UNIT 1

Quality Assurance and Quality Management Concepts

1.1 Introduction

Quality is an important factor when it comes to any product or service. With the high market competition, quality has become the market differentiator for almost all products and services. Therefore, all manufacturers and service providers out there constantly look for enhancing their product or the service quality.

In order to maintain or enhance the quality of the offerings, manufacturers use two techniques, quality control and quality assurance. These two practices make sure that the end product or the service meets the quality requirements and standards defined for the product or the service.

There are many methods followed by organizations to achieve and maintain required level of quality. Some organizations believe in the concepts of Total Quality Management (TQM) and some others believe in internal and external standards.

The standards usually define the processes and procedures for organizational activities and assist to maintain the quality in every aspect of organizational functioning. When it comes to standards for quality, there are many. ISO (International Standards Organization) is one of the prominent bodies for defining quality standards for different industries. Therefore, many organizations try to adhere to the quality requirements of ISO. In addition to that, there are many other standards that are specific to various industries. As an example, SEI-CMMi is one such standard followed in the field of software development.

Since standards have become a symbol for products and service quality, the customers are now keen on buying their product or the service from a certified manufacturer or a service provider. Therefore, complying with standards such as ISO has become a necessity when it comes to attracting the customers.

1.1.1 Quality Control

Many people get confused between quality control (QC) and quality assurance (QA). Let's take a look at quality control function in high-level. As we have already discussed, organizations can define their own internal quality standards, processes and procedures; the organization will develop these over time and then relevant stakeholders will be required to adhere by them.

The process of making sure that the stakeholders are adhered to the defined standards and procedures is called quality control. In quality control, a verification process takes place. Certain activities and products are verified against a defined set of rules or standards.

Every organization that practices QC needs to have a Quality Manual. The quality manual outlines the quality focus and the objectives in the organization. The quality manual gives the quality guidance to different departments and functions. Therefore, everyone in the organization needs to be aware of his or her responsibilities mentioned in the quality manual.

1.1.2 Quality Assurance

Quality Assurance is a broad practice used for assuring the quality of products or services. There are many differences between quality control and quality assurance. In quality assurance, a constant effort is made to enhance the quality practices in the organization. Therefore, continuous improvements are expected in quality functions in the company. For this, there is a dedicated quality assurance team commissioned.

Sometimes, in larger organizations, a 'Process' team is also allocated for enhancing the processes and procedures in addition to the quality assurance team. Quality assurance team of the organization has many responsibilities. First and foremost, responsibility is to define a process for achieving and improving quality.

Some organizations come up with their own process and others adopt a standard process such as ISO or CMMi. Processes such as CMMi allow the organizations to define their own internal processes and adhere by them.

Quality assurance function of an organization uses a number of tools for enhancing the quality practices. These tools vary from simple techniques to sophisticated software systems. The quality assurance professionals also should go through formal industrial trainings and get them certified. This is especially applicable for quality assurance functions in software development houses.

Since quality is a relative term, there is plenty of opportunity to enhance the quality of products and services. The quality assurance teams of

organizations constantly work to enhance the existing quality of products and services by optimizing the existing production processes and introducing new processes.

1.1.3 GMP (Good Manufacturing Practices) and Requirements of Premises, Plant and Equipment

In order to ensure production of quality drug formulation, it is necessary on the part of the manufacturer to follow well established and ethical approach involving different operations of manufacture. It was on several occasions discussed in professional meetings and conferences that there is a need for well set mandatary guidelines required to be followed by manufactures of different dosage formulations. It was with this background; Good Manufacturing Practices under Schedule M were made mandatory conditions for manufacturing operations of pharmaceutical formulations.

The quality of drug formulations is the sole responsibility of the manufacturer. He has to ensure the production of desired quality formulations and their stability until, the formulation reaches the consumer across the retailing counter. The Schedule M is covered under Rules 71, 74, 76 and 78 and is in two parts.

Part I deals with GMP relating to factory premises and materials.

Part II deals with requirement of plant and equipment.

1.1.4 PART I: Factory Premises and Materials (Salient Features)

- **General Requirements**

  Good location; free from contamination due to sewage, drain, fumes, dust, smoke, etc.; hygienic conditions; prevention of entry of insect and/or rodents; interior surface of premises should be smooth; adequate lighting; proper ventilation; humidity control; underground drainage; concealed electrical and sanitary fittings in the premises; supply of pure water; regular cleaning and disinfection of premises; proper treatment of waste water; pollution control and disposal of pollutants.

- **Warehousing Area**

  Adequate area for orderly warehousing of various categories of materials; adapted to ensure good storage condition; protection from adverse weather conditions; separate earmarked areas in same warehouse for quarantine status; separate sampling area; segregation for storage of rejected, recalled or returned materials; safe and secure areas for NDPS and hazardous substances; safe storage of printed packaging material; separate dispensing areas for Beta lactum, sex hormones, cytotoxic substances and other special categories; regular checks and rodent control.

- **Sterile Products**

  Separate enclosed area with air locks; air supply through HEPA filters; routine microbial counts; laminar flow cabinets availability and access restricted only to authorized persons.

- **Working Space**

  Adequate space for orderly placement of equipment and material; and separate storage area for raw material "under test", "approved" and "rejected". The pipe-work, electrical fittings and ventilation openings should be properly designed.

- **Health, Clothing and Sanitation of Workers**

  The workers should be free from contagious diseases. It covers regular medical check-up facilities; proper toilet facility at a distance; personal cupboards and change room for workers.

- **Medical Services**

  First-aid facility; medical examination of workers and all other staff at the time of recruitment; periodic medical check-up of all staff members once in a year; services of physicians available at short notice, proper facilities for vaccinations, etc.

- **Sanitation in Manufacturing Premises**

  No accumulated waste; no dust particles as far as possible; proper disinfection and cleaning of premises and no stagnant water. The manufacturing premises should be used for specific purpose for which it is designed.

- **Equipment**

  Properly installed to achieve operational efficiency; good quality equipment to be used. The equipment used should be such to facilitate through cleaning; prevent physical and chemical change through contact and minimize contamination. The written instructions for utilization of equipment be provided and accuracy, precision should be maintained.

- **Raw Materials**

  Properly identified; analyzed; containers of raw materials inspected for any damage; stored at optimum temperature; labeled properly; systematically sampled by quality control personnel; tested for compliance of required standards; released from quarantine by quality control personnel through written instructions; and rejected materials destroyed or returned back to the supplier.

- **Personnel Manufacture**

  Under direct supervision of competent technical staff; separate Head for Q.C. laboratory; qualified and experienced personnel for Quality

Assurance and Quality Control Operations; labeling; quarantine and storage; batch numbering; testing, records of analysis; equipment assembly and calibration; maintenance; cleaning and sanitation; personnel; pest control; complaints, and recalls made and returns received.

- **Manufacturing Operations and Controls**

  Competent technical staff supervision for weighing, measuring and other operations; nonsterile products free from *E. coli* and *Salmonella* microbes; conspicuously labelled with name, batch number, and other details; cross contamination avoided; and all process controls checked under master formula.

- **Reprocessing and Recovery**

  The reason for reprocessing should be specified, corrective measures for recovery should be spelt out only if permitted in Master Formula.

- **Product Containers**

  Compliance with pharmacopeial requirements; cleaning procedures and sterilization procedure should be properly followed. There should be written schedule for programs for cleaning of container. When bottles are not dried after washing, deionized water is used for rinsing.

- **Labels and Other Printed Materials**

  Stored properly and separately; used as and when required and should not be inter-mixed.

- **Distribution Records**

  Records properly maintained; records of complaints, adverse reactions and other reactions from consumers are also maintained.

- **Quality Control System**

  Detailed instructions for quality control of raw materials and finished product; quality control for packaging and labeling; adequacy of storage, quality control procedure revised as and when possible and qualitative examination of returned products.

1.1.5 PART II: Plant and Equipment (Salient Features)

The Part II of Schedule M gives the details of the plant and equipment required for manufacture, quality control and quality assurance of different dosage forms. The specifications of equipl!1ents are also indicated. The details of requirements are categorized into 11 groups.

1.1.5.1 External Preparations: It covers ointments, emulsions, lotions, solutions, pastes, creams, dusting powders and other identical preparations.

(a) Minimum area: 30 square meters for basic installation and 10 square meters for ancillary area.

(b) Requirements: Mixing and storage tanks, jacketed kettles of different types, electric mixer, planetary mixer, colloid mill, triple roller mill, liquid and tube filling equipments, etc.

1.1.5.2 Oral Liquid Preparations: It covers syrups, elixirs, emulsions and suspensions.

(a) Minimum area: 30 square meters for basic installation -and 10 square meters for ancillary area;

(b) Requirements: SS mixing and storage tanks, jacketed kettles of different types, electric stirrer, electric colloidal mill, emulsifier, filtration equipment, bottle filling machine, cap sealing machine, deionizer or water distillation unit, clarity testing unit, etc.

1.1.5.3 Tablets: For effective production, tablet production department is divided into four sections

Mixing, granulation and drying section

Tablet compression section

Packaging section (strip/blister)

Coating section

(a) Minimum area: A minimum of 60 square meters for basic installation and 20 square meters for ancillary area for un-coated tablets. For coated tablet, additional area of 30 square meters for coating section and 10 square meters for ancillary area.

(b) Requirements: Disintegrator, sifter, powder mixer, mass mixer, planetary mixer, rapid mixer granulator, granulator, hot air oven, weighing machines, compression machine (single, multi-punch, rotary), punches and dies storage cabinets, table de-duster, table inspection unit/belt, dissolution test apparatus, single pan balance, hardness tester, friability and disintegration test apparatus, strip/blister packaging machine, leak test apparatus, tablet counter, jacketed kettles of different types, SS coating pan, polishing pan, weighing balance, exhaust system and vacuum dust collector, air-conditioning system (wherever applicable), etc.

1.1.5.4 Powders

(a) Area: Minimum 30 square meters; additional room for actual blending

(b) Requirements: Disintegrator, electric mixer, sifter, SS vessels and scoops of suitable sizes, filling equipment, weighing balance, etc.

1.1.5.5 Capsules

(a) Area: A separate enclosed area, suitably air-conditioned and dehumidified. A minimum area of 25 square meters for basic installation and 10 square meters for ancillary area each for penicillin and non-penicillin section.

(b) Requirements (for hard gelatin capsules): Electrical mixing and blending equipment, capsule filling units (semiautomatic and automatic), capsules counters, weighing balance, disintegration test apparatus, capsule polishing equipment, etc.

1.1.5.6 Surgical Dressings

(a) Area: Minimum 30 square meters for basic installation; for medicated dressing additional room required.

(b) Requirements: Rolling, staining, cutting, folding and pressing machines; mixing tanks, hot air oven, steam sterilizer, work tables, etc.

1.1.5.7 Ophthalmic Preparations

It includes eye-ointment, eye lotions and other preparations for external use. Separate enclosed areas with air-lock arrangements required.

(a) Area: Minimum 25 square meters for basic installation and 10 square meters for ancillary area.

(b) Requirements: Hot air ovens, jacketed kettles of different types, colloid mill, ointment mill, SS-mixing and storage tanks; tube washing, drying, cleaning and filling machines; automatic vial washing machine, vial drying machines, sintered glass funnels, autoclave, liquid filling equipment, laminar flow units, air conditioning and dehumidification arrangement. rubber bung washing machine, etc.

1.1.5.8 Pessaries and Suppositories

(a) Area: Minimum 25 square meters for basic installation

(b) Requirements: Mixing, pouring and molding equipments; weighing devices. For pessaries manufactured by granulation and compression, requirements shall be as given under "tablet".

1.1.5.9 Inhalers and Vitrallae

(a) Area: Minimum 25 square meters for basic installation.

(b) Requirements: Mixing, graduated delivery and sealing equipments.

1.1.5.10 Repacking of Drugs and Pharmaceuticals

(a) Area: Minimum 30 square meters for basic installation. Exhaust system be provided in case of operations involving floating particles.

(b) Requirements: Weighing, measuring and filling equipments; powder disintegrator, electrically operated powder sifter, electric sealing machine, SS scoops and vessels, etc.

1.1.5.11 Parenteral Preparations: The whole operation of manufacture (small volume injectables and large volume parenterals) in glass and plastic preparations are divided in separate areas/rooms.

A. Parenteral Preparations in glass containers: It includes areas for water management, containers, closures preparation, solution preparation, filling, capping, sealing, sterilization, quarantine, visual inspection and packaging.

(a) Area: Minimum 150 square meters for basic installation and 100 square meters for ancillary area for small volume injectables.

(b) Requirements: Distillation unit, deionized water unit, thermostatically controlled water storage tank, transfer pumps, SS service lines for carrying water, automatic rotary ampoule/ vial/bottle washing machine, automatic closures, washing machine, dryer, double ended sterilizer; storage equipment for ampoules, vials, bottles and closures, SS benches/stools, dust proof storage cabinets, mixing SS tanks, portable stirrer, filtration equipment, transfer pumps, automatic ampoule/vial/bottle filling, capping, sealing machines under laminar air flow work station; gas lines for nitrogen, oxygen and carbon dioxide; steam sterilizer, hot air sterilizer, storage cabinets, visual inspection units, batch coding, machine labeling unit, pressure leak test apparatus, etc.

For large volume parenterals the minimum area required is 150 square meters each for basic installation and ancillary area.

B. Parenteral Preparations in Plastic Containers by Form - FiII-Seal/Blow, FiII- Seal technology

The operational activities are in separate areas for water management, solution preparation, container-moulding-cum-filling, sealing, sterilization, quarantine, visual inspection and packaging.

(a) Area: Minimum 250 square meters for basic installation and 150 square meters for ancillary area. Areas for formulations meant for external and internal uses shall be separately provided. A minimum of 100 squares meters be provided for packaging materials for large volume parenterals.

(b) Requirements: Deionized water treatment unit, distillation unit (multi-column with heat exchangers), thermostatically controlled water storage tank, transfer pumps, storage tanks, solution preparation tanks, transfer pumps, cartridge and membrane filters, sterile form fill-seal machine, plastic granules feeding device, super-heated steam sterilizer, adequate number of platforms, racks for storage, visual inspection unit, pressure leak test apparatus, batch coding machine, labelling unit, etc.

1.2 TQM

In order to understand "Total quality management", first we have to understand what does 'Quality' actually mean?

'Quality' is generally referred to a parameter which decides the inferiority or superiority of a product or service. It is a measure of goodness to understand how a product meets its specifications. Usually, when the expression "quality" is used, we think in the terms of an excellent product or service that meets or even exceeds our expectations. These expectations are based on the price and the intended use of the goods or services. In simple words, when a product or service exceeds our expectations, we consider it to be of good quality. Therefore, it is somewhat of an intangible expression based upon perception.

1.2.1 Definition of TQM

Total Quality Management is defined as a customer-oriented process and aims for continuous improvement of business operations. It ensures that all allied works (particularly work of employees) are toward the common goals of improving product quality or service quality, as well as enhancing the production process or process of rendering of services. However, the emphasis is put on fact-based decision making, with the use of performance metrics to monitor progress.

1.2.2 The Key Principles of Total Quality Management

Commitment from the management:

- Plan (drive, direct)
- Do (deploy, support, and participate)
- Check (review)
- Act (recognize, communicate, revise)

Employee Empowerment

- Training
- Excellence team

- Measurement and recognition
- Suggestion scheme

Continuous Improvement

- Systematic measurement
- Excellence teams
- Cross-functional process management
- Attain, maintain, improve standards

Customer Focus

- Partnership with Suppliers
- Service relationship with internal customers
- Customer-driven standards
- Never compromise quality

1.2.3 Benefits of Total Quality Management

The benefits arising from the implementation of a Total Quality Management in an organization are:

- This will increase the awareness of quality culture within the organization.
- A special emphasis on teamwork will be achieved.

1.2.4 Beliefs about Total Quality Management

Following are the universal Total Quality Management beliefs:

- Satisfaction of the customer/owner is the measure of quality.
- Everyone is an owner.
- Continuous Quality improvement must be there.
- Analysis of the processes is the key to quality improvement.
- Constant TQM is not possible without consistent, active and enabling leadership by managers at all levels.
- It is important to incessantly improve quality of the products and services which we are supposed to provide to our customers/owners.

1.2.5 The 8 Primary Elements of TQM

Total quality management can be summarized as a management system for a customer-focused organization that involves all employees in continual improvement. It uses strategy, data, and effective communications to integrate the quality discipline into the culture and activities of the organization. Many of these concepts are present in modern Quality

Management Systems, the successor to TQM. Here are the 8 principles of total quality management:

A. Customer-focused

The customer ultimately determines the level of quality. No matter what an organization does to foster quality improvement-training employees, integrating quality into the design process, upgrading computers or software, or buying new measuring tools-the customer determines whether the efforts were worthwhile.

B. Total employee involvement

All employees participate in working toward common goals. Total employee commitment can only be obtained after fear has been driven from the workplace, when empowerment has occurred, and management has provided the proper environment. High-performance work systems integrate continuous improvement efforts with normal business operations. Self-managed work teams are one form of empowerment.

C. Process-centered

A fundamental part of TQM is a focus on process thinking. A process is a series of steps that take inputs from suppliers (internal or external) and transforms them into outputs that are delivered to customers (again, either internal or external). The steps required to carry out the process are defined, and performance measures are continuously monitored in order to detect unexpected variation.

D. Integrated system

Although an organization may consist of many different functional specialties often organized into vertically structured departments, it is the horizontal processes interconnecting these functions that are the focus of TQM.

Micro-processes add up to larger processes, and all processes aggregate into the business processes required for defining and implementing strategy. Everyone must understand the vision, mission, and guiding principles as well as the quality policies, objectives, and critical processes of the organization. Business performance must be monitored and communicated continuously.

An integrated business system may be modeled after the Baldrige National Quality Program criteria and/or incorporate the ISO 9000 standards. Every organization has a unique work culture, and it is virtually impossible to achieve excellence in its products and services unless a good quality culture has been fostered. Thus, an integrated system connects business improvement elements in an attempt to

continually improve and exceed the expectations of customers, employees, and other stakeholders.

E. Strategic and systematic approach

A critical part of the management of quality is the strategic and systematic approach to achieving an organization's vision, mission, and goals. This process, called strategic planning or strategic management, includes the formulation of a strategic plan that integrates quality as a core component.

F. Continual improvement

A major thrust of TQM is continual process improvement. Continual improvement drives an organization to be both analytical and creative in finding ways to become more competitive and more effective at meeting stakeholder expectations.

G. Fact-based decision making

In order to know how well an organization is performing, data on performance measures are necessary. TQM requires that an organization continually collect and analyze data in order to improve decision making accuracy, achieve consensus, and allow prediction based on past history.

H. Communications

During times of organizational change, as well as part of day-to-day operation, effective communications play a large part in maintaining morale and in motivating employees at all levels. Communications involve strategies, method, and timeliness.

These elements are considered so essential to TQM that many organizations define them, in some format, as a set of core values and principles on which the organization is to operate. The methods for implementing this approach come from the teachings of such quality leaders as Philip B. Crosby, W. Edwards Deming, Armand V. Feigenbaum, Kaoru Ishikawa, and Joseph M. Juran.

1.2.6 Influences on The Total Quality Management Philosophy

The Philosophy of TQM was born out of the concepts developed by namely **four great gurus** of Quality management.

- W. Edwards Deming
- Joseph M Juran
- Armand V Feigenbaum
- Philip Crosby

Here is a short introduction to their concepts and how these contributed to Total Quality Management Philosophy that we have today.

W. Edwards Deming

Deming's argument was that quality that is achieved through a reduction in statistical variation improves competitive position as well as productivity.

He defined Quality as being the direct result of quality of design, quality of conformance and the quality of the sales and service function.

A great believer in measuring quality by direct statistical measurement against specification, the goal of quality improvement is to reduce variation.

He developed a set of 14 points for management that express these issues. His beliefs were that quality management and improvement were the responsibility of all employees in a company.

Deming also believed that managers must change and to develop partnerships with those at the operating level of the business, one of the key elements in the Total Quality Management Philosophy.

Joseph Juran

Juran was probably the greatest contributor to the Total Quality Management Philosophy.He developed his ten-point plan which is the backbone of TQM implementation nowadays.

The Juran Method:

1. Build awareness of the need and opportunity for improvement
2. Set goals for improvement
3. Organize to reach the goals
4. Provide training
5. Carry out projects to solve problems
6. Report progress
7. Give recognition
8. Communicate results
9. Keep the score
10. Maintain momentum by making annual improvement part of the regular system and processes of the company.

Juran defined Quality as being "Fitness for Use" and really emphasized the cost of quality.

He believed that it was important to take management structure as a starting point and to build the quality improvement program from that baseline.

Armand Feigenbaum

Feigenbaum was the originator of the term "Total Quality Control". He believed that significant quality improvement could only be achieved by the participation of everyone in the organisation.

Fire-fighting quality management should be replaced with clear, customer-oriented quality management which the employees understand and can commit themselves to.

Feigenbaum believed that the goal of Quality improvement was to reduce the total cost of quality to as low a percentage as possible.

Philip Crosby

Philip Crosby's argument is that higher quality will ultimately reduce costs. He defined Quality as being the "Conformance to Requirements".

He developed a program with 14 steps that has the focus of changing an organization using action plans for their implementation.

His absolute beliefs were that

1. Quality means conformance and not elegance
2. It is always cheaper to do a job right first-time round
3. The only performance indicator is the cost of quality
4. The only performance standard is Zero Defects

1.3 ICH Guidelines

ICH is the "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use" was established in 1990 as a tripartite venture representing regulatory bodies and research-based industry. ICH is a joint initiative involving both regulators and research-based industry representatives of the EU, Japan and the US in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines.

The ICH Secretariat is based in Geneva. The biennial meetings and conferences of the ICH Steering Committee rotate between the EU, Japan, and the USA.

1.3.1 Objectives of ICH

- To increase international harmonization of technical requirements to ensure that safe, effective and high-quality medicines are developed.
- To harmonize technical requirements for registration or marketing approval.

- To develop and register pharmaceuticals in the most efficient and cost-effective manner.
- To promote public health.
- To prevent unnecessary duplication of clinical trials on humans.
- To minimize the use of animal testing without compromising safety and effectiveness of drug.

1.3.2 Purpose of ICH

- To promote international harmonization by bringing together representatives from the three ICH regions (EU, Japan and USA)
- To discuss and establish common guidelines.
- To make information available on ICH, ICH activities and ICH guidelines to any country or company that requests the information
- To promote a mutual understanding of regional initiatives in order to facilitate harmonization processes related to ICH guidelines regionally and globally
- To strengthen the capacity of drug regulatory authorities and industry to utilize them.

1.3.3 Participants of ICH

- ICH is comprised of representatives from six parties that represent the regulatory bodies and research-based industry in the European Union, Japan and the USA.
- In Japan, the members are the Ministry of Health, Labour and Welfare (MHLW), and the Japan Pharmaceutical Manufacturers Association (JPMA).
- In Europe, the members are the European Union (EU), and the European Federation of Pharmaceutical Industries and Associations (EFPIA).
- In the USA, the members are the Food and Drug Administration (FDA), and the Pharmaceutical Research and Manufacturers of America (PhRMA).
- Additional members include Observers from the World Health Organization (WHO), European Free Trade Association (EFTA), and Canada. The Observers represent non-ICH countries and regions.

