Pharmaceutical QC & QA Elective Course

By Ayalew Desye Abegaz (B.Pharm)
Pharmaceutical Chemistry Course & Research Unit
Department of Pharmacy
College of Medicine & Health Sciences
Wollo University
Dessie, Ethiopia

Pharmaceutical Quality Assurance

- Out line
  - Introduction and definitions
  - Quality assurance of medicines
  - Elements of quality assurance for pharmaceuticals
  - QC & operational task of QC
  - Quality assurance of drug procurement

Rationale for this Module

- Quality medicines are safe, effective and efficient tools for treatment of disease
- Poor quality (sub-standard) medicines may not produce desired effects, may cause harm
- Errors in production can lead to sub-standard medicines
- Quality Assurance principles can be used to:
  - detect errors or problems in production
  - ensure suppliers conform to standards and expectations

Pharmaceutical Analysis

- To ensure the *safety, efficacy and quality* of pharmaceutical products
  - It is important to gain the information about the qualitative and quantitative composition of substances
    - i.e. to find out what a substance is composed of and exactly how much.

- *Quantitative test*
  - measures the **amount** of a substance present
- *Qualitative test*
  - determines whether the substance being tested for is **present** or **absent**
- Video

Pharmaceutical analysis …

- What to test? the drug product
- Why to test? ensures the *safety, efficacy and quality* of pharmaceutical products
- How to test? compendial and non-compendial methods presented in regulatory documents
- Analytical method used to achieve Qualitative and quantitative analysis

Determinants of Medicine Quality

- Identity: Active ingredient
- Purity: Not contaminated with potentially harmful substances
- Potency: Usually 90–110% of the labeled amount
- Uniformity: Consistency of color, shape, size
- Bioavailability: **Interchangeable** products?
- Stability: Ensuring medicine activity for stated period

Quality is…..

Invisible when GOOD

Impossible to ignore when BAD

What is Quality?

- Quality:
  - The totality of features & characteristics of a medicinal product and its ability to **satisfy** the stated &/or implied needs
  - Meeting requirements of specific customer **needs**
  - Compliance with **specifications**
- Quality can be achieved by three **managerial** processes which include:
  - Quality planning (QP):
    - The initial activity of the plan is to **identify** the customers and their need
    - Then **develop** product and process design to respond to the need of the customers

Quality …

- Quality control (QC):
  - A regulatory process which **measures** the quality performance of the products
  - The activities of QC involve **laboratory** procedures
- Quality improvement (QI):
  - Facilitates in **improving** deficiencies through the feedback from customers or regulatory bodies
  - The only way to achieve quality is to manufacture the product correctly
  - Quality cannot be achieved merely by checking, examination and testing.

- "There should not be any compromise for quality"

Quality …

- Quality control is a concept, which strive
  - to produce a perfect product by series of measures designed to prevent and eliminate errors at different stages of production.
- In popular practice, the quality of medicines or pharmaceutical products is assured through quality control.
- Quality assurance department must adopt "good laboratory practice"
  - to ensure ***reliability*** and ***accuracy*** of results given out by them.
- Consequently the manufacture and the control of drugs are very responsible task and they need substantial knowledge of the science.

Terminology

- Quality Assurance (QA)
  - It is the sum of all activities and responsibilities intended to ensure the products meet all the applicable quality specifications in the final dosage form.
  - "a planned system of activities designed to ensure effective quality control."
  - Efficient QA program:
    - To monitor and evaluate effectiveness of policies and procedures of quality control

Terminology …

- Good manufacturing practice (GMP)
  - The part of the QA that products are consistently produced and controlled to the quality standard appropriate to their intended use.

Terminology …

- Quality control (QC)
  - The part of GMP concerned with sampling, specification and testing and organization, documentation and release of procedure to ensure the quality of the drug.
  - "a planned coherent system of activities designed to provide quality product."
  - involve **in-process**, **post-process & finished goods** control including **stability** testing – ***TQC (Total Quality Control)***

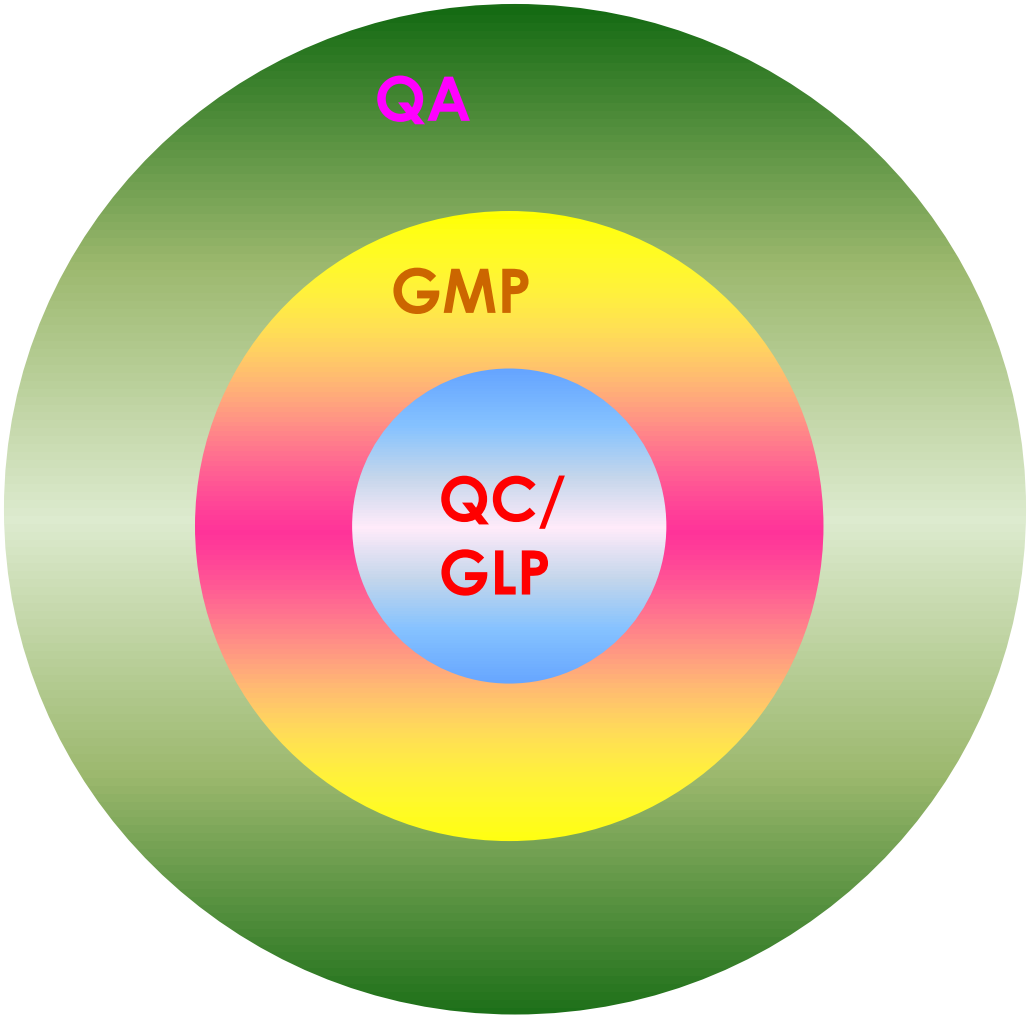
Quality Relationship

Quality Management

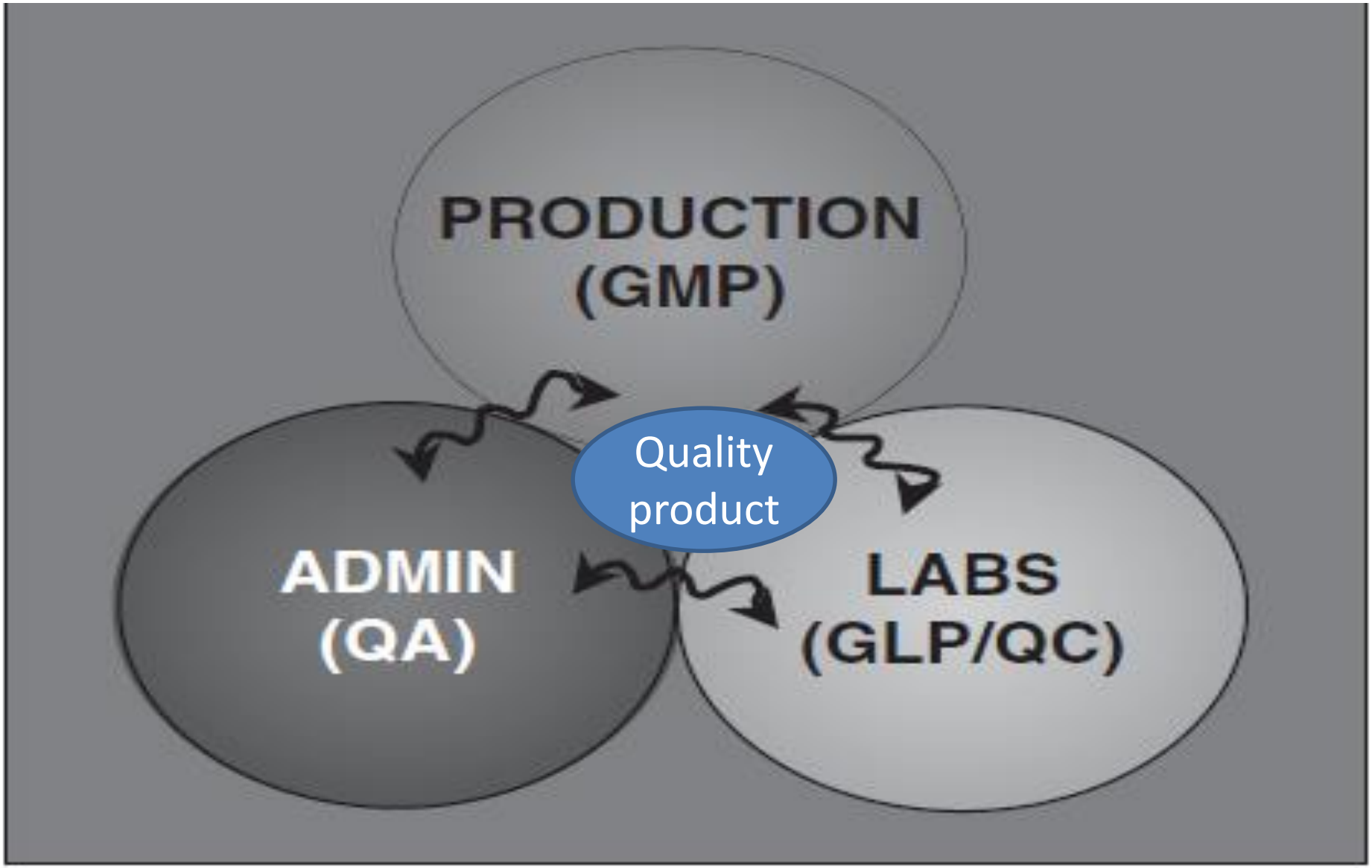
Quality Assurance

GMP

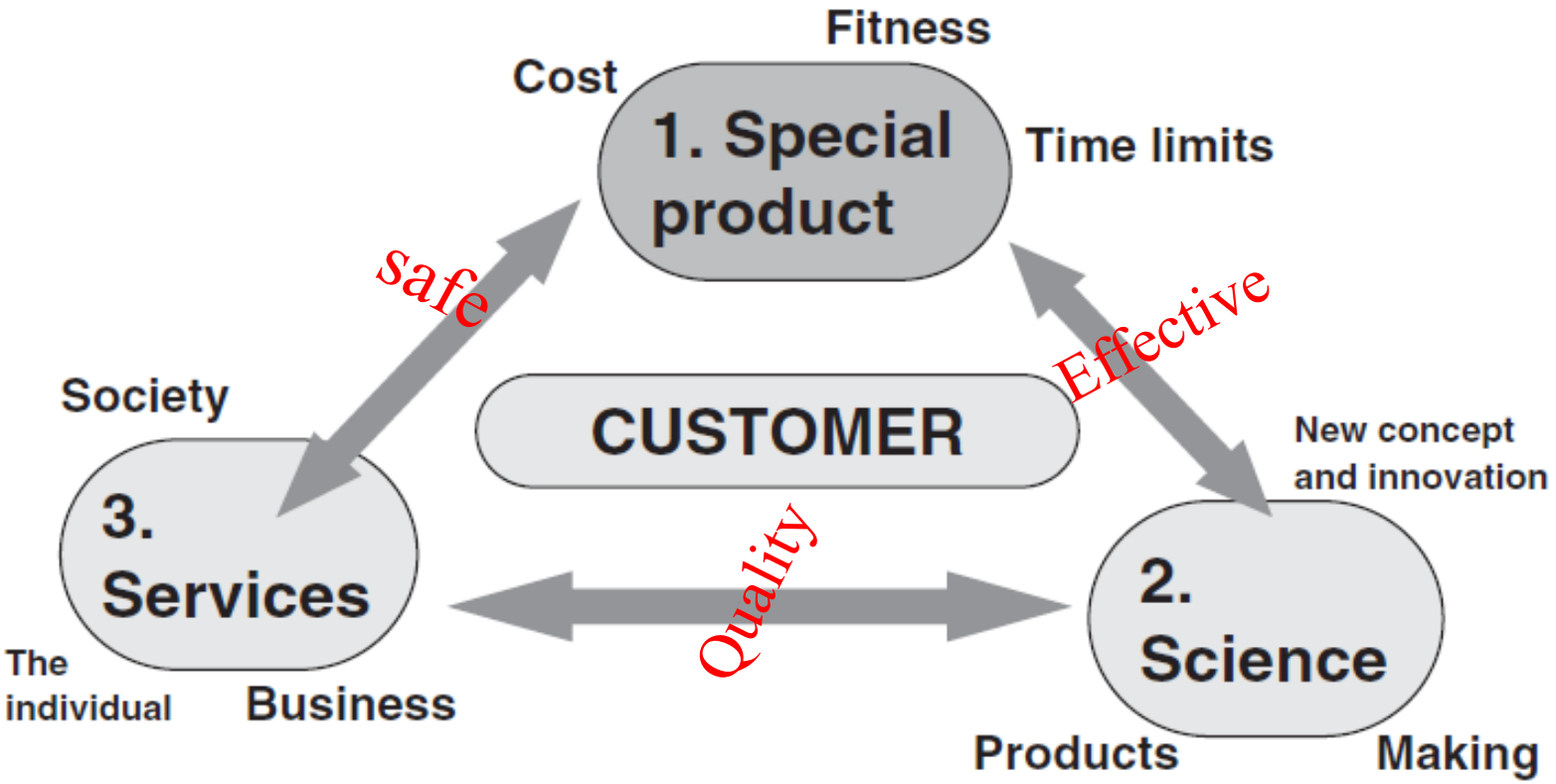
Quality Control



Pharmaceutical manufacturing



- The customer sits at the centre of the quality system activities
- The customer, meaning the patient in terms of pharmaceuticals, is served by three bodies (**special product**, **services** and **science**)

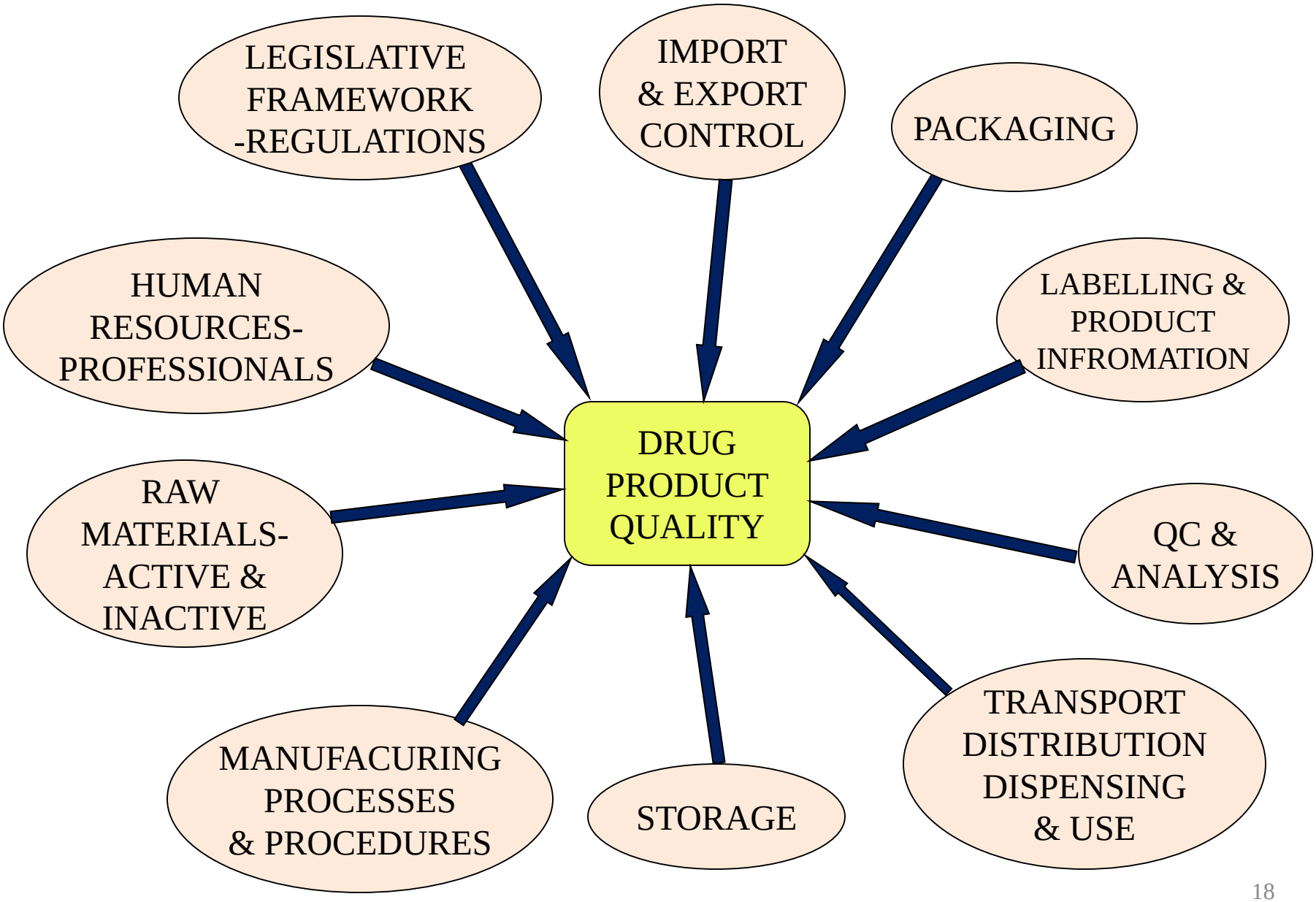


The influence of the customer is felt by 1–3

Quality Assurance

- QA:
  - Covers all maters that individually or collectively influence the quality of the product
  - Is not the duty of one organization unit in the company alone
    - The responsibility of all staff members who can influence product quality
  - Must be independent of financial pressure
  - Must ensure the quality policies are followed

FACTORS IN DRUG QUALITY ASSURANCE



Components of Quality Assurance

- Internal Quality control: IQC
  - Nature: Concurrent
  - Performed by: lab staff
  - Objective: Reliable results on a daily basis
- External quality assessment: EQA
  - Nature: Retrospective to evaluate IQC
  - Performed by: Independent agency
  - Objective: Ensure inter-laboratory comparability

Quality systems

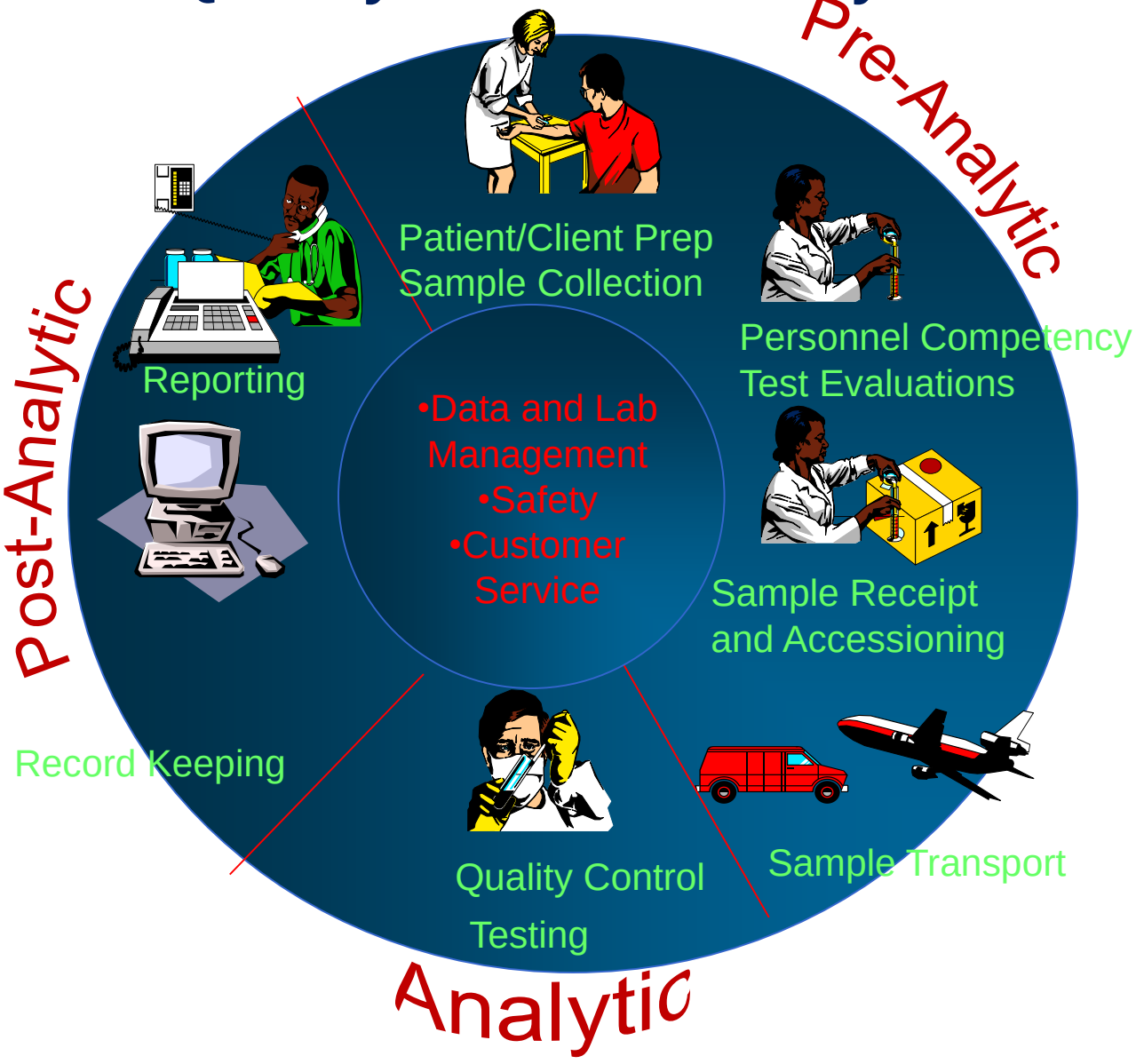
Objectives

- To prevent risks
- To detect deviations
- To correct errors
- To improve efficiency
- To reduce costs

Factors influencing quality

Pre analytical	Analytical	Post analytical
Right specimen	**Laboratory professionals**	Recording
Right collection	**Reagents**	Interpretation
Right labeling	**Equipment**	Turnaround time
Right quantity	**Selection of test - SOP**	Report to right user
Right transport	Records	
Right storage	**Bio-Safety**	

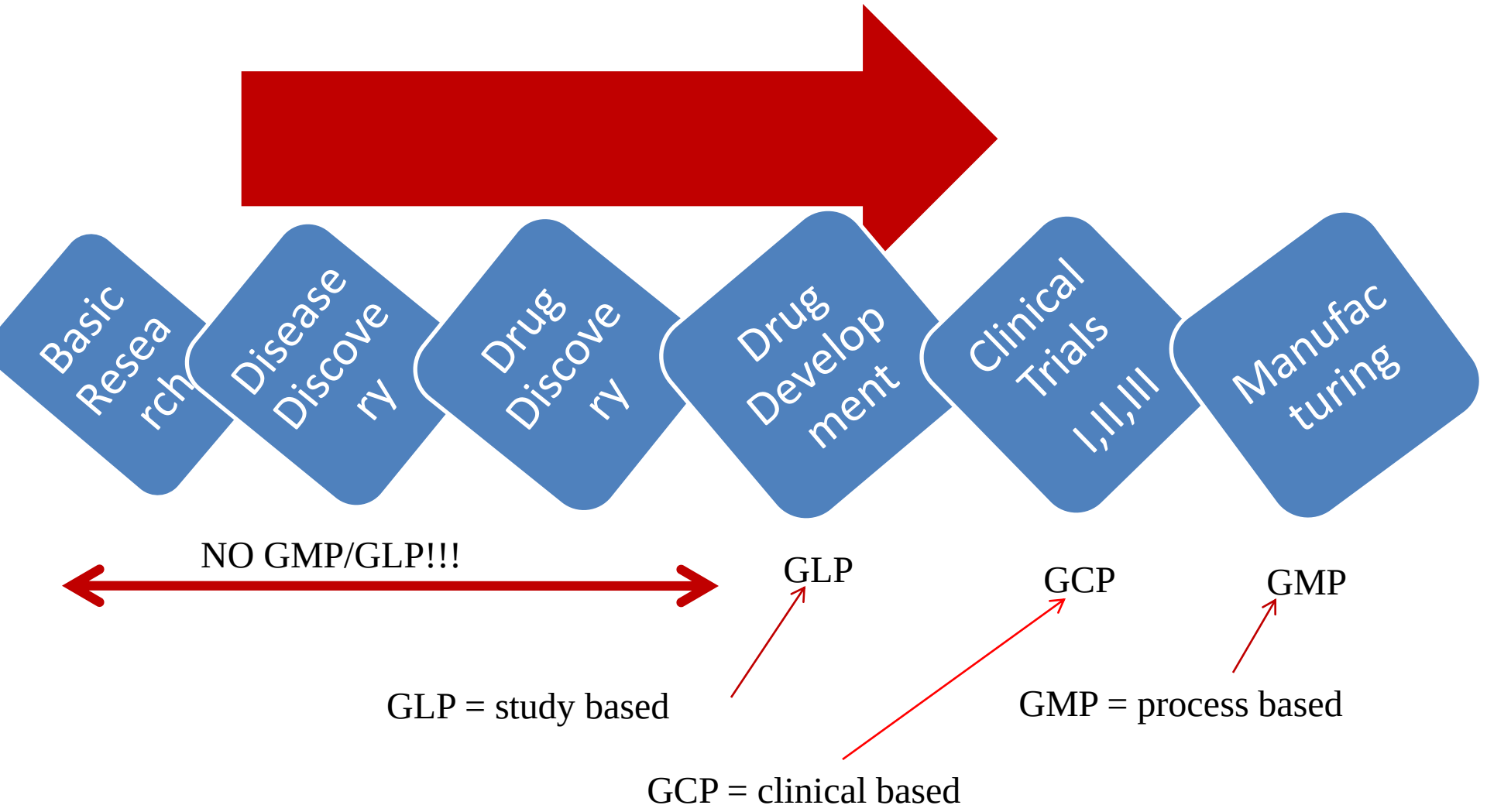
The Quality Assurance Cycle



Principal Activities of QA

1. QA ensures that products are formulated and developed in accordance with QA principles
   - Product quality begins with development process
   - All of the development work should be undertaken with a commitment to QA
   - Enable easier adherence to QA principle in other area of manufacturing

GxP Regulation Along the Drug Life



Principal Activities of QA …

2. QA identify all management responsibilities, with written job description and organization diagram.

   – Assist in ensuring that there are sufficient qualified & experienced people available to carry out their responsibilities.

3. QA provides SOPs for all manufacturing and testing methods.

   – State what should be done and how?

Principal Activities of QA …

4. QA ensures that there are up-to-date written procedures for supply and use of starting and packaging material.
   - Includes all the procedures relating to purchasing, reception, sampling and testing materials.

Principal Activities of QA …

5. QA ensures that there are up-to-date, written procedures to control all starting materials, intermediate and bulk products

   – Proper management of all the handling & storage of materials is essential

      • Apply to all materials whether incoming, intermediate or finished goods for sale.

Principal Activities of QA …

6. QA system must also ensure that there are written, up-to-date SOPs describing how the product is to be processed and checked.
7. QA ensures that no product is released for distribution before it has been checked by the authorized person
   - Product has been *produced and controlled* in accordance with the established SOPs and requirements of the marketing authorizations.

Principal Activities of QA …

8. QA ensures that appropriate conditions are provided for all storage & distributions

   – During product development – Stability testing indicates condition under which product must be stored

   – Arrangement should be in place throughout the storage and distribution chain to ensure that *the product will not be exposed to conditions that could adversely affect it.*

Principal Activities of QA …

9. A QA system must ensure that there is a self inspection process available and implemented, leading to program of critical self evaluation and continuous improvements.
   - There should be an internal audit function within department (self–inspection)
   - Is back up by quality audit, charged with looking at all department & assessing the application of the quality system within a company.

Composition of QA program

1. Appropriate up-to-date **methodology**

- Analytical methodologies are dynamic
  - Old methods get either replaced by new ones or modified b/c of the advantages of **sensitivity** and **selectivity**
- Procedures that should be fulfilled with regard to methodology

A. Analytical measurements should be performed using

» Standard official method (USP, BP, EP)

» Procedures developed & certified by the manufacturers

» Procedures valid through peer reviewed in literature

Composition of QA program …

B. Methods modified/ adopted should be always evaluated by a written protocol prior to use.

- Approach
  - Evaluating in the presence of acceptable comparative method
  - Evaluating in the absence of documented methods (linearity, precision, accuracy)

C. Written guideline for SOPs

Standard Operating Procedures (SOPs)

- SOP
  - An authorized written procedure giving instructions for performing operations
    - not necessarily specific to a given process, product or material
  - describe in a detailed form the activities performed in the laboratory
  - Provide uniformity, consistency and reliability in each of the activities performed in the laboratory
  - Reduce systematic errors
  - Provide training & guidance for new staff

SOPs …

- SOPs should be
  - written instructions that specify:
    - ✓ how a test or procedure is to be performed
    - ✓How a piece of equipment is operated, maintained and calibrated.
  - Written by the person performing the procedure or who knows the procedure well.
  - Supervisor reviewed for completeness and content.
  - QA or QC staff approved

SOP …

- QA is impossible without written guidelines of SOP containing pre-analytic, analytic, and post analytic instructions to perform a test.
- A particular SOP should have:
  i. A title (concise & descriptive)
  ii. Test name, test procedure, reagent used including the limitation of the procedure and calculation explanation

SOP…

III. Principle of the test (type of rxn, sample or test organism involved, reason for performing the test, formula to determine the final result)

iv. Sample storage preservative condition

v. Report handling procedure (reporting range, test & critical value)

vi. Chemical handling technique

vii. Reference materials pertinent to specific procedure

Composition of QA program …

2. Laboratory material & supplies

- uninterrupted supply of high quality reagents and chemicals and other laboratory materials

3. Laboratory facilities and instruments

- Purchasing the equipment, instrument and other laboratory that meet the objective of *the laboratory & designed method*.
- Instrument calibration for proper function of the instrument

Composition of QA program …

4. Quality assurance personnel management

- Training of staffs and periodic performance evaluation complements the Lab's quality assessment program.

A Guiding Philosophy for Quality Assurance in the Pharmaceutical Industry

Poor Quality Medicines:

- Are a health hazard
- Waste money for governments and consumers
- May contain toxic substances that have unpredictable, unintended consequences
- Will not have a desired therapeutic effect
- Does not save anyone any money in the long term
- Hurt everyone – patients, health care workers, policy makers, regulators, manufacturers

- **Good quality is a saleable commodity**

Consequences of QA breaches

- Poor Treatment Outcomes
- High Health Bills
- Treatment Failures & Deaths
- Loss of Confidence in the Health Services
- Enormous Economic Losses
- National Security Issue

Causes of Proliferation of Poor Quality Drugs

- Poor health systems in developing countries
- Lack of legislation
- Weak or absent drug regulatory
- Weak law enforcement and penal sanctions
- High drug demands with short supplies
- Illegal trade in the borders & informal markets
- Corruption & conflict of interest
- High cost of drug – lucrative business (business with great deal of profit)

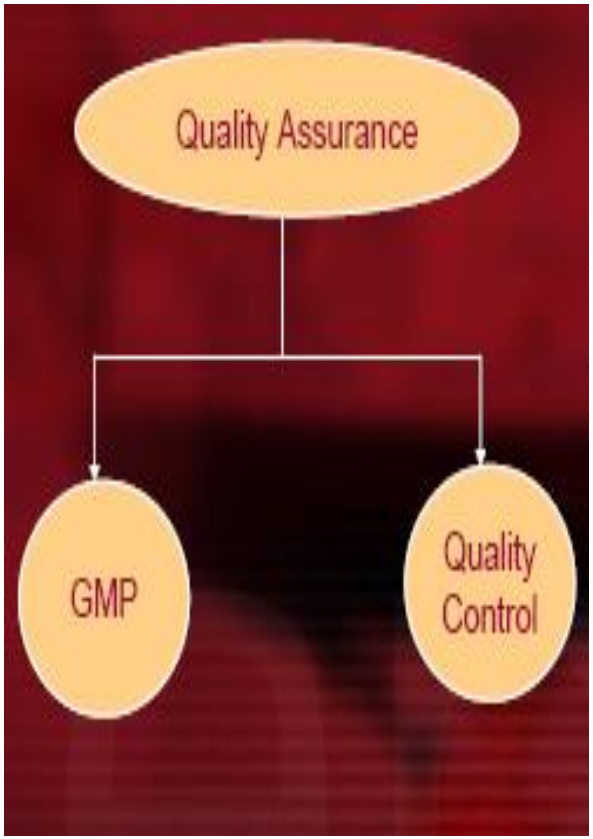
- How to minimize the flow of poor-quality medicines?
  - Inspection
  - Port-of-entry control
  - Document verification
  - Registration

- Quiz1

Concept of Good Manufacturing Practice (GMP)

INTRODUCTION

What is good manufacturing practice (GMP)?



- Part of QA which ensures that products are consistently produced & controlled to the quality standards appropriate to their use
- GMP covers **ALL aspects of production;** from the starting materials, premises and equipment to the training and personal hygiene of staff

Good Manufacturing Practice (GMP) …

- The regulation developed FDA for pharmaceutical industry
  - minimum requirements in the manufacturing processing
- A basic principle of GMP is that **quality cannot be tested into a batch of product** but **must be built into each batch of product during all stages of the manufacturing process**
- It is designed to **minimize the risks involved in any pharmaceutical production** that cannot be eliminated through testing the final product
- Quality should also be maintained during production stage

GMP Implementation by Countries

Different country may use different GMP Guidelines:

- WHO Guidelines
- Country specific Guidelines (e.g. FDA)

How do GMPs of different countries compared?

- At a high level, GMPs of various nations are very similar; most require :
  - Equipment & facilities being properly designed, maintained, & cleaned
  - SOPs be written & approved
  - An independent Quality unit (like QC and/or QA)
  - Well trained personnel & management

What is c-GMP?

- GMP is also sometimes referred to as "cGMP"
- Usually see **“cGMP”** where c = current, to emphasize that the expectations are **dynamic**
- C refers to current rules & regulations that serve strictly follow the guidelines and manufacturing procedures that are current & most up to date.

What is c-GMP?

- Manufacturers who agree to follow the cGMP guidelines but still use 20-25 year old machinery and equipment to produce healthcare products
- GMP forced many manufacturers to give up on old practices and switch over to latest production processes
- Helped in avoiding contamination, errors and mix ups while at the same time helping in production of highest quality healthcare and pharmaceutical products

Advantages of GMP

a. Prevent errors that cannot be eliminated through quality control of finished products

- **unexpected contamination of products**
- **incorrect labels on containers**, which could mean that patients receive the wrong medicine.
- **insufficient or too much active ingredient**, resulting in ineffective treatment or adverse effects.

b. Grantees credibility

- A drug that contains **little or none of the claimed ingredient** will not have the intended therapeutic effect
- **Poor Quality medicine** leads to loss for:
  - Manufacturers, Healthy care workers, Governments, end users

Advantage of GMP …

c. Ensure all units of a medicine are of the same quality (with in a specified parameters)

d. GMP helps boost pharmaceutical export opportunities

- Most countries will only **accept import and sale of medicines** that have been manufactured to internationally recognized **GMP**
- Governments seeking to **promote their countries export of pharmaceuticals** can do so by
  - making GMP mandatory for all pharmaceutical production, &
  - training their inspectors in GMP requirements

Basic Requirements for GMP

1. Appropriate resource:

- Qualified and trained personnel;
- Adequate premises and space; Suitable equipment
- Correct materials, containers and labels;
- Approved procedures and instructions;
- Suitable storage and transport; to produce a quality product

Basic Requirements for GMP …

2. Validated critical steps of production process

- Due to variability in ***quality of materials & performance of equipments***, there is a need to check whether the process works with all variability that can arise
- Process of checking and documenting variability is known as ***validation***
- It carry out controlled experiments to ensure that whatever variables do occur, they can still produce products meeting specifications.
- Validation is required if there is a change in any part of the process (material or equipment used)

Basic Requirements for GMP …

3. **Clearly written manufacturing procedure**

- Including ***batch manufacturing*** and ***testing instructions*** and *the* ***SOPs*** needed for every department

4. **Proper storage and distribution of the products**

- When a product is developed, ***stability testing*** is under taken in order to determine the storage condition and its shelf life
- ***Proper storage and distribution*** of the product minimize the risk to their quality

Basic Requirements for GMP …

5. **Complete document of manufacturing process**

- appropriate investigations are carried out if quality problem come up.
  - ***It must also have records that show what is actually done each time it makes and tests those products***
- The records are very important in the future as they show what was done by whom and whether the work confirmed to standards

Basic Requirements for GMP …

6. **A recall system, in case quality problems are detected after release of products**

- If a product in the market is found to be defective, there need of getting that the product off the market. (recall)
- Recall can be done in d/t way and with d/t degrees of severity, depending up on the reason for recall

Basic Elements of GMP…

1.Personnel

2.Premises

3. Equipment

4.Documentation

5. Production Control

6. Quality Control

7. Complaint and Product Recall

Personnel

- The establishment and maintenance of a satisfactory system of **QA** and **the correct** manufacture of quality products relies upon **people**
- Personnel requirements:
  - **Adequate number** of persons
  - With necessary **qualifications**
  - With **practical experience**
  - **Individual responsibilities** should be clearly understood by the individuals
  - All personnel should be aware of GMP: Must receive training in GMP: initial training, continuing training including hygiene standards
  - All responsible staff should have specific duties recorded in individual written job descriptions
  - Prevent unauthorized access to Production areas, Storage areas , Quality control

Personnel …

- Training, in accordance with a written, approved programme
  - Personnel in the production areas;
  - In the control laboratories; &
  - Those whose activities could affect the quality of the product
- Training programmes should be available, approved by either the head of Production or the head of Quality Control

Key Personnel

- Key personnel (which normally should be full-time) positions include:
  - Authorized person
  - Head of Production
  - Head of Quality Control
- Heads of Production and Quality Control should be independent of each other

Personnel …

Key Personnel …

1. Should possess appropriate qualifications

- Scientific education such as:
  - pharmaceutical sciences and technology
  - Chemistry
  - microbiology
  - chemical engineering

Personnel …

Key Personnel …

2. Should posses appropriate experience

- Practical experience
  - Manufacture and quality assurance
  - Preparatory period under professional guidance sometimes needed
- Education and experience should enable personnel
  - to take difficult decisions in **an independent, professional and scientific way**
  - To resolve the problems encountered **in manufacturing and QC**

Personnel …

Head of Production: Responsibilities

- Approval and implementation of production instructions, in-process QC and ensure strict implementation
- Ensures that production records are evaluated and signed by designated person
- Checks maintenance of production department, premises and equipment
- Ensures process validation and equipment calibration
- Ensures initial and continuous training of production personnel

Personnel…

Head of Quality Control: Responsibilities

- Approval or rejection of materials, e.g. packing materials, intermediates, bulk and finished products, in accordance with specifications
- Ensures carrying out of necessary testing
- Approval of quality control procedures, e.g. sampling and testing; specifications
- Checks maintenance of quality department, premises and equipment
- Ensures validation (including analytical procedure validation)
- Ensures initial and continuous training of QC personnel

Personnel …

The Quality assurance head : Responsibilities

- Ensuring Compliance with regulatory requirements and international standards
- Approval of the release of finished product for sale
- Establishment and implementation of quality system
- Review of all
  - QC testing results,
  - production documents,
  - results of in-process control, &
  - overall compliance to the specification for the finished product prior to release

Personnel …

Visitors or Untrained Personnel

- Preferable not to enter production and control areas
- If this is unavoidable, then they must be given information in advance, particularly about
  - personal hygiene
  - protective clothing requirements
- Must be accompanied and closely supervised at all times

Hygiene

- A high level of hygiene should be practiced in every aspect of the manufacture of pharmaceutical products
- The scope of sanitation covers
  - personnel
  - premises
  - equipment and apparatus
  - production materials and containers
  - products for cleaning and disinfection, and
  - anything that could become a source of contamination to the product

Personnel Hygiene

- A high level of personal hygiene is required in production areas
- should be instructed to wash their hands before entering production areas
- Eating, drinking, chewing or smoking, in the production and storage areas should be prohibited
- Direct contact should be avoided between
  - the operator's hands and the exposed product
  - with any part of the equipment that comes into contact with the products
- Every person entering the manufacturing areas should wear protective garments

Premises

- Important aspects to be kept in mind to ensure the suitability of the operations to be carried out in a given premises:
  - Location
  - Design
  - Construction
  - Maintenance
- must be located, designed, constructed, adapted and maintained to suit the operations to be carried out
- should be situated in an environment which, presents minimal risk of causing contamination of products

Premises …

Location

- The land and buildings where the manufacturing operations are located must contribute towards the quality of the products
- Premises must be located to
  - minimize risks of cross-contamination
  - permitting effective cleaning and maintenance
  - minimizing the build-up of dirt and dust

Premises ...

The design should aim to:

- Minimize risks of errors
- Permit effective cleaning and maintenance
- Avoid cross-contamination, build-up of dirt and dust
- Avoid any adverse effect on the quality of products
- Prevent the entry of insects, birds and animals into the building
- Prevent the migration of extraneous material from the outside into the building and from one area to another

Premises …

Construction

- Should be of Suitable materials
  - To ensure proper cleaning, no cracks, and the building can withstand pressures, vibrations and other effects
- Electrical supply is required
- Suitable lighting (especially for visual on-line checks)
- Temperature and relative humidity control should be provided
  - materials and products have to be stored or processed under controlled conditions.
- Appropriate and effective ventilation

Premises ...

Maintenance

- Careful maintenance done
- Repairs and maintenance should not present any hazard to the quality of the products
- Maintenance workshops should be separated from production areas

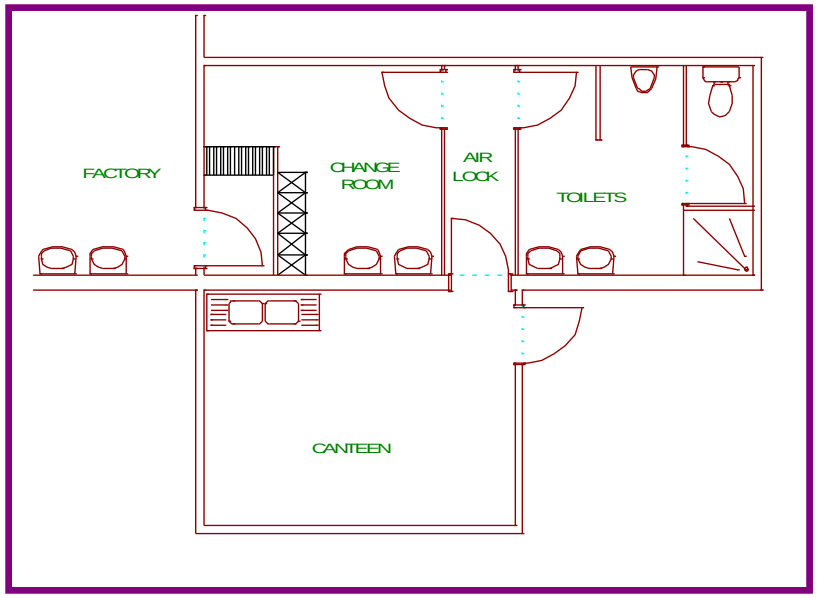
Premises …

Specific areas

- Ancillary areas
- Storage areas
- Production areas
- Quality control areas

Ancillary Areas

- Rest and refreshment rooms should be separated from production & QC laboratory areas
- Changing, washing and toilet areas should be available and in appropriate numbers
- Maintenance workshops separated from production



Premises …

Storage areas

- Storage areas of sufficient capacity
- Separate and segregated areas for different materials are recommended
  - starting materials
  - packaging materials
  - finished products
  - quarantined, released, rejected, returned and recalled products and materials
- Appropriate temperature and relative humidity conditions within defined limits

Premises ...

Production areas ...

- Designed to Minimize risk of cross-contamination:
- Separate facilities for other products such as some antibiotics, hormones, cytotoxic substances
- Non-pharmaceuticals normally not produced in the same facility, e.g. pesticides, herbicides
- Production areas should be effectively ventilated, with air control facilities (including temperature and humidity)
- Should have adequate and appropriate spaces for:
  - Personnel changing rooms, offices
  - Equipments
  - Documents and records
  - Sample storage
  - Testing areas

Premises …

Quality Control areas

- QC laboratories should be separated from production areas
- Suitable design with sufficient space to avoid mix-ups and cross-contamination
- Suitable space for storage of samples, reference standards, solvents, reagents and records
- should be provided with effective ventilation and separate air supply from production is recommended
- Separate rooms for some instruments to protect them from interference (e.g. electrical, vibration, moisture, etc.)
  - Balances and Dissolution apparatus (Vibration free)
  - IR and KF (Moisture sensitive)

Equipment ...

- Equipment used in the manufacture and testing of pharmaceutical products must be
  - Located,
  - Designed,
  - Constructed, &
  - Maintained, to suit the operations to be carried out
- The equipment should be located in areas of production or testing to support
  - the operators in ensuring that the manufacturing process or testing procedure is followed correctly
  - can prevent omission of steps in the process
  - avoid possible cross-contamination

Equipment …

Design

- can assist in easy cleaning and maintenance of equipment
- Equipment design must aim:
  - to minimize cross-contamination, dust
  - to permit effective cleaning and maintenance
  - To avoid any adverse effect on the quality of products

Cross- contamination

- contamination in tablet compression and packaging machines is a common problem area
- use of compressed air is common for moving dust and dirt from inaccessible places on machines

Equipment……

Construction material

- should suit the operation
- Should allow its use for the range of products (production or testing)
- Should not corrode or deteriorate
- Should not influence the manufacturing or testing procedure
- Should not react with the product (very high quality stainless steel)

Equipment …

Maintenance

- Maintenance of equipment is important to ensure that the equipment will operate or perform in accordance with its specifications
- There must exist maintenance schedules for major pieces of equipment

Production equipment

- should be designed so that it can be easily and thoroughly cleaned
- Should not present any hazard to the products
- Parts that come into contact with the product must be non-reactive
- The equipment must be correctly labelled at all times (to show it is clean or dirty, and ready for use)
- Defective equipment
  - removed, or
  - clearly labelled (status label) (to prevent it from being used when it is no longer capable of producing a good quality product)

Equipment …

Quality Control Laboratory Equipments

- The general principles of GMP are applicable to production and QC equipments
- Most requirements for Production Equipments are applicable for laboratory equipment
- maintenance, calibration, records, etc.
- Defective equipment should be removed or labelled to prevent analysts from using equipment for testing

Good Laboratory Practice (GLP)

- is one of the components of QA
- Concerned with the ***activities of QC laboratories carrying out tests & assay methods*** required to establish the compliance of the product with specification claimed for them.
- Main goal is to help laboratories obtain results which are ***reliable, repeatable and recognized worldwide*** & thus help to ensure: ***safety, efficacy & overall quality***

Good Laboratory Practice (GLP) …

- The quality of the product is achieved through GMP & monitored with GLP guideline
- The guideline provide guidance to the laboratory control of pharmaceutical products performed either in:
  - The manufacturing firm
  - Regulatory laboratories
  - Research laboratories

Objectives of GLP

- makes sure that the data submitted are a true reflection of the results that are obtained during the study
- makes sure that data is traceable
- Promotes international acceptance of tests

Basic Elements of GLP

1. Personnel

- Should have appropriate ***qualification, experience and training in QC***
- Availability of protective clothing and other safety facilities
- Availability of periodic training program for all personnel
- Sufficient people

2. Facilities

- Include laboratory building, furniture, etc
- The laboratory should have ***suitable size, construction & location*** to facilitate the proper condition of the test

Basic Elements of GLP …

Design & construction guideline

- Locate in area free from ***noise, vibration, etc to prevent interference***
- QC lab should be designed of sufficient space:
  - to suit the analytical operation to be performed
  - to avoid mix-up and cross contamination etc.
- QC lab should have adequate ***storage*** for sample to be analyzed
- Physico-chemical and microbiological laboratories etc. should be separated each other

Basic Elements of GLP …

Equipments

Equipment design

- Equipments shall be appropriate design and suitably located for operation, cleaning & maintenance
- Major instruments of a testing laboratory
  - *Analytical balance, IR , UV-Visible, GC, pH meter, dissolution & disintegration test apparatus, potentiometer, KFT, HPLC, flame photometer, AAS, HPTLC*
- Equipment for microbiological laboratory
  - Autoclave, microscope, incubators, centrifuge with refrigerator, membrane filters

Basic Elements of GLP …

Maintenance & calibration

- Availability of qualified & experienced personnel
  - Detailed SOPs which describe: the instrument, calibration standards & limits, calibration for each instruments, record keeping requirements etc.
- Preventive maintenance:
  - Is very important for assuring that the instrument is in good operating condition

Basic Elements of GLP …

Testing operation

SOPs

- Are written documents specifying the procedure that must be followed to carry out the operations
- Benefits:
  - Prevents introduction of errors & variations by avoiding word of mouth communication or reliance on memory
  - Used to train personnel & thus help to prevent misunderstanding
  - Eliminate need to develop the procedure every time an operation is performed etc

Basic Elements of GLP …

Chemical, reagent & solutions

- Storage should follow the storage conditions recommended on the label
- Highly toxic chemicals should be stored in appropriate place
- Solution & reagents to be prepared in the laboratory should follow the procedure in the pharmacopeia & label properly

Requirements:

- Reagents and solutions shall be labeled
- Deteriorated or outdated reagents and solutions shall not be used
- Include date opened
- Stored under ambient temperature
- Expiration date

Basic Elements of GLP …

Reference standards

- The *accuracy and precision* of test results and test methods is dependant on
  - the reliability, authenticity and control over reference standards, reagents and stock solutions
  - Similarly the retrospective testing of materials and product is dependant on the *protection and storage of retention samples*
- *Primary Standards may be obtained from*
  - National reference labs
- *In House Secondary Standards*
  - Standardized against primary standards using definitive methods

Basic Elements of GLP …

Test articles:

- Drug testing laboratories receive d/t type of samples for test and control among which are:
  - finished pharmaceutical products
  - APIs
  - Dressing, suturing materials
  - Medical devices

Basic Elements of GLP …

Record & reports

Records:

- Records regarding the d/t ***test applied & all readings and calculation*** should be maintained in a bound laboratory book
- Record of the ***preparation of solution & reagents, standardization of solutions, raw data*** etc

Type of documents

- Standard operating procedures , Protocols of tests, results & Reports

Basic Elements of GLP …

Laboratory records

- Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards
  - Description and identification of sample received
  - Description of method of testing
  - Record of all data secured in the course of the test
  - Record of test results and how they compare with standards of identity, strength and quality
  - Record of all deviations and modification of test
  - Record of standardization of reference standards
  - Record of calibration of equipments

Basic Elements of GLP …

Reporting of results

- It is a GLP requirement that a final report should be reported for each analytical work completed

E.g. tablets & capsule

- *Name of the sample*
- *Date of receipt of the sample*
- *Analytical report No*
- *Batch/lot No*
- *Protocol of the test applied – description, identification, weight uniformity, disintegration time, result of assay*
- *Signature of analyst*
- *Opinion & signature of the approved analyst*
- *Signature of the laboratory head*

Quality Control (QC)

- Each holder of a manufacturing authorization should have a quality control department
  - ***QC department should be independent from other departments.***
- The QC department must have ***adequate resource***.
  - Adequate **laboratory facilities** or access to them.

    e.g. government or contract laboratories
  - Appropriately qualified, trained & experienced **personnel**
  - Approved written **procedures**

The operational task of the quality control department

- ***Sampling***
- ***Inspecting***
- ***Analytical testing***
- ***Monitoring of all materials & environmental conditions in the factory***
- ***Releasing or rejecting material for production use & finished products***

The targets of these activities are:

- Starting materials
- Packaging materials
- Intermediates
- Bulk products
- Finished products
- Environmental conditions

Basic requirements for quality control

1. **Sampling** should be undertaken by methods and personnel approved by the QC department
   - It must be carried out in such a way that it is representative of the batch & in accordance with an SOP
   - QC personnel must have access to the **production area** to undertake sampling when necessary.

Basic requirements for quality control …

2. Validated test methods should be applied.

- The validation of test methods include verification of:
  - Accuracy
  - Precision
  - Linearity
  - Repeatability
  - Robustness
  - Specificity
- Test methods should be challenged to be able to demonstrate that the tests are able to give an accurate result on repeatable bases.

Basic requirements for quality control …

- The method must be capable of being applied with **precision**
- The results obtained must be **linear** over a range of acceptable response
- Finally the result must be **repeatable** over a number of identical tests.

3. **Records for sampling, inspecting, testing** of materials, intermediates and bulk and finished products need to be kept

- This means that there will be traceability on what happened.

Basic requirements for quality control …

4. The QC department should review and evaluate relevant production documentation
   - This review need to cover all quality aspects
   - Ensures manufacturing documentations & the QA documentation are in harmony.
5. The QC department should generate or review records for deviations & failure investigations
   - it is important that all deviation from the normal manufacturing procedure are recorded or documented.
   - Any impact on product quality must be assessed.

Basic requirements for quality control …

6. *QC ensures that ingredients used comply with the qualitative and quantitative composition of the finished product* as approved in market authorization.
7. *QC ensures that proper containers are used*
8. *QC ensures correct labeling of finished products*
9. *QC ensures batches are released by appropriate authorization*.

Basic requirements for quality control …

10. Sample of starting materials & products are retained.

- Sufficient retention samples of the starting materials and the finished products in its final pack should be kept for one year past the expiry date.
- This is to allow for an evaluation of the product after it has been distributed should there be a need.
- It will also allow ongoing **stability** trial to be done

QC department has other duties to carry out, including:

1. Establishing, validating and implementing all QC procedures
2. Evaluating, maintaining & storing reference standards
   - RS are among the most critical materials that QC has to handle
   - The result of much testing rely upon comparison with analytical RS.
   - If RS has not been looked after properly then all the test results may be incorrect.

QC department has other duties …

3. Ensuring correct labeling of containers of materials and products
   - It is nearly impossible for operator to see that an error has occurred.
   - System must be in operation as the main safeguard.
   - If equipment such as **bar code readers** are in operation it must be regularly checked for **effectiveness**.

QC department has other duties …

4. Stability testing of active ingredients and finished products

- A stability testing program should be developed for all products, described in the form of an SOP.
- Stability of active pharmaceutical ingredients should be monitored
- Active ingredients should be regularly tested within their shelf life to confirm suitability for continued use.
- QC should ensure that samples are taken for stability testing program and that analysis is undertaken at the right time

QC department has other duties….

5. Participating in complaint investigation.

- Complaints offer an opportunity for the company to learn from mistakes or product design failures.
- In this way actions can be taken to prevent reoccurrence.

6. Participating in environmental monitoring.

- With regard to products, the environment refers to that which can immediately affect product quality.
- E.g. **swab** testing and settle **plates** in a sterile area, testing of **temperature** and **humidity** control.

Assessment of finished products should embrace all relevant factors

- Including the production **condition**
- The results of **in-process** testing
- The manufacturing (including packaging) **documentation**
- **Compliance** with the specification for the finished product, and
- An **examination** of the finished pack

QC personnel must have access to production areas

- For example sampling & inspection
- This must be balanced because it may not be appropriate
  - QC staff enter aseptic filling suites, or
  - Areas where there is highly potent dangerous material such as oncology/ cytotoxic materials.

Head of QC responsibilities

- Approval or rejection of materials:
  - Starting & packaging materials, intermediate, bulk and finished products
- Evaluation of batch records
- Carrying out necessary testing
- Approval of necessary QC procedures:
  - Sampling instruction, Specifications, Test methods and other QC procedures.
- Maintenance of quality department, premises and equipment
- Validation (including analytical procedure and calibration of equipments)
- Initial and continuous training of QC personnel

Testing references: Pharmacopeial standards (USP, EP, BP, etc)

- Specification consists of test methods and their associated acceptance criteria
- Criteria applicable to all drug products:
  - Identity
  - Strength
  - Purity
  - Testing methods
    - Physicochemical analysis
    - Microbiological analysis

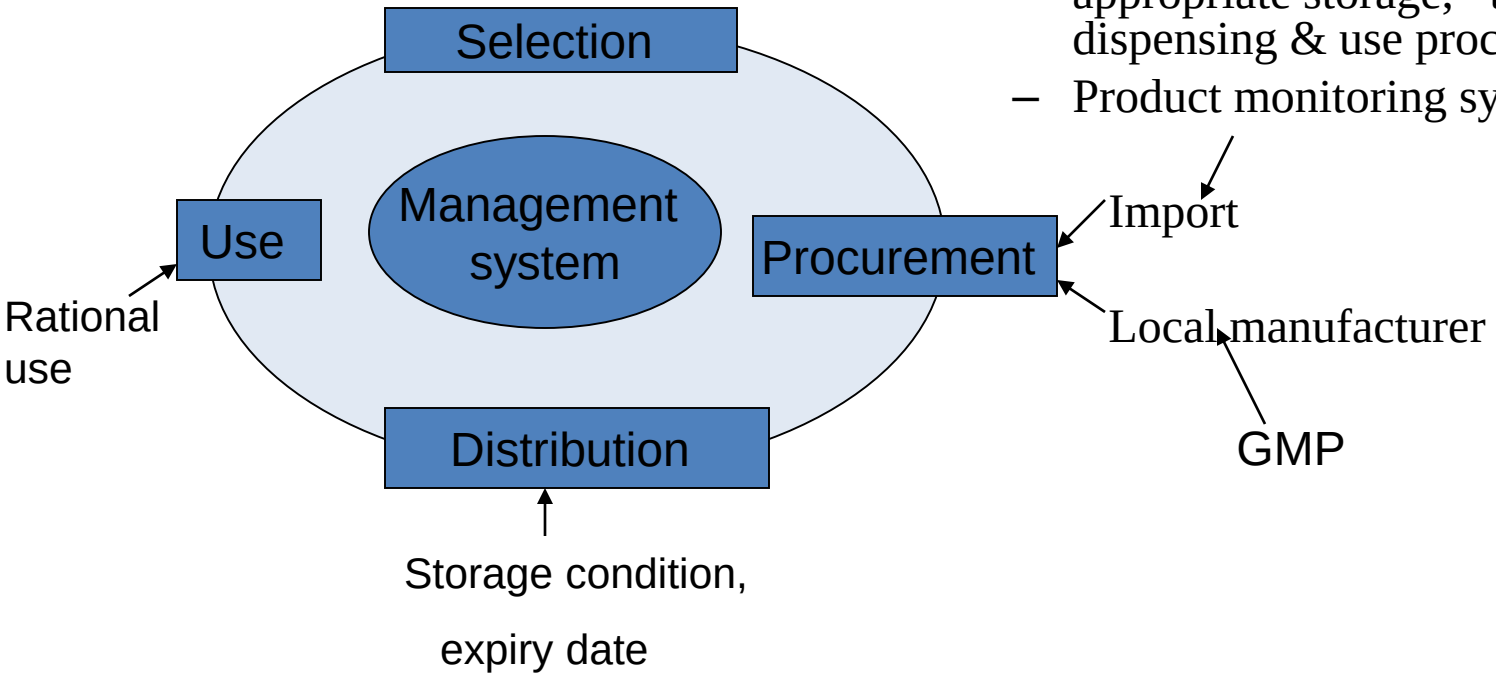
Additional specifications

- *Tablet & capsules*
  - *Disintegration*
  - *Dissolution*
  - *Stereo isomeric purity*
  - *Moisture (water)*
  - *Residual solvents*

- Suspension and solutions
  - pH of solution
  - Particle size of suspending drug
  - Clarity of solution (turbidity)
  - Color of solution
  - Viscosity
  - Volume of fill
  - Preservative testing
  - Microbial limits

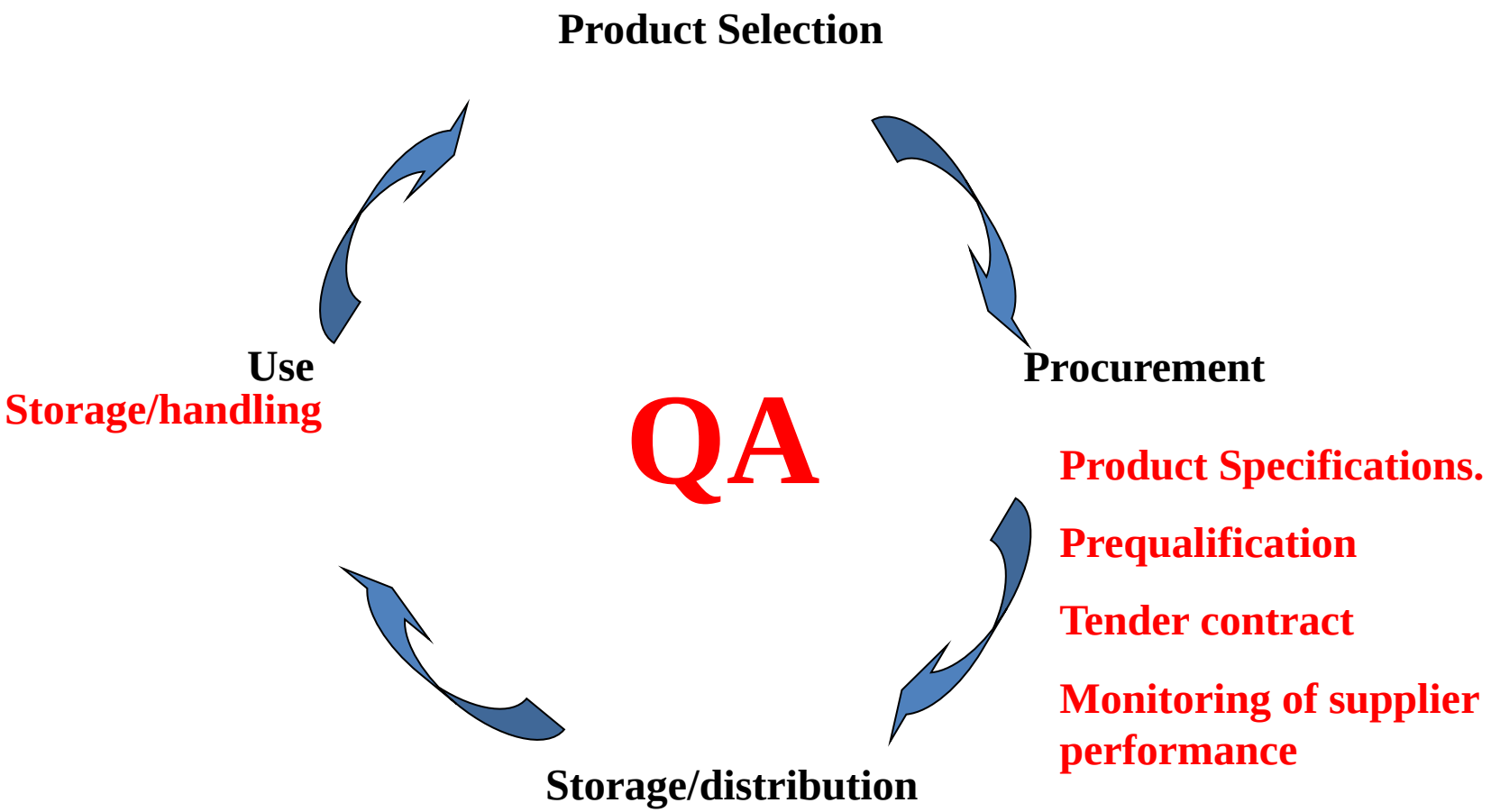
Quality Assurance for drug supply management

- Critical Elements in QA for **Procurement**
  - Product selection
  - Supplier qualification for medicine selection
  - Product certification
  - Contract specification
  - Inspection of shipment
  - laboratory testing
  - appropriate storage, transport, dispensing & use procedure
  - Product monitoring system



GMP, inspection and licensing

Evaluation of product dossier



Goals of Medicine QA Programs

- To make certain that each medicine reaching a patient is safe, effective, and of standard quality
  - Obtaining quality products that are safe and effective through structured *selection* and *procurement* methods
  - Maintaining quality products through the appropriate *storage, distribution, monitoring, and use* by prescribers, dispensers, and consumers

Characteristics of a Comprehensive QA Program-1

- Medicines are selected on the basis of safety and efficacy, in an appropriate dosage form with the longest shelf life
- Suppliers with acceptable quality standards are selected
- Medicines received from suppliers and donors are monitored to meet quality standards
- Medicine packaging meets contract specifications

Characteristics of a Comprehensive QA Program -2

- Repackaging activities and dispensing practices maintain quality
- Adequate storage conditions in all pharmaceutical areas are maintained
- Transportation conditions are adequate
- Product quality concerns are reported & monitored

Pharmaceutical QA

- Pharmaceutical **product** QA
- Pharmaceutical **service** QA
  - Quality of raw materials, intermediate & finished products
  - Maintaining quality products through the appropriate storage, distribution, monitoring, & use by prescribers, dispensers, & consumers
  - Drug use review
  - Clinical pharmacy services
  - Other pharmacy services

- **The following areas (GxP Quality Guidelines) are monitored under Pharmaceutical QA**
  - GMP – Good **Manufacturing** Practice
  - GLP – Good **Laboratory** Practice
  - GDP – Good **Distribution** Practice includes all **procurement** & **transportation** processes
  - GSP – Good **Storage** Practice
  - GPP – Good **Prescribing** Practice
  - GDP – Good **Dispensing** Practice
  - GRP – Good **Review** Practice, …

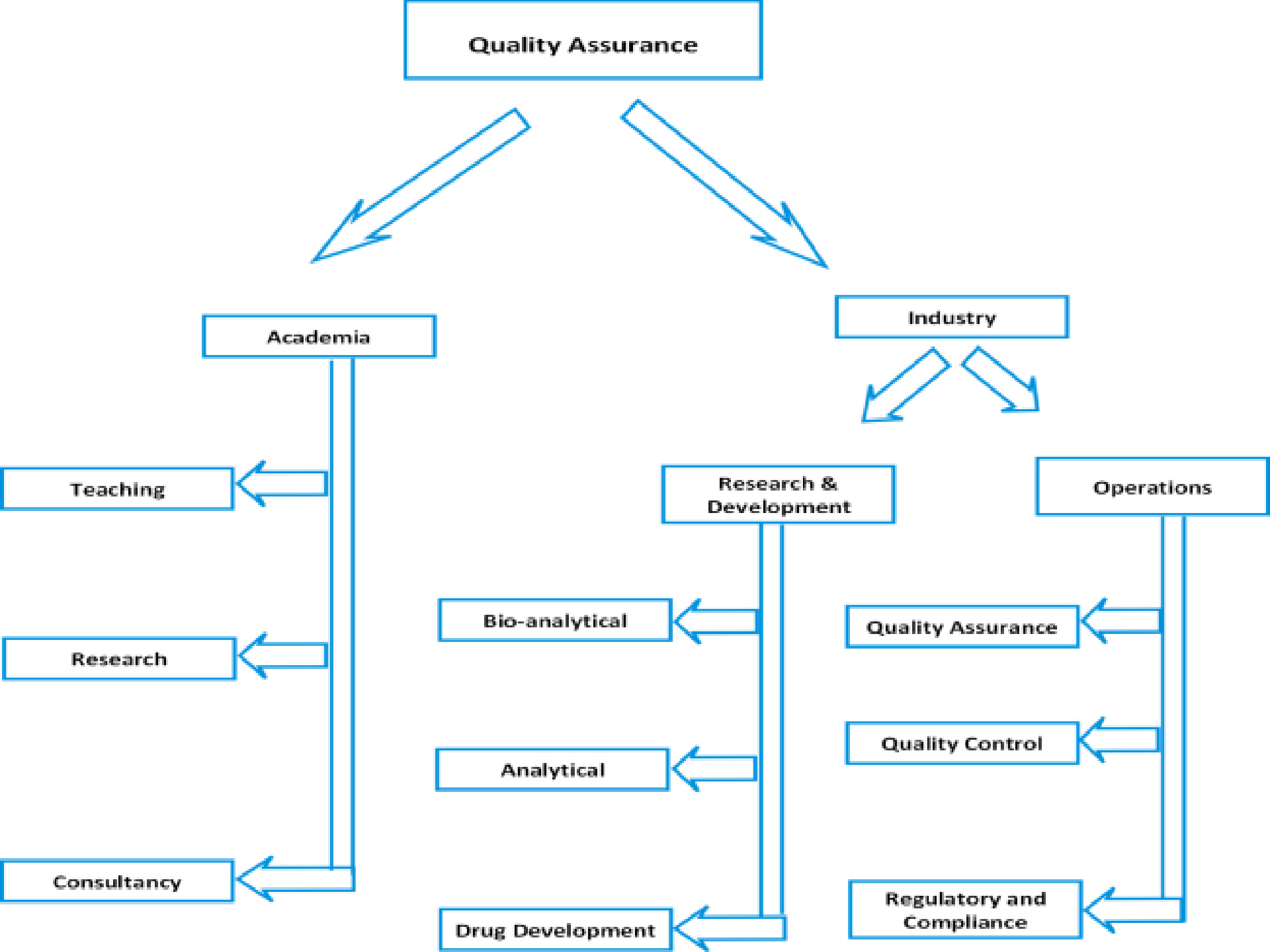
Pharmaceutical Quality Assurance Framework

- Five critical elements to achieve the expected treatment outcome:

1. Active pharmaceutical ingredients (**API**) has been shown to be **safe** & **effective** for the treatment
2. Product is of suitable **quality** to provide an effective outcome
3. Prescriber has accurately identified the **need** for the treatment
4. Prescriber or dispenser has properly **instructed** the patient on how to use the product
5. Patient **compliance** with the prescribed regimen correctly

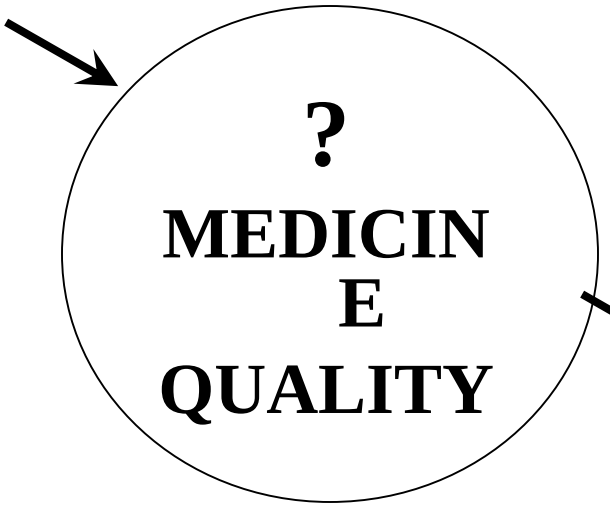
Pharmaceutical Quality Assurance Framework …

- The first **2 items** are **product-specific issues**, which are the most easily addressed technically, whereas
- **Items 3 & 4** are **prescriber-specific** & depends on the prescribers' education, knowledge, & skills as well as the rigorous enforcement of performance standards
- **Item 5** is **patient-specific** issue that depends on the patient's knowledge & commitment & the patient's access to services


Quality Assurance
Academia
Industry
Teaching
Research
Consultancy
Research & Development
Operations
Bio-analytical
Analytical
Drug Development
Quality Assurance
Quality Control
Regulatory and Compliance

Impacts of Low-Quality Medicines

- Manufacturing process
- Packaging
- Transportation
- Storage condition



- ✓Lack of therapeutic effect:
  - ➢Prolonged illness
  - ➢Death
- ✓Toxic and adverse reaction
- ✓Waste of limited financial resources
- ✓Loss of credibility

How Is Quality Assessed?

- **INSPECTION** of products on arrival
  - Visual inspection
  - Product specification review (including expiration dates)
- LABORATORY TESTING for **compliance** with pharmacopoeial standards
  - International Pharmacopoeia
  - European Pharmacopoeia
  - U.S. Pharmacopeia
  - British Pharmacopoeia
  - National Pharmacopoeia

COA

- **BIOAVAILABILITY** DATA

How Is Medicine Quality Assured? (1)

- **Product selection**
  - Long shelf-life ; Acceptable stability
  - Acceptable bioavailability
- **Selection of appropriate suppliers**
  - Supplier pre-qualification; Request samples from new suppliers
  - Request specific reports and data for certain medicines (e.g., bioavailability and stability studies)
  - Collect and maintain information on supplier performance
- **Product certification**
  - GMP certificate of manufacturer
  - Product/batch certification (COA)
  - Random local testing

How Is Medicine Quality Assured? (2)

- **Contract and procurement specifications**
  - Pharmacopeia reference standard
  - Local language for product label
  - Standards for packaging to meet specific storage and transport conditions

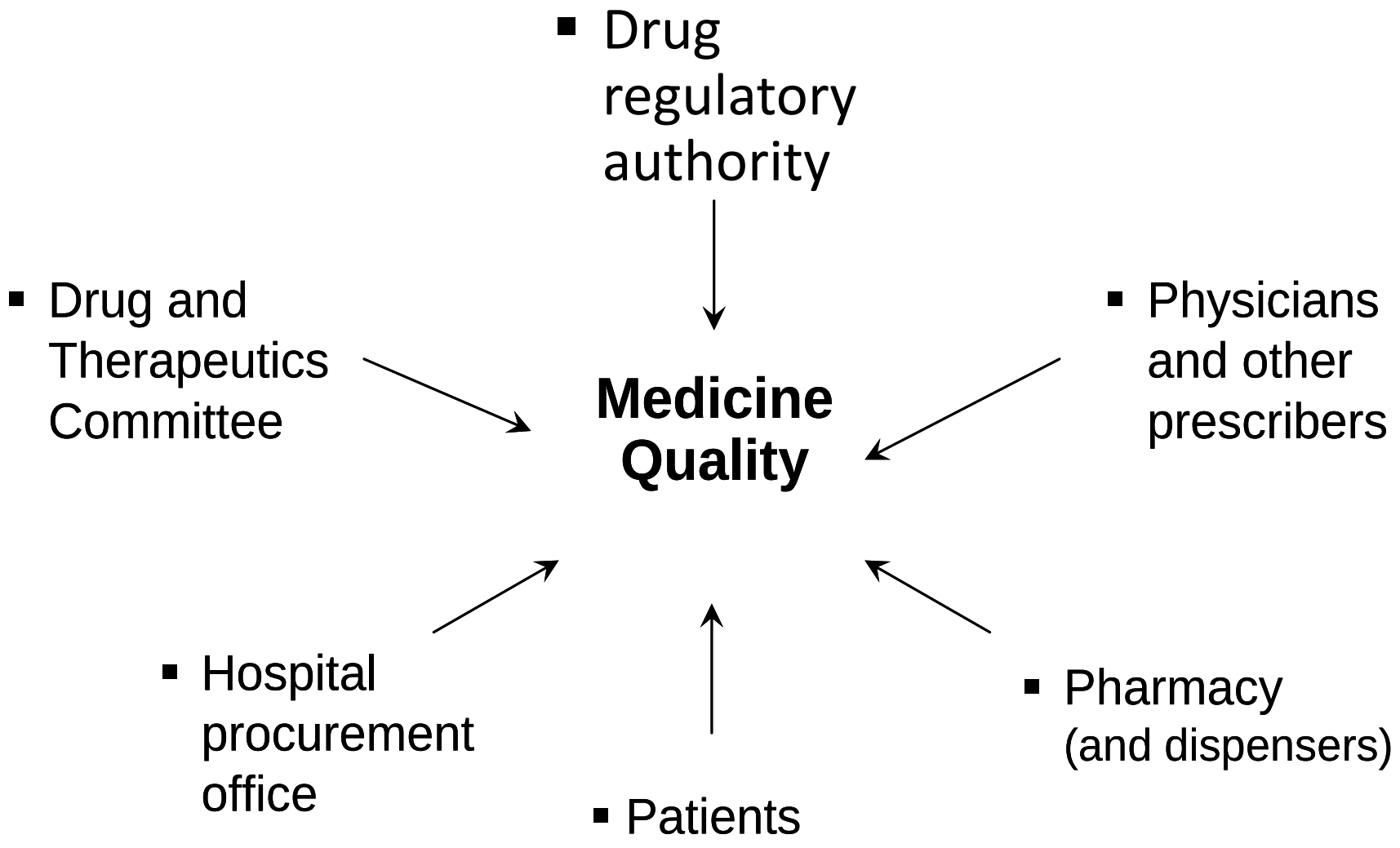
How Is Medicine Quality Assured? (3)

- **Appropriate storage, transport, dispensing, and use procedures**
  - Pharmaceutical distribution & inventory control procedures
  - Provision for appropriate storage & transport including adequate T° control, security, and cleanliness
  - Explicit enforcement of cold chain procedures
  - Appropriate dispensing: containers, labeling, counseling
  - Avoidance of repacking unless quality control in place

How Is Medicine Quality Assured? (4)

- Product monitoring system
  - Problem reporting: who, how, where, and to whom; what additional measures; what follow-up information
  - Product recalls: hospital or country level

Who Ensures Medicine Quality?



Implications of Pharmaceutical QA for the DTC

- Providing technical advice on procurement of pharmaceuticals
  - Defining product specifications
    - Generic medicines
    - Bioavailability issues
    - Stability issues
  - Defining minimum laboratory testing

Implications of Pharmaceutical QA for the DTC …

- Providing technical advice to hospital departments
  - Medicine transportation and storage
  - Dispensing
- Analyzing product problem reports
  - Quality complaints
  - Medicine recall system

Quality assurance in drug supply management

- Targets:
  - Product selection and specification
  - Suppliers selection
  - Product certification
  - Contract specification
  - Inspection of shipment
  - Targeted laboratory testing
  - Maintaining drug quality during storage, distribn & use

Difference between QA & QC

SN	QA	QC
1	Helps us to build processes	Helps us to implement the built processes
2	Is duty of the complete team	Is only the duty of the testing team
3	Comes under the category of verification	Comes under the category of validation
4	Is considered process oriented exercise	Is considered product oriented exercise
5	Prevents the occurrence of issues, bugs, or defects in the application	Always detects, corrects & reports the bugs or defects in the application
6	Doesn't involve executing the program or code	Always involves executing the program or code

Difference between QA & QC ...

SN	QA	QC
7	Is done before quality control	Is done only after QA activity is completed
8	Can catch errors & mistakes QC cannot catch, that is why it is considered low level activity	Can catch errors QA cannot catch, that is why it is considered high level activity
9	Is human-based checking of documents or files	Is computer-based execution of program or code
10	Planning done for doing a process	Means action has been taken on the process by executing it

Difference between QA & QC ...

SN	QA	QC
11	Mainly focuses on preventing defects or bugs in the system	Mainly focuses on identifying defects or bugs in the system
12	Is not considered a time consuming activity	Is always considered a time consuming activity
13	Makes sure that you are doing the right things rightly, that is why it always comes under the category of verification activity	Makes sure that whatever we've done is as per the requirement, means it is as per what we've expected, that is why it comes under the category of validation activity
14	Is pro-active means it identifies weaknesses in the processes	Is reactive means it identifies the defects & also corrects the defects or bugs

In-process Quality Control (IPQC)

IN PROCESS QUALITY CONTROL (IPQC)

"TESTING"

IPQC ...

- Definition: "It is a planned system in which samples are taken and tested at various critical steps during the manufacturing in accordance with the written directions".

- It monitors all the features of the product that may affect its quality and prevent errors during processing

- Areas controlled by IPQC
  - Manufacturing area
  - Packaging area

PURPOSE

- To control the **procedure** involved in manufacturing
- To monitor **all features** which affect the quality
- To **detect** significant human errors
- To ensure quality of final product
- To monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications
- It sometimes identifies a defective product batch that can be corrected by rework

Various Instruments Used in IPQC Dep't

- Disintegration apparatus
- Dissolution apparatus
- Analytical balance
- Friability testing apparatus
- pH meter
- Tablet hardness tester
- Chromatographic methods
- U.V Spectroscopy
- Karl fisher Titrimeter

Conditions for Designing of IPQC Test

- Identify the types of formulation (tab, liquids, ointments)
- Identify the critical steps involved in manufacturing of the product
- Identify the specification of parameters which conform the parameters are within control
- Define the frequency of checking for each parameter

IPQC Tests for Various Dosage Forms

Tablets

a) Content uniformity

b) Dissolution test

c) Assay of active ingredients

d) Weight variation

e) Hardness test

f) Disintegration test

g) Friability

IPQC Tests for Various Dosage Forms …

Syrups & Suspension

a) Content uniformity

b) Assay of active ingredients

c) pH = affects the stability of the product

d) Appearance – color , odor, taste

- Product is checked for uniform distribution of color absence of air bubbles

e) Clarity test

IPQC Tests for Various Dosage Forms …

INJECTABLES

a) Content uniformity

b) Clarity test

c) pH

d) Pyrogen test

e) Stability test

f) Leakage test

g) Sterility test

IPQC Tests for Various Dosage Forms …

Capsules

- Wt variation
- Assays
- Content uniformity
- Dissolution test
- Disintegration time
- Moisture content

IPQC Tests for Various Dosage Forms …

PACKAGING

- **Line clearance** must be given before starting packaging operation
- **Print details** on labels must be certified
- **Leakage testing** bottles, ampoules, vials must be performed

Objectives of Line clearance

- To assure that no traces of previous product
- To assure that correct materials brought for processing/ packing

Packaging Materials Testing

Packaging Materials Testing

Pharmaceutical packaging

- is the means of providing protection, presentation, identification, information, convenience and stability of the product
- pharmaceuticals should retain their therapeutic effectiveness from the time of packaging till they are consumed

Packaging Materials Testing …

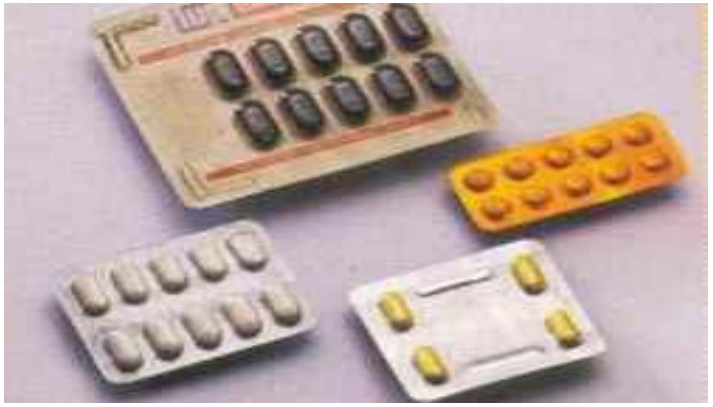
Functions of packaging

- Product Identification
- Product Protection
  - Protects the contents of a product from spoilage, breakage, leakage
- Facilitating the use of product
  - Packaging should be convenience to open, handle and use for the consumers
- Product Promotion
  - used for promotional and attracting the attention of the people while purchasing

Packaging Materials Testing …

There are two types of packaging materials

1. Primary: e.g. vials, plastic bottles, blister packs



2. Secondary: e.g., boxes, cartons, labels, leaflets

Packaging Materials Testing …

- The choice of packaging material will depend upon:
  - The degree of protection required
  - Compatibility with the dosage form
  - Customer convenience e.g. size, weight of dosage form
  - cost
- Composition of package

A. Container

B. Closure

C. Carton

- **Container's**
  - one in which the product is placed
  - a device that holds the drugs and may be in direct contact with the preparation

Packaging Materials Testing …

QUALITY CONTROL OF PACKAGING MATERIALS

- The testing of packaging materials is requirement for any pharmaceutical industry
- There are various tests for determination of quality of packaging materials
- They should pass the specifications of tests before it reached the local markets

Packaging Materials Testing …

Materials used for Making of Containers

a. Glass
b. Plastic
c. Metal

Tests on Glass container

1. LEAKAGE TEST:

- Drug filled container is placed in a container filled with coloured solution (due to the addition of dye) which is at high pressure compared to the pressure inside the glass container
- The coloured solution enters the container if any cracks or any breakage is present

TYPES OF PLASTICS

- They are made up of polymers such as polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), & polystyrene (PS)

Evaluation of Plastic

- Leakage test
- Collapsibility test
- Transparency test

Tests on Plastic Container

1. Leakage Test

- Fill ten container with water
- Fit with intended closures and keep tem inverted at room temperature for 24 hour
- There are no signs of leakage from any container

2. Collapsibility Test

- applicable to containers which are to be squeezed in order to remove the contents
- carried out by squeezing the container to remove the contents which should yield the 90% of the contents at the required rate of flow at room temperature
- Then it indicates the passes the test

Tests on Closures

- Closure is the component which is used to close the different types of containers

Purpose

- It prevents loss of material by spilling or volatilization
- It avoids contamination of the product from dirt, micro-organism or insects
- It prevents deterioration of the product from the effect of the environment

Materials used for making of Closures

a. Glass
b. Plastic
c. Rubber

Evaluation of closures

1. Penetrability

- measured to check the force required to make a hypodermic needle penetrate easily through the closure
- It is measured by using the piercing machine
- The piercing force must not exceed a stated value
- If it exceeds that stated value, the hypodermic needle can be damaged as a result of undesirable hardness of the closures

Documentation

Documentation

- A GMP document is any written record associated with the manufacture, control and distribution of the pharmaceutical product
- Documentation is a method of preparing a written material, which describes the process in terms of specifications, instructions etc
- Good documentation is an essential part of the QA system
- Should exist for all aspects of GMP

Documentation ...

Purpose

- Defines specifications and procedures for all materials and methods of manufacture and control
- Ensures all personnel know what to do and when to do it
- Ensure that authorized persons have all information necessary for release of product
- It provides the working details necessary for manufacturing, packaging, quality control
- Help in decreasing the batch to batch variation
- To ensure the existence of documented evidence, traceability

“If it hasn't been documented, then it hasn't been done!”

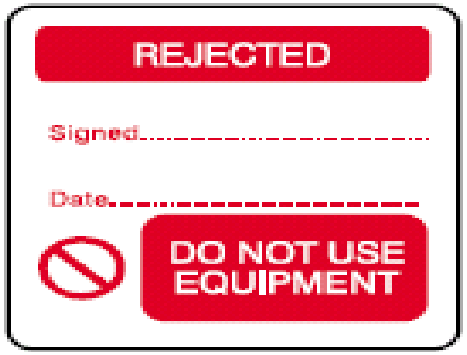
Documentation …

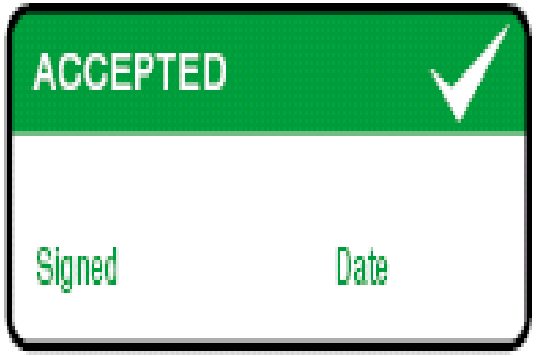
GMP guidelines specify certain documents to be maintained necessarily:

1. Labels
2. Specifications
3. Records
4. SOPs

Labels

- Labels are used for identification or status of containers, equipment and premises
- According to status of container the following color labels are used
  - Quarantine ⟶ yellow
  - Approved ⟶ green
  - Rejected ⟶ red
- Different types of labels, e.g. cleaning status, production stage, status of materials





Labels …

- Labels can indicate the status of materials such as "quarantine“
- materials are under "quarantine“ and cannot be used until released by QC

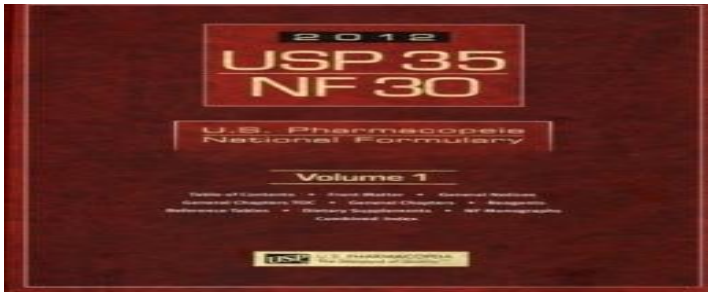
Finished Product Label ...

- Label of all finished drug products contains
  - the name of the drug product
  - a list of the active ingredients
  - the amount of each ingredient
  - the batch number
  - the expiry date
  - precautions and warnings
  - storage conditions & directions for use
  - the name and address of the manufacturer

Documentation …

2. Specifications

- Lists of detailed requirements with which the products or materials used during manufacture have to conform
- important to ensure quality and compliance with a quality standard
- Materials including starting materials, packaging materials, intermediates, bulk and finished pharmaceutical products should have specifications
- Specifications includes tests for identity, content, purity and quality
- Pharmacopoeias, reference standards and reference spectra should be available in the QC laboratory



Documentation …

Specifications for finished products should include:

- the name of the product
- the formula
- a description of the dosage form and package details
- the qualitative and quantitative requirements
- acceptance limits
- the storage conditions and precautions

Records

- Documents maintained in production department are:
  - Raw material records
  - Batch production records
  - Quality control records

Documentation …

Standard Operating Procedures (SOPs):

- written documents specifying the procedures that must be followed to carryout operations
- "are written specifications for all aspects of manufacturing“
- The purpose of a SOP is to provide detailed instructions on how to carryout task so that any employee can carryout a task correctly every time
- There should be written SOP for each operation
    a. equipments
    b. sampling
    c. testing
    d. process
    e. packaging


PURITY

Definition & Aspects of Purity

- Purity: the state of chemical compound when no impurity can be detected by any experimental method
  - No other molecules differing in any way can be present in a pure preparation of a chemical substance.
  - In practice absolute purity is never achieved
    - B/c there is no as such experimental method for recognizing or proving the ideal state of purity

- Official compendia are legitimate to ensure purification by monitoring
  - Undesired by-products arose during synthesis or isolation,
  - Decomposition of dosages of pharmaceuticals under normal condition of storage for stipulated period, etc.
- Specify descriptive as well as informative details
- All pharmaceutical substances, chemicals & dosage forms must rigidly conform to laid-out standards

- Some of the parameters include to ensure purity in official compendia are:
  - Description of the drug or finished products
  - Identification test
  - Physical test
  - Assay of active ingredients
  - Limit test
  - Storage condition

- The purity of a product cannot be ensured merely by inspection and lab analysis
- A control system has to be built from the very beginning of the manufacture of a drug through GMP, beside:
  - QC measures of raw material
  - Process control
  - Assessing the shelf-life & bioavailability of a finished product.

Assay Method of Purity & Attainable Standards

- The standards of pharmaceutical chemicals and dosage forms should fulfill the criteria set by various official compendia. These include:
- Broad based highest attainable standards for chemical purity:
  - It is always fixed though there may be difference in method of manufacturing and changing pattern of stability

    e.g. Chloramphenicol : 98-102%

    Aspirin: 99.5-100.5%
- Attaining the desired biological response:

➢ Attaining the desired biological response:

- Includes retention of acceptable level of potency and free from toxicity.
- The fixed (set in range) standards of biological responses could ensure in order to:
  - Facilitate the production of reasonably reproducible products in d/t manufacturing companies
  - Minimize the difference in active ingredients in various lots
  - Retain acceptable level of potency
  - Avoid toxicity during usage and storage

Biological Response Vs Chemical Purity

I- Biological response

a) