliers and other approved alternative suppliers, if any

In-process Items Control

- Conformance to compendial standards as the sole basis for judging the quality of a final dosage form can be grossly misleading. As the final dosage forms are produced in millions of units, the no. Of units assayed at the end is not likely to be representative of more than a small fraction of the actual production.
- The FDA-CGMP regulations emphasize environmental factors to minimize cross- contamination of products and errors, however, they do little to minimize within-batch and batch-to- batch variation. Therefore, it is important function of the IPQA program to ensure that the final produts have uniform purity and quality.

There are some critical steps to be followed in this:

QA before start-up:

- Environmental and microbiologic control and sanitation
- Manufacturing Working Formula Procedures
- Raw Materials
- Manufacturing Euipment

QA at start-up:

- Raw Material Processing
- Compounding
- Packaging Materials Control
- Labels Control
- Finished Product Control

TABLE 27-5. *Quality Assurance Operating Procedure*

Page	No.	
Date	Supersedes	
	NEW	Sanitation Control—Pest Control
Written by	Checked by	

Certox: Insecticide

Type of action
Kills on contact

Formula	*Approximate %*
Petroleum distillates	71.8%
Technical piperonyl butoxide*	12.0
Pyrethrine	1.2
Inert ingredients	15.0

Dilution
Dilute 1 gallon of concentrate with 4 gallons of water.

Time interval
To be used once weekly after working hours on Friday evenings.

Area designation
Floor and drains

Equipment
Spray unit for Certox
Certox concentrate
Safety equipment

Removal of waste materials
Removal of waste materials remaining in the spray units after exterminating shall be the responsibility of the exterminator.

Effectiveness inspection
It will be the responsibility of the quality assurance department to perform routine area checks to ascertain the effectiveness of the frequency of spraying.

It will be the responsibility of the area supervisor, however, to take necessary action immediately upon seeing any infestation.

Special restrictions and cautions
1. Foods should be removed or covered during treatment.
2. Do not store or use near heat or open flame.
3. Apply only as designated on area designation assignments.

Toxicity in humans
Severe allergic dermatitis and systemic allergic reactions are possible.

Toxic symptoms
Large amounts may cause nausea, vomiting, tinnitus, headache, and other CNS disturbances.

Government status

Manufacturing Variation Control

- Monitoring environmental conditions under which products are manufactured/stored
- Monitoring of air and water systems to prevent contamination– Air Handling Units
- Monitoring of personnel
- Feedback and follow-up

Quality Assurance Management Procedure

1. How to write Standard Operating Procedure?

- SOP describes standard SOP format that you can use immediately for your quality procedure.
- SOP has instructions on how to write a formal operating procedure for your systems which your people can follow everyday.

2. All Document-Classifications, Definitions and Approval Matrix

- In this SOP you will find all type of quality and Technical/Master file documents to build up a good quality management system for your manufacturing sites, definition of documents, their classification, approval requirements and retention requirements.
- This procedure has schematic diagrams for your understanding of how different types of documents are prepared and stored in a typical

documentation.

3. Quality Documentation Management and Change Control

- This SOP describes how to generate new quality documents or change control of existing documents, review of quality documents, satellite file management, role of document author, approver, document control officer and satellite file administrator.
- In this SOP you will also find numbering systems of different quality documents like audit files, SOP's, forms, manuals, training files, QA agreements, project files etc and their effective archiving system.

4. Documentation Rule for GMP Documents

- This SOP describes the principles to be followed in GMP documents, entry of data and information, signature requirements and correction technique of incorrectly entered data or information.

5. Quality Documentation- Tracking, Control and Distribution

- In this SOP you will find mainly the role of document control officer during the initiation, creation, circulation and approval of new quality related documents.
- It also describes the procedure of modification and review of existing document using a documentation database.
- Management of existing and superseded documents is also a art of this procedure.
- You will see all the forms referred during the instruction are attached at the end of the procedure.

6. Preparation, Maintenance and Change Control of Master Documents

- This SOP particularly focused on the management of master file documents like specifications, control methods, raw materials, finished goods and packaging specification and test reports, formulation, stability files etc required to generate during the product registration in the market.
- This SOP gives instruction on their creation, change control, numbering system, approval requirements and maintenance in a simple master file database.
- You will see all the forms referred during the instruction are attached at the end of the procedure.

7. Deviation Report System

- It is a regulatory requirement to capture all sorts of deviations evolves in your systems in order to maintain the continuous improvement to your processes and systems.
- This SOP describes how to categorize the deviations between production, audit, quality improvements, technical deviations, customer complaints and environmental, health and safety deviations.
- It describes the management responsibilities of initiating deviation, capture data, analysis, investigation, determination of assignable causes, generation of management report and initiatives to be taken on corrective and preventative actions.

8. Example- Checklist for Batch Documentation

- This SOP describes the identification of all documentation relevant to a production process in the form of “Batch Documentation Checklists” and to ensure their collection by completion of the checklists by Authorized Persons.
- This procedure is based on an example of tablet packaging process described in the ‘Manufacturing’ category.

9. Evaluation of Batch Documentation and Release of Sale

- This procedure describes the process of collection, evaluation and record of batch related document generated during the production of a batch before an authorized person can release the batch for sale.

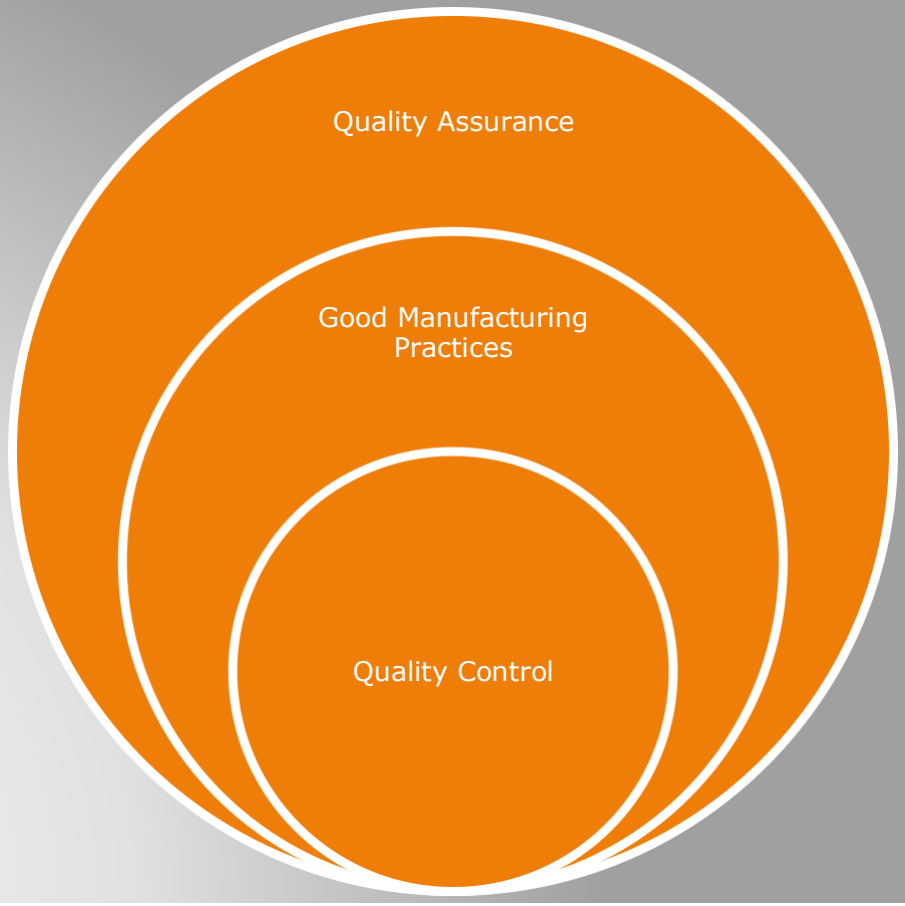
10. Raw Materials- Laboratory Testing and Documentation

This SOP describes the procedure for sampling, location, pre-testing, testing and documentation of all raw materials and components subject to test, out of specification results, microbiological tests and release procedure for passed raw materials and components.

11. Finished Goods- Laboratory Testing and Documentation

This SOP describes the procedure for sampling, location, pre-testing, testing and documentation of all finished products subject to test, reagents and standards to be used for analysis, management of out of specification results, microbiological tests and release procedure for passed finished goods.

Relationship Between QA, QC and GMP



Total Quality Control (TQC)

- The concept of total quality control refers to the process of striving to produce a perfect product by a series of measures requiring an organised effort at every stage in production.
- Although the responsibility for assuring product quality belongs principally to QA personnel, it involves many departments and disciplines within a company.

  To be effective, it must be supported by team effort.
- Quality must be built into a drug product during product and process, and it is influenced by the physical plant design, space, ventilation, cleanliness and sanitation during routine production.

- In products and process designing, it considers many parameters like:
  - Materials
  - In-process and product control
  - Specification and tests for active ingredients, excipients
  - Specific stability procedures of the product
  - Freedom from microbial contamination and proper storage
  - Containers, packaging and labelling
  - Product protection from moisture, light, volatility, and drug/package interaction

Total Quality Management(TQM)

According to ISO, TQM is defined as: "A management approach of an organisation centred on quality, based on the participation of all its members and aiming at long term success through customer satisfaction and benefits to all members of the organisation and society."

- The pharmaceutical industry is a vital segment of health care system which is regulated heavily because; any mistake in product design or production can severe, even fatal. The poor qualities of drug are not only a health hazard but also a waste of money for both government and individual consumers. So, the maintenance of the quality with continuous improvement is very important for pharmaceutical industries. From this concept Total Quality Management (TQM) was established. The aim of

TQM is prevention of defects rather than detection of defects. So TQM is very important for pharmaceutical industries to produce the better product and ensure the maximum safety of healthcare system and also protect waste of money for both government & individual consumers.

- Total Quality Management consists of organization-wide efforts to install and make permanent a climate in which an organization continuously improves its ability to deliver high-quality products and services to customers. While there is no widely agreed-upon approach, TQM efforts typically draw heavily on the previously developed tools and techniques of quality control.
- The production of quality pharmaceuticals products requires embracing the principles of TQM.

- Additionally, TQM will serve to improve productivity and customer satisfaction.
- The concept of TQM requires the total commitment of senior level management and supervision of all departments, operators, suppliers, and costumers.
- It continually strives for process improvement that begins with product development and only concludes when feedback and follow-up have been completed.

Activities in TQM

TQM is the foundation for activities, which include:

- Commitment by senior management and all employees
- Meeting customer requirements
- Reducing development cycle times
- Just in time/demand flow manufacturing

- Improvement teams
- Reducing product and service costs
- Systems to facilitate improvement
- Line management ownership
- Employee involvement and empowerment
- Recognition and celebration
- Challenging quantified goals and benchmarking
- Focus on processes / improvement plans
- Specific incorporation in strategic planning

Functions of TQM

- Product quality criteria are established, and detailed specifications are written. Meticulous, written procedures must be prepared for production and control. Raw material must be characterised and then purchased from reputable, approved suppliers.

- Facilities must be designed, constructed, and controlled to provide the proper stable environment for protecting the integrity of products. Equipments must be selected that is efficient and can be cleaned readily and sanitised.
- Personnel must be trained properly. The directions they use must be in writing, approved by responsible individuals.
- Distribution departments are responsible for controlling the shipping and handling of products, using inventory-control systems.
- The marketing department must be sensitive to the costumers' needs and be responsive to complaints.
- QA is ever present and gives approval only after assessing and being assured that the entire production process has been completed satisfactorily and that all the aspects of the GMPs have been satisfied.

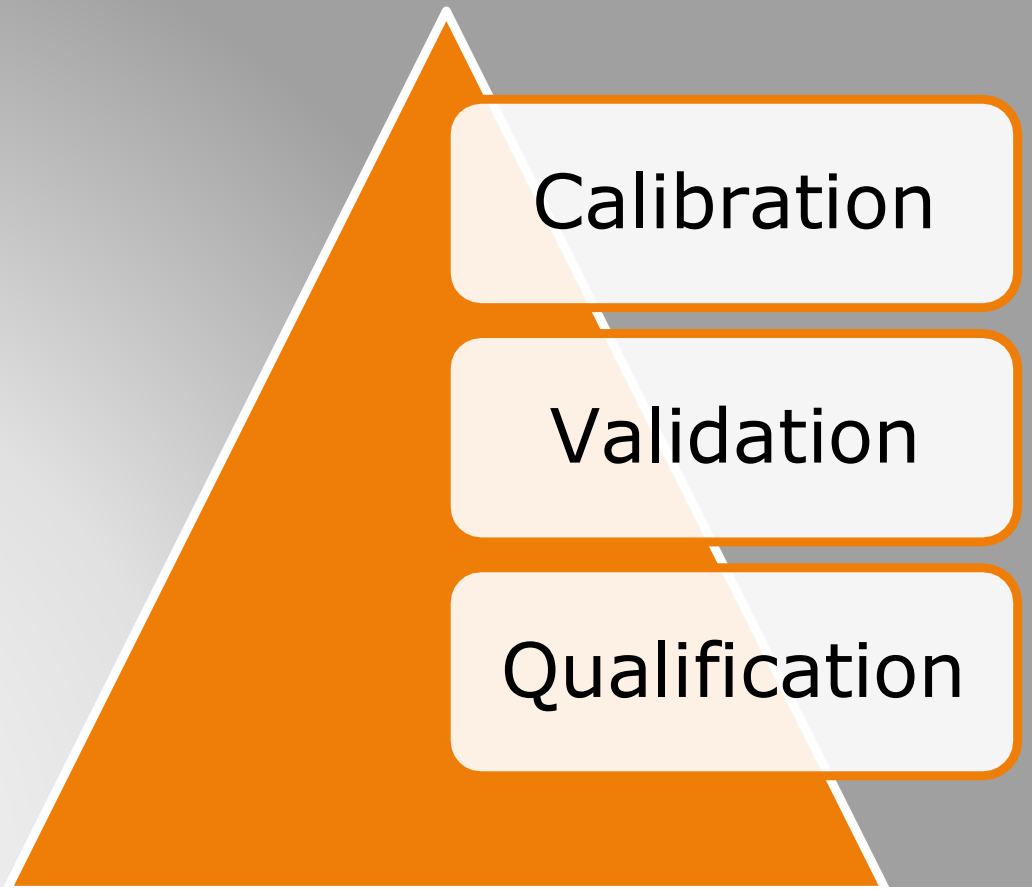
Advantages of TQM

- Improves reputation- faults and problems are spotted and sorted quicker.
- Higher employee morale- workers motivated by extra responsibility, team work and involvement indecisions of TQM
- Lower cost- decrease waste as fewer defective products and no need for separate.
- Quality control inspector

Disadvantages of TQM

- Initial introduction cost.
- Benefits may not be seen for several years.
- Workers may be resistant to change

Major Keywords of Quality Assurance



Calibration

Calibration is defined as operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties (of the calibrated instrument or secondary standard) and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication.

Qualification

Qualification is defined as action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Qualification includes the following steps:

- Design qualification (DQ)- Demonstrates that the proposed design (or the existing design for an off- the-shelf item) will satisfy all the requirements that are defined and detailed in the User Requirements Specification (URS). Satisfactory execution of the DQ is a mandatory requirement before construction (or procurement) of the new design can be authorised.
- Installation qualification (IQ) – Demonstrates that the process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place.
- Operational qualification (OQ) – Demonstrates that all facets of the process or equipment are operating correctly.
- Performance qualification (PQ) – Demonstrates that the process or equipment performs as intended in a consistent manner over time.

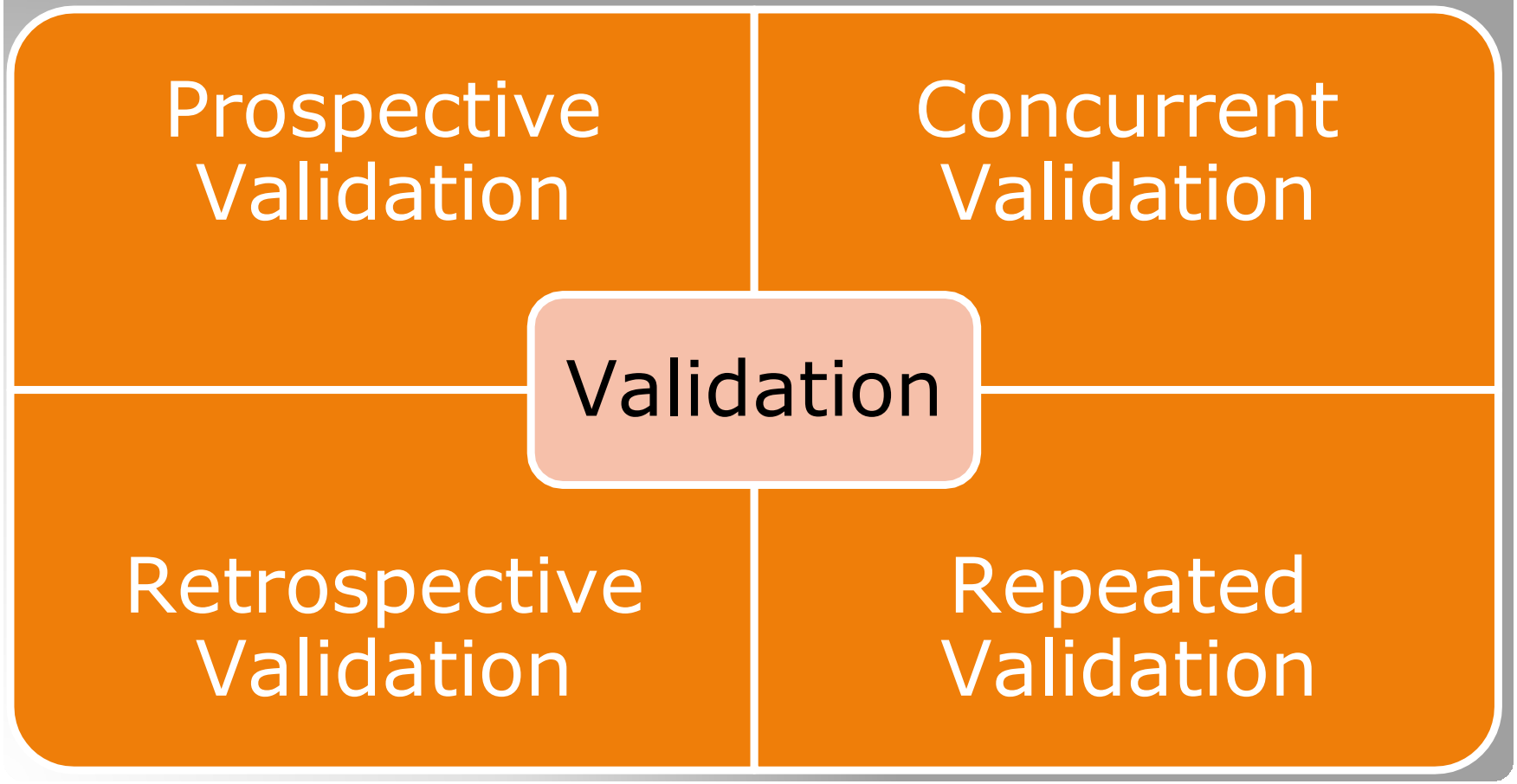
Validation

Validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages. In Pharma Industry it is very important apart from final testing and compliance of product with standard that the process adapted to produce itself must assure that process will consistently produce the expected results. Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

- Equipment validation
- Facilities validation
- HVAC system validation
- Cleaning validation
- Process Validation

- Analytical method validation
- Computer system validation
- Packaging validation
- Cold chain validation

Types of Validation



Prospective Validation

- Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps: these are then evaluated on the basis of past experience to determine whether they might lead to critical situations.
- Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory.

  Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the

production scale, e.g. in the preparation of injectable products.

Concurrent Validation

- Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process.
- Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

Retrospective Validation

- Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of

process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.

- Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products.

Revalidation or Repeated Validation

- Revalidation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality.

Role of QA in Pharma Industries

1.To establish Quality Audit

- Establish the quality management system to describe how the firm complies CGMPs and operates to maintain a state of control
- Keep current with good industry practices, and applicable to the mission of your operation.

2. To audit compliance to the Quality System

- Audit for compliance to policies and procedures: on paper vs. practice
- Report on the performance of the quality system, including trends, that help decision making for targeted actions.

3. To establish procedures and specifications

- Ensure that procedures and specifications are appropriate and followed.

- Ensure that the procedures and specifications of firms under contract are also appropriate and followed, i.e., maintain control and take responsibility for third-party services providers (contract manufacturers, contract laboratories, etc.)

4. To establish manufacturing controls

- Ensure that appropriate manufacturing in- process controls are implemented.
- Ensure in-process controls are performed during manufacturing operations and results are satisfactory

5. To perform laboratory tests

- Perform laboratory testing of components, containers, in-process materials, packaging materials and drug product using validated methods against scientifically-derived, fit-for-purpose specifications
- Approve or reject drug products manufactured, processed, packed,

or held undercontract by another company, i.e., final product release is not delegated to a contractor

- Perform retests or reexamine approved components, drug product containers and closures after long storage or exposure to adverse conditions.

6. To review and approve or reject

- Review and approve/reject any document that gives work instructions and set requirements such as procedures, protocols, test methods, and specifications—including changes to these documents
- Review and approve/reject reprocessing and rework procedures
- Review and approve/reject production batch records and make the final decision to release a product lot into commerce.

7. To ensure investigation of nonconformance

- Ensure investigation is conducted and root cause is eliminated for production and control record errors, discrepancies, and failure to meet specification, including quality attributes
- Review complaints to determine if it relates to a failure to meet specification, if so investigate and report to FDA if it is serious and unexpected

8. To keep management informed

- Report on product, process and system risks
- Report on outcome of regulatory inspections and ensure responses are complete and managed to verifiable closure

9. To describe responsibilities in writing

- Have a complete and compliant procedure that describes responsibilities
- Follow the procedure

10. To remain independent

- Ensure there is no conflict of interest between regulatory responsibilities and actual daily activities
- Be independent reviewer and approver with respect to manufacturing and process/ product development units

Control and Assurance of Manufacturing Practices

1. Personnel

Important parts for a successful personnel are:

- Proper selection
- Training
- Motivation of Production
- Packaging
- Control

It is essential that the qualified personnel be employed to supervise the formulation, Processing, Sampling, testing, packaging and labelling of the drug product, and that competent staff be placed in charge of the maintainance of machinery, equipment and sanitation.

2. Equipments and Buildings

- The building should provide adequate space for the orderly placement of materials and equipment to minimize any risks of mix-ups or cross-contamination between the drugs, excipients, packaging and labelling from the time the materials are received to the time the products are released.
- The desired characteristics of equipments for producing quality products are numerous, however, the equipment should be of suitable size, accuracy and reproducibility.

3. Control of records

The records, such as Master Formula and Batch production records, should be prepared and maintained in accordance with established procedures.

4. Control of Production Procedures

To ensure that products have the intended characteristics of identity, strength, quality, and purity, production and the related in-process quality control procedures should be rigidly followed as required by the master formula record or batch production record.

5. Packaging Control

A packaging record bearing an identification number is issued to the packaging section. This record specifies the packaging materials to be used, operations to be performed, and the quantity to be packaged.

6. **Validation**

Validation of a process is the demonstration that controlling the critical steps of a process results in products of repeatable attributes or causes a reproducible event.

7. Control and Assurance of Finished Products

- Unless the testing procedures by which the product quality is finally measured are established on an equally sound basis,the entire system may be deficient.
- Product failures causing rejections or recalls after market introduction are serious and can be easily detected and minimized by an effectively administered quality testing program.
- Therefore, the testing of the finished products for compliance with the established standards prior to release of the material for distribution is a critical factor for quality control and assurance.

ICH International Conference on Harmonization

- ICH

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

ICH (April 1990)

International Conference on Harmonization

It is a joint initiative involving regulators & industry as equal partners in the scientific & technical discussion of the testing procedure which are

recquired to ensure and assess the Quality, Safety, & efficacy of medicines

Mission

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

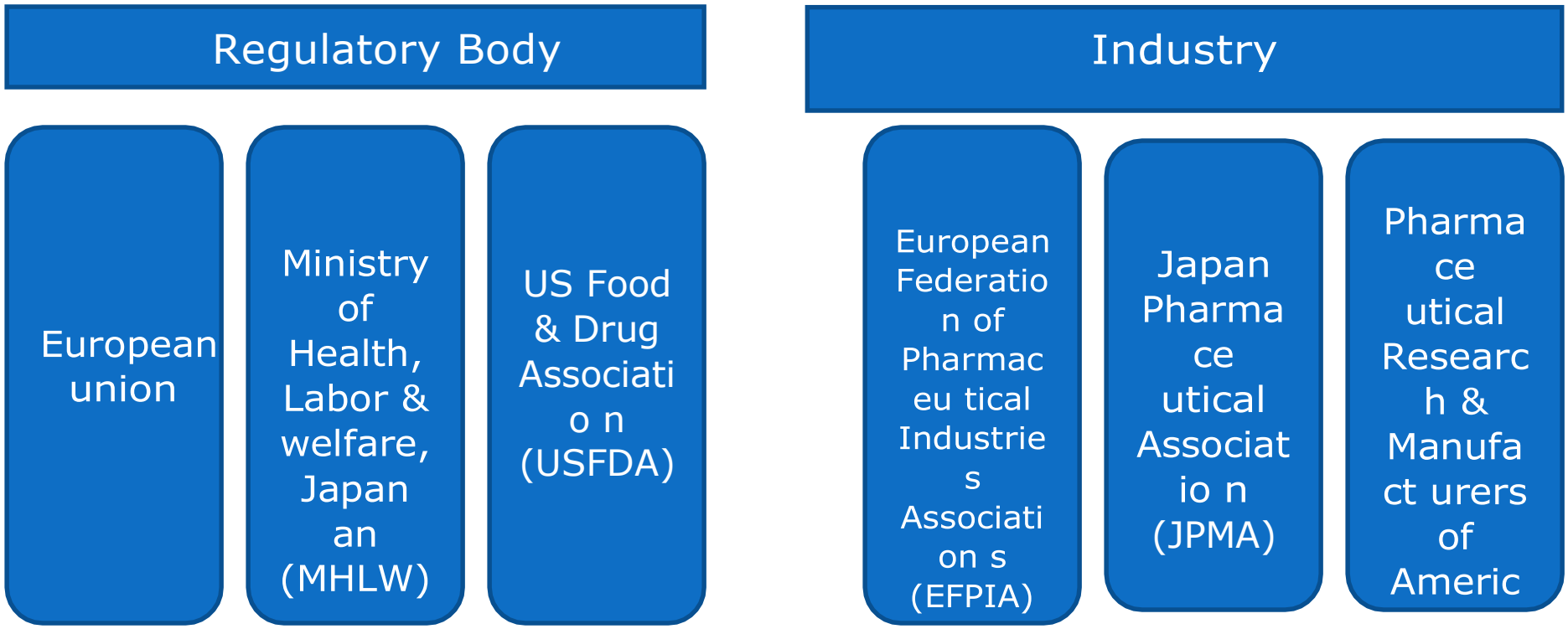
Need to Harmonize

- Realisation was driven by tragedies, such as that with thalidomide in Europe in the 1960s.
- The 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on Quality, Safety and Efficacy of new Medicinal products.
- Divergence in technical requirements from country tocountry.

Observers

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

Structure



Process of Harmonization

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

The Guidelines – Q S E M

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

- Terminology, electronic standards, common documents

Quality

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

Safety

- S1- Carcinogenicity Studies
- S2- Geno-toxicity Studies

- S3- Toxico-kinetics and Pharmacokinetics
- S4- Toxicity Testing
- S5- Reproductive toxicology
- S6- Biotechnological Product
- S7- pharmacology Studies
- S8- Imuno-toxicology Studies
- S9- Nonclinical evaluation for anticancer Pharmaceutical
- S10- Photosafety Evaluation

Efficacy

- E1&E2- Clinical Safety
- E3- Clinical Study Reports
- E4- Dose-response Studies
- E5- Ethnic Factors
- E6- Good Clinical Practice
- E7,E8,E9,E10,E11- Clinical Trials

- E12- Guidelines for Clinical Evaluation by therapeutic Category
- E14- Clinical Evaluation
- E15&E16- Pharmacogenomics

Multidisciplinary

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

Regulatory Requirements of Different Countries

European Union

- Intergovernmental political and economic union of 28 European

countries having internal single market through the standardized system oflaws.

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

The Role of EMA

EMA plays an important role in the regulation of medicines in the EU. On the basis of scientific assessments carried out. It grants and refuses, changes and suspends marketing authorizations for medicine that have been submitted via the centralized procedure.

The European comission can also take action concerning other aspects of medicine regulations:

- Right of Initiative- It can propose new legislation for pharmaceutical sector;
- Implementation- it can adopt implementing measures as well as oversee the correct application of EU law on pharmaceuticals;
- Global outreach: it ensure appropriate collaboration with relevant international partners and promotes the EU regulatory system globally.

MHRA

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

Role of MHRA

- Licencing
- Safety and efficacymonitoring
- Enforcement of laws
- Regulations of clinical trials
- Providing information to public and Health Professionals

- MHRA does not regulate dietary supplements, veterinary products and cosmetics.

TGA

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

- ARTG is computer database of information of TG
- Australia Manufacture all medicines licensed under part 4of the TG act1989.
- Once approval for marketing in australia, ARTG can be identified by AUST R (for registered Medicines) or AUST L (for listed medicine) that appears on packaging of the medicines.

ROW

Rest of the world: divided the world in 5 regions (ASIA, Emerging Europe/Turkey/Israel, Latin America, Middle East/Africa, Russia/CIS)

Key functions:

1. Product registration
2. Regulation of drug manufacturing, importation and distribution
3. Adverse drug reaction monitoring
4. Licensing of premises, person and practices.

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

Quality-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.

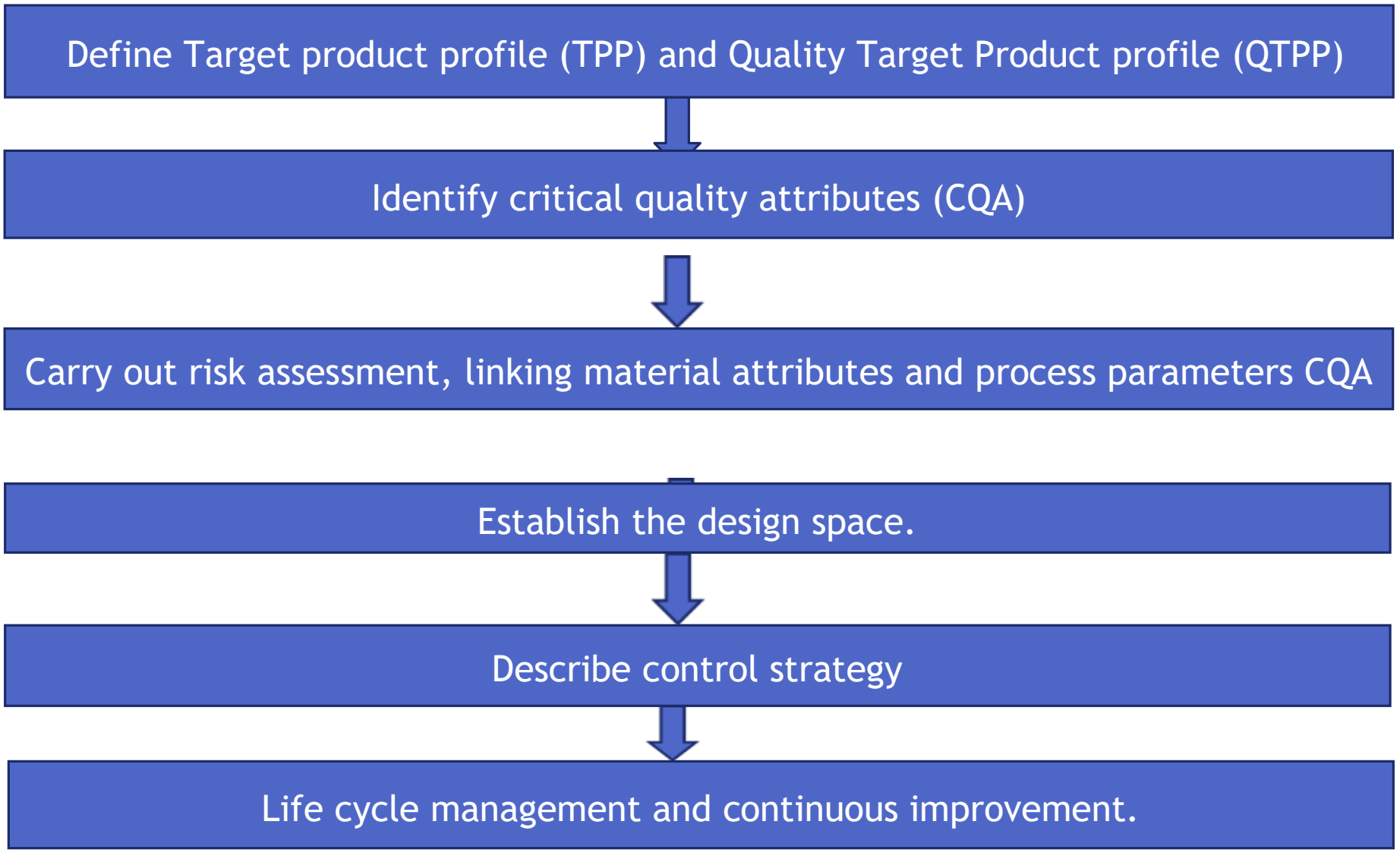
- More flexibility in decision making.
- Ensure scientific base of analysis.
- Ensures decisions made on science and not on
- empirical information.
- Improves quality of review.

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 may 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] designs 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

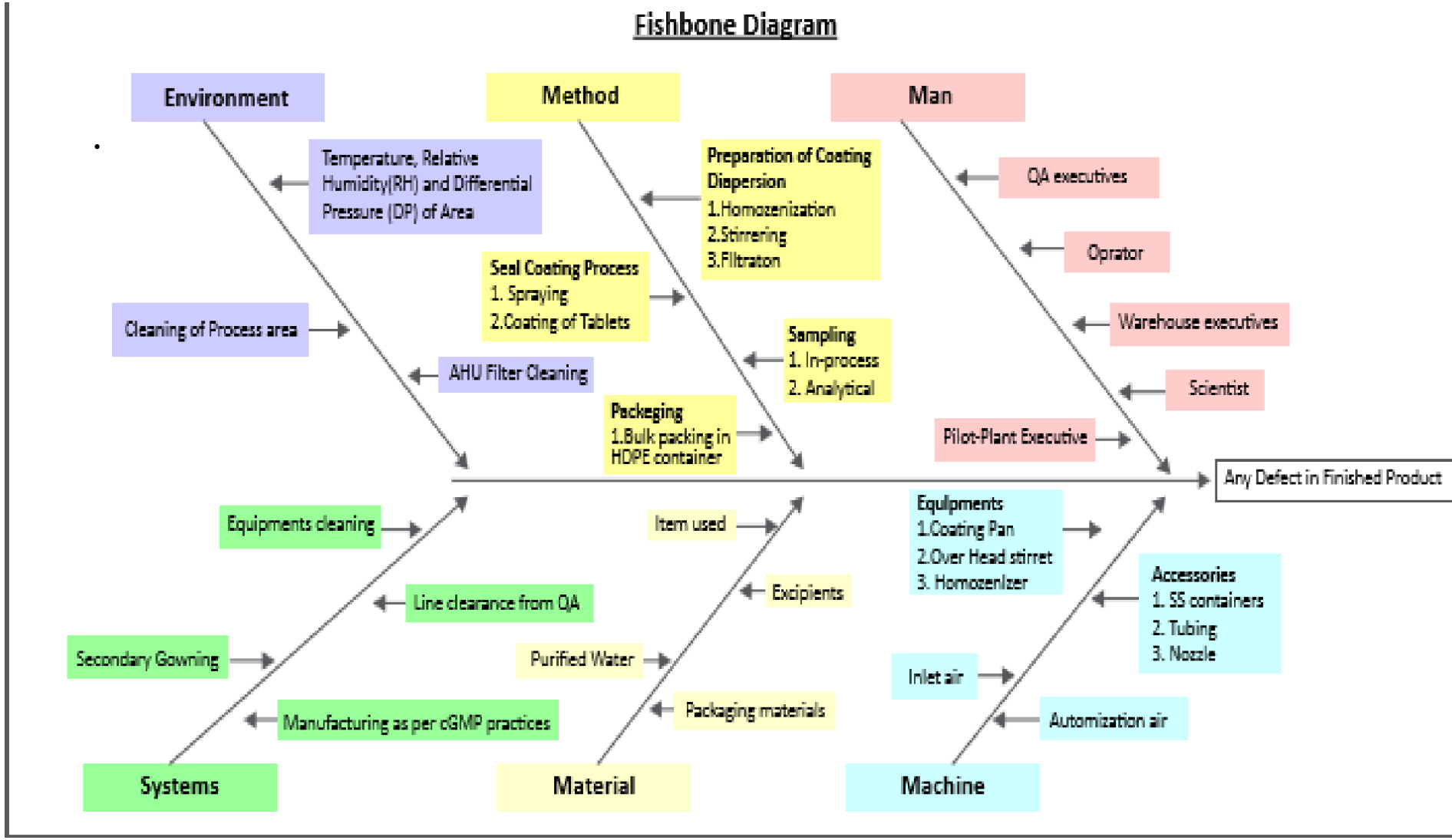
Fractional factorial design.

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.

What is NABL ?

NABL specifies the general requirements for the competence to carry out tests and calibrations, including sampling. It covers testing and calibration performed using standard methods, non-standard methods, and laboratory-developed methods.

Benefits ofAccreditation:

- Potential increase in business due to enhanced customer confidence and satisfaction.
- Savingsintermsoftimeandmoneyduetoreductionorelimination of the need for re-testing .
- Better control of laboratory operations and feedback to laboratories as to whether they have sound Quality Assurance System and are technically competent.

- Increase of confidence in Testing / Calibration data and personnel performing work.
- Customers can search and identify the laboratories accredited by NABL for their specific requirements from the directory of Accredited Laboratories.
- Users of accredited laboratories will enjoy greater access for their products, in both domestic and international markets, when tested by accredited laboratories.

Types of Laboratory can seek

Accreditation:

- Laboratories undertaking any sort of testing or calibration in the specified fields.
- Private or government laboratories.
- Small operations to large multi-field laboratories.
- Site facilities, temporary field operations and

mobile laboratories.

TESTING LABORATORIES	CALIBRATION LABORATORIES	MEDICAL LABORATORIES
• Biological • Chemical • Electrical • Electronics • Fluid-Flow • Mechanical • Non-Destructive Testing • Photometry • Radiological • Thermal • Forensic	• Electro-Technical • Mechanical • Fluid Flow • Thermal & Optical • Radiological	• Clinical Biochemistry • Clinical Pathology • Haematology & Immunohaematology • Microbiology & Serology • Histopathology • Cytopathology • Genetics • Nuclear Medicine *(in-vitro tests only)*
PROFICIENCY TESTING PROVIDERS		**REFERENCE MATERIAL PRODUCERS**

• Testing • Calibration • Medical • Inspection	• Chemical Composition • Biological & Clinical Properties • Physical Properties • Engineering Properties • Miscellaneous Properties

Approach to Accreditation

- Awareness Training
- Quality Policy & Objectives Finalization
- Gap Analysis
- Documentation / ProcessDesign
- Documentation / Process Implementation
- Internal Audit
- Management ReviewMeeting

- Shadow Audit
- Corrective –Preventive Actions
- Final Certification Audit

Step 1:- 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

Step2:-Quality Policy&Objectives

- 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.

Step 3:-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

Step 4:-Documentation /Process Design

- Quality Manual
- Functional Procedures
- Work Instructions
- System Procedures
- Formats

Step 5:-Documentation / Process Implementation

- Work–shop on process / document implementation as per ISO 17025 requirements.
- Departmental / Individual assistance in implementing the new processes / documents.

Step 6:-InternalAudit

- 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

Step7:-ManagementReviewMeeting

- Quality Policy &Objectives
- Results of internalaudit
- Results of supplierevaluation
- Results of customercomplaints
- Results of customer feedback etc.

Step 8:-ShadowAudit

- A replica of final certification audit.
- FindsdegreeofcompliancewithISO17025 standard.
- Gives an idea to the employees about the conduct of the final certification audit.

Step9:-Corrective–PreventiveActions

- On the basis of shadow audit conducted in the last step, all the non-conformities willbeassigned corrective and preventive actions.
- AcheckwillensurethatalltheNCsareclosedandtheorganizationisreadyforthe finalcertification audit.

Step10:-FinalCertificationAudit

Upon completion of various stages of accreditation audit, the audit, your organizationwillbeawarded accreditation.

Quality Standard-ISO 9000

Introduction to ISO 9000

The **ISO 9000** family of standards is related to quality management systems and designed to help organizations ensure that they meet the needs of customers and other stakeholders while meeting statutory and regulatory requirements.

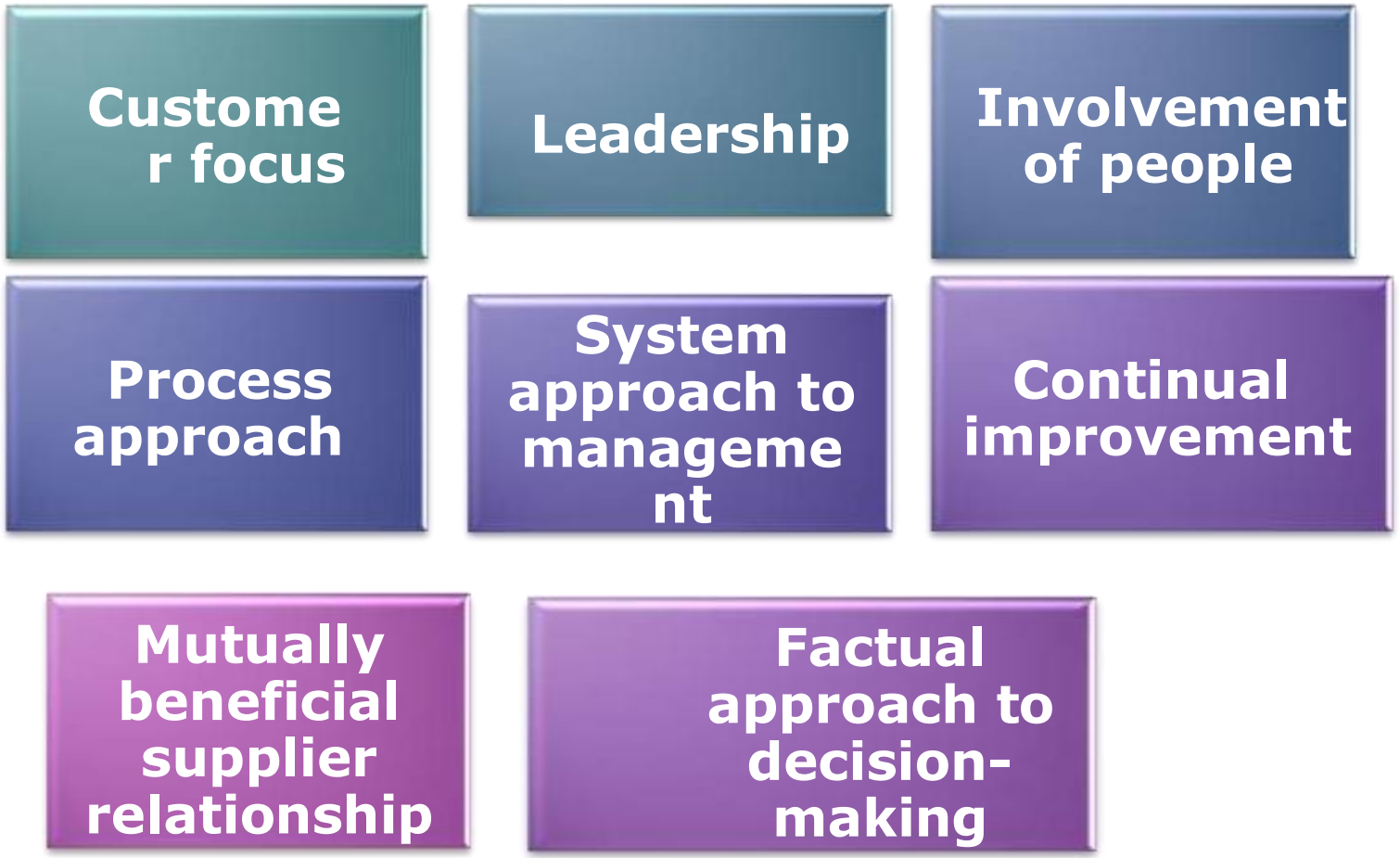
ISO 9000 deals with the fundamentals of quality management systems, including the eight management principles on which the family of standards is based.

International standards promote international trade by providing one consistent set of requirements recognized around the world.

ISO 9000 can help a company satisfy its customers, meet regulatory requirements and achieve continual improvement. It provides the base level of a quality system, not a complete guarantee of quality.

Originally published in 1987 by the International Organization for Standardization (ISO), a specialized international agency for standardization composed of the national standards bodies of 90 countries.

Eight Quality Management Principles



ISO 9000 Series

ISO 9000	Explains fundamental quality concepts and provides guidelines for the selection and application of each
ISO 9001	Model for quality assurance in design, development, production, installation and servicing.
ISO 9002	Model for quality assurance in the production and installation of manufacturing systems

ISO 9003

Quality assurance in final inspection and testing.

ISO 9004

Guidelines for the applications of standards in quality management and quality systems.

ISO 9000 and ISO 9004 are guidance standards. They describe what is necessary to accomplish the requirements outlined in standards 9001, 9002 or 9003.

Advantages

- Quality is maintained,
- ISO registration also has a significant bearing on market credibility as well.
- Opportunity to compete with larger companies,
- More time spent on customer focus,
- Confirmation that your company is committed to quality
- May facilitate trade and increased market opportunities,
- Can increase customer confidence and satisfaction.