1.3.4 ICH Structure

The ICH structure consists of the ICH Steering Committee, ICH Coordinators, ICH Secretariat and ICH Working Groups.

1.3.4.1 ICH Steering Committee

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

1.3.4.2 ICH Coordinators

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

1.3.4.3 ICH Secretariat

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

1.3.4.4 ICH Working Group

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

1.3.5 Steps in the ICH Process

Step-1: Drafts are prepared and circulated through many revisions until a "final harmonised draft" is completed

Step-2: This draft is signed by the EWG as the agreed upon draft and forwarded to the Steering Committee for signing which signifies acceptance for consultation by each of the six co-sponsors

Step-3: The three regulatory sponsors initiate their normal consultation process to receive comments.

Step-4: is reached when the Steering Committee agrees that there is sufficient scientific consensus on the technical issues. This endorsement is based on the signatures from the three regulatory parties to ICH affirming that the Guideline is recommended for adoption by the regulatory bodies of the three regions.

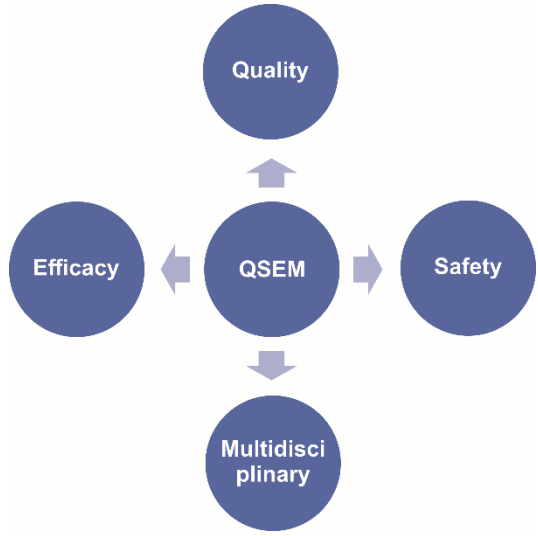
Step-5: The process is complete when the guidelines are incorporated into national or regional internal procedures (implementation in the 3 ICH regions).

1.3.6 Overview of QSEM

"Quality" Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)

Efficacy" Topics, i.e., those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)

Safety" Topics, i.e., those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)



Multidisciplinary" Topics, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories.

1.3.7 Quality Guidelines

"Quality" Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)

Q1A-Q1F---STABILITY

OBJECTIVE OF STABILITY TESTING- "…… to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity & light, & enables recommended storage conditions, re-test periods & shelf lives to be established"

Variables affecting the stability-

- Formulation
- Packaging
- Site and method of
- manufacture API Finished product
- Batch size
- Batch to batch variability Process validation Quality risk management
- Container labelling
- Changes to product

1.3.8 Adverse Effects of Instability of Drugs

- Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline)
- Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures)
- Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions)
- Loss of elegance (e.g. fading of tablets and colored solutions)
- Reduction in bioavailability (e.g. ageing of tablets resulting in a change in dissolution profile)
- Production of potential toxic materials (e.g. breakdown products from drug degradation

1.3.9 Types of Stability

- **CHEMICAL**: Each active ingredient retains its chemical integrity and labeled potency within the specified limit.
- **PHYSICAL**: The physical stability properties includes appearance, palatability, uniformity, dissolution and suspend ability are retained.
- **MICROBIOLOGICAL**: Sterility or resistance to microbial growth is retained according to specified requirement.
- **THERAPEUTIC**: Therapeutic activity remains unchanged.
- **TOXICOLOGIC**: No significant increase in toxicity occurs.

1.3.10 Stability Testing

Development studies-

- Characterize compatibility with common excipients.
- Characterize stability profile of API (e.g. susceptibility to acid, base, light, oxygen etc)
- Characterize stability profile of early formulations (Especially susceptibility to heat, humidity & light) Confirmatory studies.
- Long term & accelerated studies on the product as it is to be registered.

1.3.11 Q1A (R2): Stability Testing of New Drug Substances and Products

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light,

and to establish a re-test period for the drug substance or a shelf life for the drug product.

1.3.11.1 General

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

1.3.11.2 Stress Testing

Main tool that predicts the stability problems

- Foundation for developing and validating analytical methods.
- When available, it is acceptable to provide relevant data published in the scientific literature to support the identified degradation pathways and products.

1.3.11.3 Roll of Stress Testing

- Stress testing of the active substance can help in
- Identification of degradants
- Identification of degradation pathways
- Determination of which type(s) of stress affect the molecule: Photo-stability High Temperature Low Temperature Oxidation pH extremes Water

Oxidation

- Typically done by placing the drug substance in aqueous solution of hydrogen peroxide.
- Goal is significant degradation (typically 10-30% of API) Can identify degradants Determine whether protective packaging is required Determine if an antioxidant should be considered for the drug product formulation.

pH

- Typically done by adding drug substance to buffered aqueous solutions at pH values from 1-10
- Decide if the molecule will survive passage through the stomach
- Is enteric coating necessary?
- the drug be given by injection?

1.3.11.4 Selection of Batches

- Data from formal stability studies should be provided on at least three primary batches of the active substance.

- The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches.

1.3.11.5 Container and Closure System

The stability studies should be conducted on the active substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

1.3.11.6 Specification

- Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.
- The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. e.g. appearance, assay, degradation.

1.3.11.7 Testing Frequency

For long term studies:

Year 1: every 3 months

Year 2: every 6 months

Subsequent years: annually

At accelerated storage conditions: (6 months study)

Minimum three points including t_0 and t_{final}

e.g. 0 (initial) 3 6 (final)

At intermediate storage conditions: (12 months study)

Four points including t_0 and t_{final}

e.g. 0 (initial) 6 9 12 (final)

1.3.11.8 Storage Condition

A drug substance should be evaluated:

- To test its thermal stability
- Its sensitivity to moisture (if applicable)
- The long-term testing (minimum of 12 months) on at least 3 primary batches at the time of submission and
- Should be continued for a period of time sufficient to cover the proposed re-test period.

1.3.11.9 General Case

Study	Storage condition	Minimum time period covered by data at submission
Long Term* (Ambient)	25º C ± 2º C 60% RH ± 5%	12 months
Intermediate** (controlled)	30º C ± 2º C 65% RH ± 5%	6 months
Accelerated	40º C ± 2º C 75% RH ± 5%	6 months

1.3.11.10 Storage in Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long Term	5º C ± 3º C	12 months
Accelerated	25º C ± 2º C 60% RH ± 5%	6 months

1.3.11.11 Storage in a Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long Term	-20º C ± 5º C	12 months

1.3.11.12 Evaluation

- Minimum of 3 batches of drug substance is tested.
- The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.
- The analyst must find batch-to-batch variability & if it is small than only it is accepted & it can be done by different statistical test's (P value for level of significance for rejection).
- Where the data show so little degradation and so little variability then it is normally unnecessary to go through the statistical analysis; providing a justification for the omission should be sufficient.

1.3.11.13 Statement/Labeling

- A storage statement should be established for the labelling based on the stability evaluation of the active substance.
- Where applicable, specific instructions should be provided, particularly for active substances that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” must be avoided.

1.3.11.14 Stability-Indicating Quality Parameter

Stability studies should include testing of those attributes of the Drug product that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. For instance, in case of tablets: appearance hardness friability moisture content dissolution time degradants assay microbial purity.

1.13.11.15 Accelerated Stability

- This stability study run under more stressful conditions than expected for long term storage to account for any changes outside the label storage conditions.
- The goal is to get a quick understanding of what may be expected from a long-term study.

Q1B: Photostability Testing of New Drug Substances and Products

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

Q1C: Stability Testing for New Dosage Forms

Gives guidelines for new formulations of already approved medicines and defines the circumstances under which reduced stability data can be accepted.

Q1D: Bracketing and Matrixing Designs for Stability

Testing of New Drug Substances and Products

Q1E: Evaluation of Stability Data

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The guideline provides recommendations on establishing shelf lives for drug substances and drug products intended for storage at or below “room temperature”.

Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

Describes harmonized global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. WHO conducted a survey amongst their member states to find consensus on 30°C/65% RH as the longterm storage conditions for hot-dry and hot-humid regions.

1.3.12 Q2-Analytical validation

Q2(R1): Validation of Analytical Procedures: Text and Methodology

- The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose
- Gives validation parameters needed for a variety of analytical methods.
- It also discusses the characteristics that must be considered during the validation of the analytical
- Procedures 18 Types of Analytical Procedures to be validated are:
  - Identification tests;
  - Quantitative tests for impurities content;
  - Limit tests for the control of impurities;
  - Quantitative tests of the active moiety in samples of drug substance or drug product or other selected components in the drug product.
- Typical validation characteristics of analytical procedures are; Accuracy, Precision (Repeatability, Intermediate Precision), Specificity, Detection Limit, Quantitation Limit, Linearity, Range.

1.3.13 Q3A- Q3D----Impurities

Q3A(R2): Impurities in New Drug Substances

- The guideline addresses the chemistry and safety aspects of impurities, including the listing of impurities, threshold limit, identification and quantification.
- Classification of Impurities: are of 3 types
- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Q3B(R2): Impurities in New Drug Products

Q3C(R4): Impurities: Guideline for Residual Solvents

- Benzene 2 ppm
- Carbon tetrachloride 4 ppm
- Dichloromethane 5 ppm
- Dichloroethane 8 ppm
- Acetonitrile 410 ppm
- Chloroform 60 ppm

- Chlorobenzene 360 ppm
- Formamide, Hexane 290 ppm
- Toulene 890 ppm
- Pyridine 200 pm
- Nitromethane 50 ppm
- Methanol 3000 ppm

1.3.14 Q4: Pharmacopoeias

Q4A: Pharmacopeial Harmonization

Q4B: Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions

This document describes a process for the evaluation and recommendation given by the Q4B Expert Working Group (EWG) for selecting pharmacopeial texts to facilitate their recognition by regulatory authorities for use, interchangeable in the ICH regions.

- Annex 1: Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions on Residue on Ignition/Sulphated Ash
- Annex 2: Test for Extractable Volume of Parenteral Preparations
- Annex 3: Test for Particulate Contamination: Sub-Visible Particles
- Annex 4A: Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests
- Annex 4B: Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-organisms
- Annex 4C: Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
- Annex 5: Disintegration Test
- Annex 6: Uniformity of Dosage Units
- Annex 7: Dissolution Test
- Annex 8: Sterility Test
- Annex 9: Tablet Friability
- Annex 10: Polyacrylamide Gel Electrophoresis
- Annex 11: Capillary Electrophoresis
- Annex 12: Analytical Sieving
- Annex 13: Bulk Density and Tapped Density of Powders
- Annex14: Bacterial Endotoxins Test

1.3.15 Q5A-Q5E---Quality of Biotechnological Products

Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

- This document is concerned with testing and evaluation of the viral safety of biotechnology products derived from cell lines of human or animal origin (i.e., mammalian, avian, insect)
- The objective is to provide a general framework for virus testing experiments for the evaluation of virus clearance and the design of viral tests and clearance evaluation studies. Three principal, complementary approaches have evolved to control the potential viral contamination of biotechnology products:
  (a) selecting and testing cell lines and other raw materials, including media components, for the
  (b) absence of undesirable viruses which may be infectious and/or pathogenic for humans;
  (c) Testing the capacity of the processes to clear infectious viruses;
  (d) testing the product at appropriate steps for absence of contaminating infectious viruses.

Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells

Used for Production of r-DNA Derived Protein Products

- This document presents guidance regarding the characterization of the expression construct for the production of recombinant DNA protein products in eukaryotic and prokaryotic cells.
- Expression construct should be analyzed using nucleic acid techniques.

Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

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

Q5E: Comparability of Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process

- The objective of this document is to provide principles for assessing the comparability of biotechnological/ biological products before and after changes are made in the manufacturing process for the drug substance or drug product.

- Therefore, this guideline is intended to assist in the collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product.

1.3.16 Q6: Specifications for New Drug Substances and Products

- Bulk drug substance and final product specifications are key parts of the core documentation for world-wide product license applications.
- This leads to conflicting standards for the same product, increased expenses and opportunities for error as well as a potential cause for interruption of product supply.

Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

- The main objective of this guideline is to establish a single set of global specifications for new drug substances and new drug products.
- A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges
- This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria which play a major role in assuring the quality of the new drug substance and new drug product during shelf life.

Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

- This document provides guidance on justifying and setting specifications for proteins and polypeptides which are derived from recombinant or non-recombinant cell cultures.
- A valid biological assay to measure the biological activity should be provided by the manufacturer.
- Examples of procedures used to measure biological activity include:
  - Animal-based biological assays, which measure an organism's biological response to the product;
  - Cell culture-based biological assays, which measure biochemical or physiological response at the cellular level;
  - Biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.

1.3.17 Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

- The main objective of this guideline is that to maintain the quality of the active pharmaceutical ingredients
- Personnel
- Buildings and Facilities
- Process equipment
- Documentation and Records

1.3.18 Q8(R2): Pharmaceutical Development

- This guideline is intended to provide guidance on the contents of Pharmaceutical Development of drug products
- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- The Pharmaceutical Development section also describe the type of dosage form and the formulation that are suitable for the intended use.
- *Q8 gives information about Drug Substance, Excipients,* Container Closure System.

1.3.19 Q9: Quality Risk Management

- The purpose of this document is to offer a systematic approach to quality risk management.
- This guideline provides principles and tools for quality risk management that can be applied to all aspects of pharmaceutical quality including development, manufacturing, distribution; and the inspection and submission/review processes throughout the lifecycle of drug substances and drug (medicinal) products, biological and biotechnological products, including the use of raw materials, solvents, excipients, packaging and labeling materials.

Principles of Quality Risk Management

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort and documentation of the quality risk management process should be commensurate with the level of risk.

1.3.20 Q10: Pharmaceutical Quality System

- This document establishes a new ICH tripartite guideline describing a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System.
- Comprehensive model for an effective pharmaceutical quality system is based on International Standards Organization (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations.

1.4 QbD

Pharmaceutical industry is moving towards quality. Many pharmaceutical companies have used several Quality Management System (QMS) for instance ISO 9001. Design process has one of the most important factors that contributing in pharmaceutical product quality. The pharmaceutical industry is used the concept of Quality by Design (QbD) to apply science-based manufacturing principles for new and existing products to assure quality of the formulation. In a first step, the QbD methodology is systematically used to establish the critical quality attribute identifies potentially critical input factor and these factors to define activities for process characterization. A process DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs, and establish design space to ensure desired CQAs. Critical material and process parameters are linked to the critical quality attributes of the product. Experiments were designed with focus on critical material and process attributes. Quality by design is an essential part of the modern approach to pharmaceutical quality. The purpose of this article is to discuss the use of Quality by Design (QbD) in pharmaceuticals and describe how it can be used to ensure pharmaceutical quality. Process parameters and quality attributes were identified for each unit operation. The design space was established by the combined use of DOE, optimization and multivariate analysis to ensure desired CQAs. Multivariate analysis of all variables from the DOE batches was conducted to study relationships between the variables and to evaluate the impact of material attributes/process parameters on manufacturability and final product CQAs.

1.4.1 Pharmaceutical Quality by Design

QbD is a novel approach in pharmaceutical industry. It places more emphasis on continuous improvement rather than end-product testing. The pharma industry, however, is just beginning to experience the benefits of QbD.

The Quality by Design approach requires having a sound understanding of their product in the company. QbD makes certain that the product is of predictable and predefined quality. The adoption of QbD includes defining a target product quality profile; designing the manufacturing process from basic principles with a very good understanding of the mechanism involved (Design of Experiment); identifying critical quality areas, process parameters and potential sources of variability; and finally controlling manufacturing process to achieve the most consistent quality.

ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." ICH Q6 emphasizes the role of specifications stating that "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities 28." As per ICH Q8 defines that pharmaceutical Quality by Design (QbD) is "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." Pharmaceutical QbD is a systematic, scientific, risk-based, approach to pharmaceutical development that begins with predefined objectives. QbD identifies characteristics that are critical to quality and translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics.

Under the QbD approach, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control.

The specification for impurities assesses another important characteristic a drug product must have to ensure its safety. Under the QbD, the acceptance criterion of an impurity should be set based on its biological safety level instead of the actual batch data. The biological safety level is generally determined by safety studies although it may be also determined by toxicity studies. It should be noted that although there is a specification for a drug product under both the QbT and QbD paradigms, the roles that the specification plays are completely different. Under the QbT, each batch has to be tested against the specification to ensure its quality and manufacturing consistency. Under the QbD, batches may not be actually tested against the specification as the process understanding and/or process control provides sufficient evidences that the batches will meet the specification if tested, which allows the real time release of the batches. Further, the specification under the QbD is solely used for the confirmation of product quality, not manufacturing consistency and process control.

Combine prior knowledge with experiments to establish a design space or other representation of process understanding & establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment. & continually monitor and update the process to assure consistent quality Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process.

1.4.2 Identify Critical Quality Attributes, Process Parameters

The FDA has stated that "Quality by Design means that product and process performance characteristics are scientifically designed to meet specific objectives." As a direct consequence, one of the core tenets of Qbd is the requirement of detailed knowledge of the critical quality attributes (CQA) of the pharmaceutical product and the critical process parameters (CPPs) that can be used to control overall product quality. Gathering the raw data needed for this endeavor can be prohit time, labour, and cost intensive without employing Design of Experiment (DOE) approach, also known as Factorial Experiment Design (FED). Even with DOE, a significant number of samples need to be processed, which has created a need for next generation.

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials. During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within the regular operating range. Lists typical tablet manufacturing unit operations, process parameters, and quality attributes for solid dosage forms. It should be noted that the equipment maintenance, operator training,

standard of operation (SOP) related to the specific product manufacturing, and facility supporting systems may link to product quality directly or indirectly.

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters. DOE results can help identify optimal conditions, the critical factors that most influence CQAs Based on the acceptable range of CQAs, the design space of CPPs can be determined.

1.4.2.1 Critical Quality Attributes

ICH Q8 (R1) defines CQAs as physical, chemical, biological or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQA is used to describe both aspects of product performance and determinants of product performance. CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material.

1.4.2.2 Critical Process Parameters

Critical process parameter as any measurable input or output of a process step that must be controlled to achieve the desired product quality and process consistency. Process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as moisture content, should have the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes.

1.4.3 Essential Five-Step for Qbd for the Purpose of Product Development

Step I: Ascertaining Drug Product Objective(s)

The quality target product profile (QTPP) is a prospective summary of quality characteristics of the drug delivery product ideally achieved to ensure

the desired quality, taking into account the safety and efficacy of the drug product. During drug product development, QTPP is embarked through brain storming among the team members cutting across multiple disciplines in the industry. Critical Quality Attributes (CQAs) are the physical, chemical, biological or microbiological characteristic of the product that should be within an appropriate limit, range or distribution to ensure the desired product quality. There are various types of CQAs associated with the drug products such as drug substance CQAs, excipients CQAs, packaging material CQAs, etc. The identification of prime CQAs from the QTPP is based on the severity of harm a patient may get plausibly owing to the product failure. Thus, after defining the QTPP, the CQAs which pragmatically epitomize the objective(s), are earmarked for the purpose.

Step II: Prioritizing Input Variables for Optimization

Material attributes (MAs) and process parameters (PPs) are considered as the independent input variables associated with a product and/or process, which directly influence the CQAs of the drug product. PPs can be of different types such as non-critical Process Parameters (non-CPPs), Unclassified Process Parameters (UPPs) and Critical Process Parameters (CPPs). Ishikawa-Fish bone diagram are used for establishment of cause-effect relationship among the input variables affecting the quality traits of the drug product. Figure 4 illustrates a typical cause-effect diagram highlighting the plausible causes of product variability and their impact on drug product CQAs. Figure 6 portrays the flow layout of overall risk assessment plan employing risk assessment and risk management for identifying the potential CMAs employing a prototype REM model. The low-resolution first-order experimental designs (e.g., fractional factorial, Plackett-Burman and Taguchi designs) are highly helpful for screening and factor influence studies. Before venturing into product or process optimization, prioritization of CMAs/CPPs using such QRM and/ or screening is obligatory

Step III: Design-guided Experimentation & Analysis

Response surface methodology is considered as a pivotal part of the entire QbD exercise for optimization of product and/or process variables discerned from the risk assessment and screening studies. The experimental designs help in mapping the responses on the basis of the studied objective(s), CQAs being explored, at high, medium or low levels of CMAs. Figure 7 diagrammatically enumerates the key experimental designs employed during QbD-based product development for response surface methodology and/or factor screening. Factorial, Box-Behnken, composite, optimal and mixture designs are the commonly used high resolution second-order designs employed for drug product optimization. Design matrix is a layout of experimental runs in matrix form generated by the chosen experimental

design, to guide the drug delivery scientists. The drug formulations are experimentally prepared according to the design matrix and the chosen response variables are evaluated meticulously.

Step IV: Modelization & Validation of QbD Methodology

Modelization is carried out by selection of apt mathematical models like linear, quadratic and cubic models to generate the 2D and 3Dresponse surface to relate the response variables or CQAs with the input variables or CMAs/CPPs for identifying underlying interaction(s) among them. Multiple Linear Regression Analysis (MLRA), Partial Least Squares (PLS) analysis and Principal Component Analysis (PCA) are some of the key multivariate chemometric techniques employed for modelization to discern the factor-response relationship. Besides, the model diagnostic plots like perturbation charts, outlier plot, leverage plot, Cook's distance plot and Box-Cox plot are also helpful in unearthing the pertinent scientific, minutiae and interactions among the CMAs too. The search for optimum solution is accomplished through numerical and graphical optimization techniques like desirability function, canonical analysis, artificial neural network, brute-force methodology and overlay plot. Subsequent to the optimum search, the optimized formulation is located in the design and control spaces. Design space is a multidimensional combination of input variables (i.e., CMAs/CPPs) and out variable (i.e., CQAs) to discern the optimal solution with assurance of quality. Figure 9 illustrates the interrelationship among various spaces like, explorable, knowledge, design and control spaces. Usually in industrial milieu, a narrower domain of control space is construed from the design space for further implicit and explicit studies.

Step V: QbD Validation, Scale-up and Production

Validation of the QbD methodology is a crucial step that forecasts about the prognostic ability of the polynomial models studied. Various product and process parameters are selected from the experimental domain and evaluated as per the standard operating conditions laid down for the desired product and process related conditions carried out earlier, commonly termed as checkpoints or confirmatory runs. The results obtained from these checkpoints are then compared with the predicted ones through linear correlation plots and the residual plots to check any typical pattern like ascending or descending lines, cycles, etc. To corroborate QbD performance, the product or process is scaled-up through pilot-plant, exhibit and production scale, in an industrial milieu to ensure the reproducibility and robustness. A holistic and versatile "control strategy" is meticulously postulated for "continuous improvement" in accomplishing better quality of the finished product.

1.4.4 Software Usage during QbD

The merits of QbD techniques are galore and their acceptability upbeat. Putting such rational approaches into practice, however, usually involves a great deal of mathematical and statistical intricacies. Today, with the availability of powerful and economical hardware and that of the comprehensive QbD software, the erstwhile computational hiccups have been greatly simplified and streamlined. Figure 10 enlist the select computer software available commercially for carrying out QbD studies in industrial milieu. Pertinent computer software available for DoE optimization include Design-Expert®, Minitab®, MODDE®, Unscrambler®, JMP®, Statistica®, etc., are at the rescue, which usually provide interface guide at every step during the entire product development cycle. Software providing support for chemometric analysis through multivariate techniques like MNLRA, PCA, PLS, etc. encompass, MODDE®, Unscrambler®, SIMCA®, CODDESA®. For QRM execution using Fish-bone diagrams, REM and FMEA matrices during risk assessment studies, etc., software like, Minitab®, Risk®, Statgraphics, FMEA-Pro, iGrafx, etc., can be made use of.

1.5 ISO

The International Organization for Standardization (ISO), established in 1947, is an international organization of national standards bodies from more than 145 countries, with one body representing each country. ISO is based in Geneva, Switzerland. Its goal is to promote the development of standardization and related activities in the world; to facilitate the international exchange of goods and services; and to develop cooperation in intellectual, scientific, technological and economic activity. ISO's work results in international agreements, which are published as International Standards and other types of ISO documents.

1.5.1 Benefits of ISO

- ISO standards add value to all types of businesses and contribute for making the development, manufacturing, and supply of products and services more efficient, safer, and cleaner.
- They make trade between countries easier and fairer.
- ISO standards also serve to safeguard consumers and users of products and services in general as well as to make their lives simpler.
- The businesses that adopt international standards are increasingly free to compete in markets around the world.

- For customers, a product or service based on an international standard will be compatible with more products or services worldwide, which increases the number of choices available.
- Each ISO national committee can adopt an international standard. When the U.S. believes in the usefulness of a standard, that standard goes through an adoption process to make it an American National Standard. When an ISO standard has been adopted by the United States, the international community knows that the United States supports the content of that standard.

1.5.2 ISO 9000

ISO 9000 is defined as a set of international standards on quality management and quality assurance developed to help companies effectively document the quality system elements needed to maintain an efficient quality system. They are not specific to any one industry and can be applied to organizations of any size.

ISO 9000 can help a company satisfy its customers, meet regulatory requirements, and achieve continual improvement. It should be considered to be a first step or the base level of a quality system.

History

ISO 9000 was first published in 1987 by the International Organization for Standardization (ISO). The standards underwent major revisions in 2000 and 2008. The most recent versions of the standard, ISO 9000:2015 and ISO 9001:2015, were published in September 2015.

The ISO 9000:2000 revision had five goals:

1. Meet stakeholder needs
2. Be usable by all sizes of organizations
3. Be usable by all sectors
4. Be simple and clearly understood
5. Connect quality management system to business processes

ISO 9000:2015 principles of Quality Management

The ISO 9000:2015 and ISO 9001:2015 standards are based on seven quality management principles that senior management can apply to promote organizational improvement.

1. Customer focus

- Understand the needs of existing and future customers
- Align organizational objectives with customer needs and expectations

- Meet customer requirements
- Measure customer satisfaction
- Manage customer relationships
- Aim to exceed customer expectations
- Learn more about the customer experience and customer satisfaction

2. Leadership

- Establish a vision and direction for the organization
- Set challenging goals
- Model organizational values
- Establish trust
- Equip and empower employees
- Recognize employee contributions
- Learn more about leadership

3. Engagement of people

- Ensure that people's abilities are used and valued
- Make people accountable
- Enable participation in continual improvement
- Evaluate individual performance
- Enable learning and knowledge sharing
- Enable open discussion of problems and constraints
- Learn more about employee involvement

4. Process approach

- Manage activities as processes
- Measure the capability of activities
- Identify linkages between activities
- Prioritize improvement opportunities
- Deploy resources effectively
- Learn more about a process view of work and see process analysis tools

5. Improvement

- Improve organizational performance and capabilities
- Align improvement activities

- Empower people to make improvements
- Measure improvement consistently
- Celebrate improvements
- Learn more about approaches to continual improvement

6. Evidence-based decision making

- Ensure the accessibility of accurate and reliable data
- Use appropriate methods to analyze data
- Make decisions based on analysis
- Balance data analysis with practical experience
- See tools for decision making

7. Relationship management

- Identify and select suppliers to manage costs, optimize resources, and create value
- Establish relationships considering both the short and long term
- Share expertise, resources, information, and plans with partners
- Collaborate on improvement and development activities
- Recognize supplier successes
- Learn more about supplier quality and see resources related to managing the supply chain

1.5.3 ISO 14000

ISO 14000 is defined as a series of international environmental management standards, guides, and technical reports. The standards specify requirements for establishing an environmental management policy, determining environmental impacts of products or services, planning environmental objectives, implementing programs to meet objectives, and conducting corrective action and management review.

History

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

1.6 NABL Accreditation

1.6.1 Introduction

Accreditation is the formal recognition, authorization and registration of a laboratory that has demonstrated its capability, competence and credibility to carry out the tasks it is claiming to be able to do. It provides feedback to laboratories as to whether they are performing their work in accordance with international criteria for technical competence. The concept of laboratory accreditation was developed to provide third-party certification that a laboratory is competent to perform the specific test or type of tests. Laboratory accreditation is a means to improve customer confidence in the test reports issued by the laboratory so that the clinicians and through them the patients shall accept the reports with confidence.

Four years ago, NABL established links with international bodies - Asia Pacific Laboratory Accreditation Cooperation and International Laboratory Accreditation Cooperation. This has imparted international recognition to NABL accredited laboratories. The international standard currently followed by NABL is ISO 15189, specific for medical laboratories

The National Accreditation Board for Testing and Calibration Laboratories (NABL) is an autonomous body under the agencies of the Dept. of Science & Technology, Govt. of India, and is registered under the Societies Act. NABL. Govt. of India has authorized NABL as the sole accreditation body for testing and calibration laboratories.

1.6.2 Objectives

- NABL was initially established with the objective to provide accreditation to testing & calibration laboratories, later on extended its services to the clinical laboratories in our country.
- The objective of NABL is to provide third party assessment of quality and technical competence.

1.6.3 WHY Accreditation

- Accreditation is the third-party attestation related to a conformity assessment body conveying the formal demonstration of its competence to carry out specific conformity assessment task. Conformity Assessment Body (CAB) is a body which includes Testing including medical Laboratory, Calibration Laboratory, Proficiency Testing Provider, Certified Reference Material Producer.
- The liberalization of trade and industry policies of the Government of India has created quality consciousness in domestic trade and provided greater thrust for export. As a consequence, testing centres and

laboratories have to demonstrably operate at an internationally acceptable level of competence.

- Laboratory accreditation is a procedure by which an authoritative body gives formal recognition of technical competence for specific tests/ measurements, based on third party assessment and following international standards.
- Similarly, Proficiency testing Provider accreditation gives formal recognition of competence for organizations that provide proficiency testing. Reference Material Producers Accreditation gives formal recognition of competence to carry out the production of reference materials based on third party assessment and following international standards.

1.6.4 Benefits of Accreditation

Formal recognition of competence of a laboratory by an Accreditation body in accordance with international criteria has many advantages.

1. Increased confidence in Testing/ Calibration Reports issued by the laboratory
2. Better control of laboratory operations and feedback to laboratories as to whether they have sound Quality Assurance System and are technically competent
3. Potential increase in business due to enhanced customer confidence and satisfaction.
4. Customers can search and identify the laboratories accredited by NABL for their specific requirements from the NABL Web-site or Directory of Accredited Laboratories
5. Users of accredited laboratories enjoy greater access for their products, in both domestic and international markets.
6. Savings in terms of time and money due to reduction or elimination of the need for re-testing of products.

1.6.5 Scope of Accreditation

NABL Accreditation is currently given in the following fields and disciplines. The multi-disciplinary CABs shall have to apply in relevant discipline separately depending upon to which discipline the scope belongs. For more details on scope of accreditation please refer the relevant specific criteria.

TESTING LABORATORIES	CALIBRATION LABORATORIES	MEDICAL LABORATORIES
• Biological • Chemical • Electrical • Electronics • Fluid-Flow • Mechanical • Non-Destructive Testing (NDT) • Photometry • Radiological Forensic • Diagnostic Radiology QA Testing • Software & IT System	• Electro-Technical • Mechanical • Fluid Flow • Thermal • Optical • Radiological • Medical Devices	• Clinical Biochemistry • Clinical Pathology • Haematology & Immunohematology • Microbiology & Infectious Disease Serology • Histopathology • Cytopathology • Flow Cytometry • Genetics • Nuclear Medicine *(in-vitro tests only)*

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

PROFICIENCY TESTING PROVIDERS	REFERENCE MATERIAL PRODUCERS
• Testing • Calibration • Medical • Inspection	• Chemical Composition • Biological & Clinical Properties • Physical Properties • Engineering Properties • Miscellaneous Properties

1.6.6 Getting Ready for Accreditation

It is very important for a laboratory to make a definite plan for obtaining accreditation and nominate a responsible person as QUALITY MANAGER

(who should be familiar with the laboratory's existing quality system) to co-ordinate all activities related to seeking accreditation.

The laboratory should carry out the following important tasks towards getting ready for accreditation:

a. Contact NABL Secretariat with a request for procuring relevant NABL documents (NABL Contact address and the list of NABL documents given in Annexure-3 and 1, respectively).
b. Get fully acquainted with all relevant documents and understand the assessment Procedure and methodology of making an application.
c. Train a person on Quality Management System and Internal Audit (4-day residential training courses conducted by NABL. Contact NABL Secretariat for details).
d. Prepare QUALITY MANUAL as per ISO 15189 standards.
e. Prepare Standard Operating Procedure for each investigation carried out in the laboratory.
f. Ensure effective environmental conditions (temperature, humidity, storage placement, etc.).
g. Ensure calibration of instruments / equipment. Only NABL ACCREDITED CALIBRATION LABORATORIES are authorized to provide calibration. NABL website gives the names of NABL accredited calibration laboratories in the various fields of Accreditation.
h. Impart training on the key elements of documentation, such as document format, authorization of document, issue and withdrawal procedures, document review and change, etc. Each document should have ID No., name of controlling authority, period of retention, etc.
i. Ascertain the status of the existing quality system and technical competence with regard to NABL standards and address the question "Is the system documented and effective OR does it need modification?".
j. Remember Quality Manual is a policy document, which has to be supplemented by a set of other next level documents. Therefore, ensure that these documents are well prepared.
k. Ensure proper implementation of all aspects that have been documented in the Quality Manual and other documents.
l. Incorporate Internal Quality Control (IQC) practice while patients' samples are analysed.
m. Document IQC data as well as uncertainty of measurements. Maintain Levy Jennings charts.

n. Participate in External Quality Assessment Schemes (EQAS). If this is not available for certain analytes, participate in inter-laboratory comparison through exchange of samples with NABL accredited laboratories.

o. Document corrective actions on IQC / EQA outliers.

p. Conduct Internal Audit and Management Review.

q. Apply to NABL along with appropriate fee.

1.6.7 Process of Accreditation

Stage I (Filling of Application)

- Prepare your laboratory's application for NABL accreditation, giving all desired information and enlisting the test(s) / calibration(s) along with range and measurement uncertainty for which the laboratory has the competence to perform. Laboratory can apply either for all or part of their testing / calibration facilities. Formats NABL 151, NABL 152 & NABL 153 are to be used by Testing, Calibration and Medical Laboratories respectively for applying to NABL for accreditation.
- Laboratory has to take special care in filling the scope of accreditation for which the laboratory wishes to apply. In case, the laboratory finds any clause (in part or full) not applicable to the laboratory, it shall furnish the reasons.
- Laboratories are required to submit five sets of duly filled in application forms for each field of testing / calibration along with five sets of Quality Manual and Application Fees.
- NABL Secretariat on receipt of application will issue acknowledgement to the laboratory. After scrutiny of application for it being complete in all respects, a unique Customer Registration Number will be allocated to laboratory for further processing of application.
- NABL Secretariat shall then nominate a Lead Assessor for giving Adequacy Report on the Quality Manual / Application submitted by the laboratory. A copy of Adequacy Report by Lead Assessor will be provided to Laboratory for taking necessary corrective action, if any. The laboratory shall submit Corrective Action Report. After satisfactory corrective action by the laboratory, a Pre-Assessment audit of the laboratory will be organised by NABL. Laboratories must ensure their preparedness by carrying out its internal audit before Pre-Assessment.

Stage II (Pre-Assessment audit)

- NABL Secretariat shall organise the Pre-Assessment audit, which shall normally be carried by Lead Assessor at the laboratory sites.

- The pre-assessment helps the laboratory to be better prepared for the Final Assessment. It also helps the Lead Assessor to assess the preparedness of the laboratory to undergo Final Assessment apart from Technical Assessor(s) and Total Assessment Man-days required vis-à-vis the scope of accreditation as per application submitted by the laboratory.
- A copy of Pre-Assessment Report will be provided to Laboratory for taking necessary corrective action on the concerns raised during audit, if any.
- The laboratory shall submit Corrective Action Report to NABL Secretariat.
- After laboratory confirms the completion of corrective actions, Final Assessment of the laboratory shall be organized by NABL.

Stage III (Final Assessment)

- NABL Secretariat shall organize the Final Assessment at the laboratory site(s) for its compliance to NABL Criteria and for that purpose appoint an assessment team.
- The Assessment Team shall comprise of a Lead Assessor and other Technical Assessor(s) in the relevant fields depending upon the scope to be assessed.
- Assessors shall raise the Non-Conformance(s), if any, and provide it to the laboratory in prescribed format so that it gets the opportunity to close as many Non-Conformance(s) as they can before closing meeting of the Assessment.
- The Lead Assessor will provide a copy of consolidated report of the assessment to the laboratory and send the original copy to NABL Secretariat. Laboratory shall take necessary corrective action on the remaining Non-Conformance(s) / other concerns and shall submit a report to NABL within a maximum period of 2 months.

Stage IV (Corrective Reassessment)

- After satisfactory corrective action by the laboratory, the Accreditation Committee examines the findings of the Assessment Team and recommends additional corrective action, if any, by the laboratory.
- Accreditation Committee determines whether the recommendations in the assessment report is consistent with NABL requirements as well as commensurate with the claims made by the laboratory in its application.
- Laboratory shall have to take corrective action on any concerns raised by the Accreditation Committee.

- Accreditation Committee shall make the appropriate recommendations regarding accreditation of a laboratory to NABL Secretariat.
- Laboratories are free to appeal against the findings of assessment or decision on accreditation by writing to the Director, NABL.
- Whenever possible NABL will depute its own technical personnel to be present at the time of assessment as Coordinator and NABL Observer. Sometimes, NABL may at its own cost depute a newly trained Technical Assessor as "Observer" subject to convenience of the laboratory to be accessed.

Stage V (Granting of Accreditation)

- Accreditation to a laboratory shall be valid for a period of 3 years and NABL shall conduct periodical Surveillance of the laboratory at intervals of one year.
- Laboratory shall apply for Renewal of accreditation to it at least 6 months before the expiry of the validity of accreditation.