Name of Unit	Quality Assurance and Quality Management
Subject/Coursename	Quality Assurance
Subject/CourseID	BP 606T
Coursecoordinator	Punam Gaba
Mobile No.	punam_gaba@yahoo.co.in
Emailid	9872959113

Learning Outcome of Unit 01

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will learnt about Quality Assurance and Quality Management Concepts	BP606.1
LO2	Students will learnt about Total Quality Management (TQM)	BP606.1
LO3	Students will learnt about ICH stability testing guidelines.	BP606.1
LO4	Students will learnt about Quality By Design (QbD) and ISO 9000 & ISO14000	BP606.2
LO5	Students will learnt about NABL Accreditation	BP606.2

MODULE CONTENT TABLE

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

QUALITYASSURANCE

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"

QualityControl

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

QA is a set of activities for ensuring quality in the processes by which products are developed.	QC is a set of activities for ensuring quality in products. The activities focus on identifying defects in the actual products produced.
QA is a managerial tool	QC is a corrective tool
QA aims to prevent defects with a focus on the process used to make the product. It is a proactive quality process.	QC aims to identify (and correct) defects in the finishedproduct. Quality control, therefore, is areactive process.
The goal of QA is to improve development and test processes so that defects do not arise when theproduct is beingdeveloped	The goal of QC is to identify defects aftera product is developed and before it's released.
Prevention of quality problems through planned and systematic activities including	The activities or techniques used to achieve and maintain the product

documentation.	quality, process and service
Establish a goodquality management system and the assessment of its adequacy. Periodic conformance audits of the operations of the system.	Finding & eliminating sources of quality problems throughtools & equipment so that customer's requirements are continuallymet.
Everyone on the team involved in developing the product is responsible for qualityassurance.	Quality control is usually the responsibility of a specific team that tests the product for defects.
Verificationis an example ofQA.	Validation is an example ofQC.

Responsibilities of QA

- The QA department is responsible for ensuring that the quality policies adopted by a company arefollowed.
- It helps to identify and prepare the necessary SOPs relative to the control ofquality.
- It must determine that the product meets all the applicable specifications and that it was manufactured according to the internal standards ofGMP.
- QA also holds responsible for quality monitoring or auditfunction. QA functions to assess operations continually and to advise and guide them towards full compliance with allapplicable internal and externalregulations.

Responsibilities of QC

- QC is responsible for the day-to-day control of quality within thecompany.
- This department is responsible for analytical testing of incoming raw materials and inspection of packaging components, includinglabelling.
- They conduct in-process testing when required, perform environmental monitoring, and inspect operations forcompliance.
- They also conduct the required tests onfinished dosageform.
- 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 QCdepartment.

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 inthedevelopment, manufacture, control, and marketing of qualityproducts.

Following variables may affect ultimate quality of product

- Rawmaterial
- In processvariations
- Packagingmaterial
- Labeling
- Finishproduct
- ManualError

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 properlyidentified.

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 QAinspector.

QA personnel should keep preservation samples of active raw materials that consists of at least 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 at least 7 years. Approved material should be rotated so that the oldest stock is usedfirst.

Raw materials may be classified into 2 groups:

- Active ortherapeutic
- Inactive orinert

In-process ItemsControl

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 ofthe actualproduction.

The FDA-CGMP regulations emphasize environmental factors to minimize cross-contamination of products and errors; however, they do little to minimize within-batch andbatch-to- batch variation. Therefore, it is important function of the IPQA program to ensure that the final products have uniform purity and quality.There are some critical steps to be followed in this:

QA beforestart-up:

- Environmental and microbiologic controland sanitation
- Manufacturing Working FormulaProcedures
- RawMaterials
- ManufacturingEquipment

QA at start-up:

Raw MaterialProcessing assayed at the end is not likely to be representative of more than a small fraction ofthe actualproduction.

The FDA-CGMP regulations emphasize environmental factors to minimize cross- contamination of products and errors; however, they do little to minimize within-batch andbatch-to- batch variation. Therefore, it is important function of the IPQA program to ensure that the final products have uniform purity and quality.There are some critical steps to be followed in this:

- Raw MaterialProcessing
- Compounding
- Packaging Materials Control
- LabelsControl
- Finished ProductControl

QUALITY ASSURANCE MANAGEMENT PROCEDURE

How to write Standard OperatingProcedure?

SOP describes standard SOP format that you can use immediately for your qualityprocedure.

SOP has instructions on how to write a formal operating procedure for your systems which your people can followeveryday.

All Document-Classifications, DefinitionsandApproval 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 retentionrequirements.

This procedure has schematic diagrams for your understanding of how different types of documents are prepared and stored in a typical documentation.

Quality Documentation Managementand 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 fileadministrator.

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.

Documentation Rule for GMPDocuments

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.

Quality Documentation- Tracking, ControlandDistribution

In this SOP you will find mainly the role of document control officer during the initiation, creation, circulation and approval of new quality relateddocuments.

It also describes the procedure of modification and review of existing document using a documentationdatabase.

Management of existing and superseded documents is also art of this procedure.

You will see all the forms referred during the instruction are attached at the end of the procedure.

Preparation, Maintenance and ChangeControlof 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 themarket.

SOP gives instruction on their creation, change control, numbering system, approval requirements and maintenance in a simple master filedatabase.

All the forms referred during the instruction are attached at the end of the procedure.

Deviation Report System

It is a regulatory requirement to capture all sortsof deviations evolves in your systems in order to maintain the continuous improvement to your processes andsystems.

This SOP describes how to categorize the deviations between production, audit, quality improvements, technical deviations, customer complaints and environmental, health and safetydeviations.

It describes the management responsibilities of initiating deviation, capture data, analysis, investigation, determination of assignable causes, generation of management report and initiativesto be taken on corrective and preventativeactions.

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 AuthorizedPersons.

This procedure is based on an example of tablet packaging process described inthe 'Manufacturing' category.

Evaluation of Batch DocumentationandRelease 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.

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.

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 finishedgoods.

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 organized effort at every stage inproduction.

Although the responsibility for assuring product quality belongs principally to QA personnel, itinvolves many departments and disciplines within acompany.

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 routineproduction.

In products and process designing, itconsiders many parameters like:

- Materials
- In-process and productcontrol
- Specification and tests for active ingredients, excipients
- Specific stability procedures of theproduct
- Freedom from microbial contamination and properstorage
- Containers, packaging andlabeling
- Product protection from moisture, light, volatility, and drug/package interaction

Total Quality Management (TQM)

According to ISO, TQM is definedas: "A management approach of an organization centered 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 organization 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 governmentand 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 & individualconsumers.

Total Quality Management consists of organization-wide efforts to install and make permanent a climate in which an organization continuously improves itsability 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 qualitycontrol.

The production of quality pharmaceuticals products requires embracing the principles of TQM. Additionally, TQM will serve to improve productivity and customersatisfaction.

The concept of TQM requires the total commitment of senior level managementand supervision of all departments, operators, suppliers, andcostumers.

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 allemployees
- Meeting customerrequirements
- Reducing development cycletimes
- Just in time/demand flowmanufacturing
- Improvementteams
- Reducing product and servicecosts
- Systems to facilitateimprovement
- Line managementownership
- Employee involvement andempowerment
- Recognition andcelebration
- Challenging quantified goals andbenchmarking
- Focus on processes / improvementplans
- Specific incorporation in strategicplanning

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 characterized and then purchased from reputable, approvedsuppliers.
- Facilities must be designed, constructed, and controlled to provide the proper stable environment for protecting the integrity of products. Equipment must be selected that is efficient and can be cleaned readily and sanitized.
- Personnel must be trained properly. The directions they use must be in writing, approved by responsibleindividuals.
- Distribution departments are responsible for controlling the shipping and handling of products, using inventory-control systems.
- The marketing department mustbe sensitive to the costumers' needs and be responsive to complaints.

Advantages of TQM

- Improves reputation- faults and problems arespotted and sortedquicker.
- Higher employee morale- workers motivated by extra responsibility, team work and
- involvement indecisions ofTQM
- Lower cost- decrease waste as fewer defective products and no need forseparate.
- Quality controlinspector

Disadvantages of TQM

- Initial introductioncost.
- Benefits may not be seen for several years.
- Workers may be resistant tochange

PHILOSOPHY OF TQM

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

W. Edwards Deming

- Deming's argument was that quality that is achieved though 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 programme 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 organization. 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 programme 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.

ICH GUIDELINES

ICH Guidelines were created by The International Council for Harmonization of Technical **Requirements** for Pharmaceuticals for Human Use (**ICH**). **ICH** aims to provide uniform **standards** for technical **requirements** for pharmaceuticals for human use. They are developed by regulatory and pharma industry authorities.

Mission

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

Need to Harmonize

- Realization was driven by tragedies, such as that with thalidomide in Europe in the 1960s.

- The 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on Quality, Safety and Efficacy of new Medicinal products.

Divergence in technical requirements from country tocountry

Q1A Stability testing of new drugs substances and products

Approvals given by the steering committee of the second revision directly under step 4 without further public constitution to include consequences of the adoption of Q1F (stability data package for registration applications in climatic zone 3&4) and recruitment for adoption to the 3 ICH regulatory bodies. The following guideline is a revised version of the ICH Q1A guideline and defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guideline.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidelines Q1C and Q5C, respectively. 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 and recommended storage conditions.

Guidelines

Drug substances

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

Includes

- Stress testing.
- Selection of batches
- Container closure system
- Specification
- Testing frequency

- Storage condition
- Stability commitment
- Evaluation
- Statements / labeling

Drug product

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

Includes

- Photo stability testing.
- Selection of batches.
- Container closure system.
- Specification.
- Testing frequency.
- Storage conditions.
- Stability commitment.
- Evaluation.
- Statements/ labeling.

The purpose of this is to outline the changes made in Q1A(R) that result from adoption of ICH Q1F "Stability Data Package for Registration Applications in Climatic Zones III and IV".

These changes are:

1. The intermediate storage condition has been changed from 30 °C±2 °C/60% RH±5% RH to 30 °C±2 °C/65% RH±5% RH in the following sections:

Drug Substance - Storage Conditions - General Case

Drug Product - Storage Conditions - General Case

Drug products packaged in semi-permeable containers

2. 30 °C±2 °C/65% RH±5% RH can be a suitable alternative long-term storage condition to 25 °C±2 °C/60% RH±5% in the following sections:

Drug Substance - Storage Conditions - General Case

Drug Product - Storage Conditions - General Case

3. 30 °C±2 °C/35% RH±5% RH has been added as a suitable alternative long-term storage condition to 25 °C±2 °C/40% RH±5% and the corresponding example for the ratio of water-loss rates has been included in the following section: Drug products packaged in semi-permeable containers

4. Mid-stream switch of the intermediate storage condition from 30 °C±2 °C/60% RH±5% RH to 30 °C±2 °C/65% RH±5% RH can be appropriate provided that the respective storage conditions and the date of the switch are clearly documented and stated in the registration application.

It is recommended that registration applications contain data from complete studies at the intermediate storage condition 30 °C±2 °C/65% RH±5% RH, if applicable, by three years after the date of publication of this revised guideline in the respective ICH tripartite region.

Q1B Stability testing

Photo stability testing of new drug substances and products

The ICH harmonized tripartite guideline covering the stability testing of new drug substances and Products (hereafter referred to as the Parent Guideline) notes that light testing should be an integral part of stress testing. This document is an annex to the Parent Guideline and addresses the recommendations for photo stability testing.

Drug substances and drug product

- Presentation of samples
- Analysis of samples
- Judgment of results

Immediate (primary) pack is that constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Marketing pack is the combination of immediate pack and other secondary packaging such as a carton.

Q1C Stability testing for new dosage form

The ICH harmonized tripartite guideline on stability testing of new drug substances and products was issued on October 27, 1993. This document is an annex to the ICH parent stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.

New dosage form

A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.

Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems. (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).

Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (eg. 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases

Q1D Bracketing and matrixing designs for stability testing of new drug substances and products

This guideline is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH Q1A(R) Harmonized Tripartite guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline).

This document provides guidance on bracketing and matrixing study designs. Specific principles are defined in this guideline for situations in which bracketing or matrixingcan be applied.

Bracketing

As defined in the glossary to the parent guideline, bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all times point as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container sizes and/or fills selected for testing are indeed the extremes.

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but are not limited to capsules of different strengths made with different fill plug sizes from the same powder blend, tablets of different strengths manufactured by

compressing varying amounts of the same granulation, and oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants, flavorings).

With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

In cases where different excipients are used among strengths, bracketing generally should not be applied.

Matrixing

As defined in the glossary of the parent guideline, matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems.

Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend

tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants or flavorings).

Other examples of design factors that can be matrixes include batches made by using the same process and equipment, and container sizes and/or fills in the same container closure system.

With justification, matrixing designs can be applied, for example, to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used or to different container closure systems. Justification should generally be based on supporting data. For example, to matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapor transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the drug product is not affected by oxygen, moisture, or light

Q1E Evaluation of stability data

This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline "Q1A(R) Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) to propose a retest period or shelf life in a registration application. This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by "available data from the stability study under the long-term storage condition" (hereafter referred to as long-term 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 retest periods and shelf lives for drug substances and drug products intended for storage at or below "room temperature"*. It covers stability studies using single- or multi-factor designs and full or reduced designs.

*Note: The term "room temperature" refers to the general customary environment and should not be inferred to be the storage statement for labeling.

ICH Q6A and Q6B should be consulted for recommendations on the setting and justification of acceptance criteria and ICH Q1D should be referenced for recommendations on the use of full- versus reduced-design studies.

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life

Q2 (R1) Validation of analytical procedures

Text and methodology

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the EC, Japan and USA. This document does not necessarily seek to cover the testing that may be required for registration in, or export to, other areas of the world. Furthermore, this text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation. These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of the EC, Japan and USA.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

Types of analytical procedures to be validated

- The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures: 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 component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures are equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard;
- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test;

- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
- Repeatability
- Intermediate Precision
- Specificity
- Detection Limit
- Quantization Limit
- Linearity
- Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- Changes in the synthesis of the drug substance;
- Changes in the composition of the finished product;
- Changes in the analytical procedure.

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well

Q3A (R2) Impurities in new drug substances

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin.

Impurities in new drug substances are addressed from two perspectives:

Chemistry aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures; and

Safety aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

Classification of impurities

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts

- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Guideline Q3C on Residual Solvents).

Excluded from this document are: (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as Good Manufacturing Practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

Q3B (R2) Impurities in new drug products

This document provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state.

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as “degradation products” in this guideline). Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products.

Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guideline:

Biological/biotechnological products, peptide, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin. Also excluded from this document are: (1) extraneous contaminants that should not occur in new drug products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

Q3C (R5) Residual solvents

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Classification of residual solvents by risk assessment

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance.

Residual solvents they were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day

Q3D Guidelines for elemental impurities

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. There are three parts of this guideline: the evaluation of the toxicity data for potential elemental impurities; the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern; and application of a risk-based approach to control elemental impurities in drug products. This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialyses solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This guideline does not apply to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). In some regions, these products are known as advanced therapy medicinal products.

Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH.

Q4B Evaluation and recommendation of pharmacopeia texts for use in "ICH" regions

This document describes a process for the evaluation and recommendation by the Q4B Expert Working Group (EWG) of selected pharmacopoeia texts to facilitate their recognition by regulatory authorities for use as interchangeable in the ICH regions

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 characterized cell lines of human or animal origin (i.e., mammalian, avian, insect) and outlines data that should be submitted in the marketing application/registration package. For the purposes of this document the term virus excludes nonconventional transmissible agents like those associated with Bovine Spongiform Encephalopathy (BSE) and scrape. Applicants are encouraged to discuss issues associated with BSE with the regulatory authorities.

Q5B Quality of biotechnological 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. This document is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA derived proteins. This document is not intended to cover the whole quality aspect of rDNA derived medicinal products.

Q5C Quality of biotechnological products

Stability testing of biotechnological/biological products

The guidance stated in this annex applies to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors and tumor necrosis factors), erythropoietin's, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulin, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the appropriate regulatory authorities. The document does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components

Q5D Derivation and characterization of cell substrates

This guideline covers cell substrates having a cell banking system. In this document, "cell substrate" refers to microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the desired biotechnological/biological products for human *in vivo* or *ex vivo* use. Reagents for *in vitro* diagnostic use are outside the scope of this document. Animal sources of cell lines include all those of metazoan origin. Both continuous cell lines of indefinite *in vitro* lifespan and diploid cells of finite *in vitro* lifespan are included. Microbial sources include bacteria, fungi, yeast, and other unicellular life forms

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. The document does not prescribe any particular analytical, nonclinical or clinical strategy. The main emphasis of the document is on quality aspects

Q6A Specifications: test procedures and acceptance criteria, for new drug substances and new drug products

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.

Q6B Specifications: Test procedures and acceptance criteria for biotechnological/biological products

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

Q7 Good manufacturing practice guide for active pharmaceutical ingredients

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this Guide “manufacturing” is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In this Guide the term “should” indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms “current good manufacturing practices” and “good manufacturing practices” are equivalent.

Q8 (R2) Pharmaceutical development

This guideline is intended to provide guidance on the contents of section 3.2.P.2 (pharmaceutical development) for drug products as defined in the scope of module 3 of the common technical document (ich guideline m4). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities

Q9 Quality risk management

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labelling materials in drug (medicinal) products, biological and biotechnological products).

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, formality and documentation of the quality risk management process should be commensurate with the level of risk

Q10 Pharmaceutical quality system

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of each stage

Q11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)

It addresses aspects of development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities. In addition, ICH Q11 provides further clarification

on the principles and concepts described in ICH Guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of drug substance.

Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the firm's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation.

Q13 Continuous manufacturing of drug substances and drug products

The new ICH guideline will establish harmonized scientific and technical requirements needed to fulfill regulatory expectations for the implementation and assessment of CM to improve access to medicines. An ICH guideline would facilitate international harmonization and could reduce barriers to the adoption of CM technology.

Q14 Analytical procedure development

The new guideline is proposed to harmonize the scientific approaches of Analytical Procedure Development, and to provide the principles relating to the description of Analytical Procedure Development process. This new guideline is intended to improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures

QUALITY-BY-DESIGN IN PHARMACEUTICAL DEVELOPMENT

Introduction

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).

Background:

Quality by Design is a concept first outlined by Joseph M. Juran in various publications

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 fewer problems.
- Benefits FDA
- Provide better consistency.
- More flexibility in decision-making.
- Ensure scientific base of analysis.
- Ensures decisions made on science and noton
- Empirical information.
- Improves quality of review.

QbD development process includes:

- Begin with a target product profile that describes the use, safety and efficacy of the product

- Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development
- Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation
- Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile.
- Design a manufacturing process to produce a final product having these critical material attributes.
- Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. 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/or 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 when appropriate

Traditional approach & Enhanced QbD approach

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended

Aspects	Current	QbD
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

QbD activities within FDA

Specifically, the following activities are guiding the overall implementation of QbD:

- In FDA's Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding.
- Implementation of a pilot program to allow manufacturers in the pharmaceutical industry to submit information for a new drug application demonstrating use of QbD principles, product knowledge, and process understanding. In 2006, Merck & Co.'s Januvia became the first product approved based upon such an application.
- Implementation of a Question-based Review (QbR) Process has occurred in CDER's Office of Generic Drugs.
- CDER's Office of Compliance has played an active role in complementing the QbD initiative by optimizing pre-approval inspectional processes to evaluate commercial process feasibility and determining if a state of process control is maintained throughout the lifecycle, in accord with the ICH Q10 lifecycle Quality System.
- Implementation of QbD for a Biologic License Application (BLA) is progressing.

While QbD will provide better design predictions, there is also a strong recognition that industrial scale-up and comercial manufacturing experience provides new and very important knowledge about the process and the raw materials used therein. FDA is aware that knowledge is not static and builds throughout the manufacturing lifecycle.

FDA's release of the Process Validation guidance in January 2011 notes the need for companies to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are quickly corrected. This vigilant and nimble approach is explained by FDA to be essential to best protect the consumer (patient).

ISO 9000 and 14000

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.

ISO 9000 VS. 9001

ISO 9000 is a series, or family, of quality management standards, while ISO 9001 is a standard within the family. The ISO 9000 family of standards also contains an individual standard named ISO 9000. This standard lays out the fundamentals and vocabulary for quality management systems (QMS).

ISO 9000 series of Standards

The ISO 9000 family contains these standards:

- ISO 9001:2015: Quality Management Systems - Requirements
- ISO 9000:2015: Quality Management Systems - Fundamentals and Vocabulary (definitions)
- ISO 9004:2018: Quality Management - Quality of an Organization - Guidance to Achieve Sustained Success (continuous improvement)
- ISO 19011:2018: Guidelines for Auditing Management Systems

ASQ is the only place where organizations can obtain the American National Standard Institute (ANSI) versions of these standards in the ISO 9000 family.

ISO 9000 history and revisions: ISO 9000:2000, 2008, and 2015

ISO 9000 was first published in 1987 by the International Organization for Standardization (ISO), a specialized international agency for standardization composed of the national standards bodies of more than 160 countries. 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.

ASQ administers the U.S. Technical Advisory Groups and subcommittees that are responsible for developing the ISO 9000 family of standards. In its standards development work, ASQ is accredited by ANSI.

ISO 9000:2000

ISO 9000:2000 refers to the ISO 9000 update released in the year 2000.

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 9000:2000 was again updated in 2008 and 2015. ISO 9000:2015 is the most current version.

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.

ISO 9000 Quality Management Principles

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

What is ISO 14000?

Essentially, **ISO14000** is a series of international, voluntary environmental management standards as well as guides and technical reports. It specifies the requirements for establishing an Environmental policy determining the environmental impacts of products or services, planning environmental objectives, implementing programs to meet the various objectives, and conducting corrective action and management review. The first and foremost objective of the **ISO 14000** series of standards is to promote effective environmental management systems in organizations. Besides, the standards seek to provide cost-effective tools that make use of best practices for organizing and applying information about environmental management. Actually, the ISO 14000 family was developed in response to a recognized industry need for standardization. The comparisons of system and collaboration had proved difficult with different organizational approaches to environmental management.If you need any information regarding **International Standardization** or **types of ISO certification** then must follow our **blog**.

History of ISO 14000

According to history, the first environmental management system, BS 7750 was published in 1992 by the BSI group. The International Organisation for Standardization (ISO) created the ISO 14000

family of standards in 1996. In 2004, **ISO 14001** underwent to revision and the current revision of ISO 14001 was published in September 2015.

Series of ISO 14000

Following are the aspects of environmental management addressed by the ISO series:

- Environmental Management Systems (EMS)
- Environmental Auditing & Related Investigations (EA&RI)
- Environmental Labels and Declarations (EL)
- Environmental Performance Evaluation (EPE)
- Life Cycle Assessment (LCA)
- Terms and Definitions (T&D)

What are the compliances to an ISO 14000 EMS?

Following are the compliances for the ISO 14000 EMS:

- Assurance to the customers of your commitment to demonstrable environment management
- Public relations must be excellent
- Investor criteria must be satisfied and improve access to capital
- Insurance must be obtained at a reasonable cost
- Image enhancement and market share
- Registration requirements must be met with the clients
- Cost control must be improved by identifying and eliminating waste and inefficiency
- Lessen the incidents end up in liability
- Reduction in the consumption of materials and energy
- Facilitates the attainment of permits and authorizations
- Decrease the cost of Complying with environmental regulations
- Relations between industry and government improves

Registration of ISO 14000

The registration of ISO 14000 is a formal recognition of an organization's ability to conform to the requirements of an EMS. Any organization can simply declare that their EMS meets the requirements of **ISO 14001** (self- declaration). In addition to this, many organizations choose to have their EMS registered and it happens usually to provide greater assurance to clients and the public or because regulators and clients require it.

What are the basic Principles behind the ISO 14000 series?

Following are the key principles of the ISO 14000 standards:

1. Result in better environmental management
2. Encompass environmental management system and the aspects of environmental products
3. Applicable in all countries.
4. Promote the broader interests of the public as well as users of these standards.
5. Cost-effective as well as non-perspective and flexible so they are able to meet the differing needs of organizations of any type or size, worldwide
6. Flexibility to be suitable for internal and external verification
7. Scientifically based
8. Last but not least, Practical, useful and usable.

What are the benefits of getting ISO 14000 Certified?

Following are the benefits of getting the ISO 14000 certification:

1. It identifies and controls the environmental impact of its activities, product or services.
2. Continuously improve its environmental performance
3. Helps in implementing a systematic approach to setting environmental objectives to achieving these and to demonstrating that they have been achieved.
4. Ensuring legal compliance.

Apart from this, there are several other benefits also which is categorized under Internal benefits and External benefits:

Internal Benefits:

- **Assurance to the management:** It is in the control of the organizational procedures and activities having an impact on the environment.
- **Assure employees:** It assures the employees that they are working for an environmentally responsible organization.

External Benefits:

- It provides assurance on environmental issues to the external stakeholders such as customers, community and regulatory agencies.
- Comply with the regulations of the environment.
- **Claims and communication**: It supports the organization's claims and communication about its own environmental policies, plans, and actions by gaining its EMS certificate.

- **Demonstrate conformity:** It provides a framework for the demonstration conformity via suppliers' declarations of conformity, assessment of conformity by an external stakeholder such as business client and for certification of conformity by an independent certification body.

What are the various standards of ISO 14000 based on Organization and Product?

ISO 14000 is a series that falls into basically two major groupings i.e Organization oriented and Product oriented documents. Under organization oriented standards, it provides a complete guidance for establishing, maintaining and evaluating an EMS. It is also concerned with other organization-wide environmental systems and functions.

Following is the list of the published organization-oriented ISO 14000 standards, TRs and Guides:

1. **ISO 14001:2004,** Environmental Management Systems— Guidance with the specification for use
2. **ISO 14004:2004,** Environmental Management Systems— Complete guidelines on principles, systems and supporting technique
3. **ISO 14010:1996,** Guidelines for Environmental Auditing— Complete guidelines for environmental Auditing (General Principles)
4. **ISO 14011:1996,** Guidelines for Environmental Auditing— Complete guidelines for environmental Auditing, Audit procedures, Auditing of Environmental Management systems
5. **ISO 14012:1996,** Guidelines for Environmental Auditing— Complete guidelines for Environmental Auditing, Qualification criteria for environmental Auditors
6. **ISO 14031:1999,** Environmental Management— Evaluation of environmental performance (guidelines)
7. **ISO/TR 14032:1999,** Environmental Management— Examples of environmental performance evaluation (EPE)
8. **ISO/TR 14061:1998,** Information to assist Forestry Organisations in the use of Environmental management system standards ISO 14001 and ISO 14004.

NABL ACCREDITATION: PRINCIPLES AND PROCEDURES

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.

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

The **objective** of NABL is to provide third party assessment of quality and technical competence. 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.

Principle 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:

1. 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).
2. Get fully acquainted with all relevant documents and understand the assessment Procedure and methodology of making an application.

3. Train a person on Quality Management System and Internal Audit (4-day residential training courses conducted by NABL. Contact NABL Secretariat for details).
4. Prepare QUALITY MANUAL as per ISO 15189 standards.
5. Prepare Standard Operating Procedure for each investigation carried out in the laboratory.
6. Ensure effective environmental conditions (temperature, humidity, storage placement, etc.).
7. 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.
8. 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.
9. 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?"
10. 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.
11. Ensure proper implementation of all aspects that have been documented in the Quality Manual and other documents.
12. Incorporate Internal Quality Control (IQC) practice while patients' samples are analysed.
13. Document IQC data as well as uncertainty of measurements. Maintain Levy Jennings charts.
14. 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.
15. Document corrective actions on IQC / EQA outliers.
16. Conduct Internal Audit and Management Review.
17. Apply to NABL along with appropriate fee.

Accreditation Process

An applicant laboratory is expected to submit to NABL 5 copies of the application and 5 copies of Quality Manual. The Quality Manual will be forwarded by NABL to a Lead Assessor to judge the adequacy of the Quality Manual as to whether it is in compliance with ISO 15189 standards. Thereafter the Lead Assessor will conduct a PreAssessment of the laboratory for one day. Based

on the Pre-Assessment report the laboratory may have to take certain corrective actions, so as to be fully prepared for the final assessment. It is essential for the applicant as well as accredited laboratories to satisfactorily participatein Proficiency testing/ Interlaboratory comparisons/External quality assessment programme as Asia Pacific Laboratory Accreditation Cooperation (APLAC) Mutual Recognition Arrangement calls for mandatory participation in such programmes. Finally when the laboratory is ready, the Lead Assessor and a team of technical assessors will conduct the final assessment. The number of technical assessors will depend on the number of disciplines applied for. The accreditation process involves a thorough assessment of all the elements of the laboratory that contribute to the production of accurate and reliable test data. These elements include staffing, training, supervision, quality control, equipment, recording and reporting of test results and the environment in which the laboratory operates. The laboratory may have to take certain corrective actions, after the final assessment. After satisfactory corrective actions are taken by the laboratory (within a period of 3 months), the Accreditation Committee will examine the report and if satisfied recommend accreditation.

The time required for the process of accreditation will depend upon the preparedness of the laboratory and its response to the non - conformances raised during the pre-assessment and final assessment. The total duration ranges between 6 and 8 months.

Short Questions (2marks)

1. Define QMS.
2. Write down the elements of quality management system.
3. What are the purposes of QMS?
4. What is ICH Q1010?
5. What is the difference between calibration and validation?
6. What do you mean by qualification?
7. What is TQM?
8. Write the name of famous quality philosopher (guru)?
9. What are the seven tools of quality control?
10. What is QbD.
11. What are the elements of Qbd.
12. What is the process analytical technology?

Long questions (5marks)

1. Describe the control quality variation in pharma industry.
2. What do you mean by total quality management? Discuss its advantages and importance in pharma industry.
3. Discuss the philosophies of TQM.

Very Long questions (10marks)

1. What is QbD. Discuss its different element in details?
2. Explain concept of ISO.
3. Describe ISO 14000.
4. Describe the National Accreditation Board for testing and calibration laboratories.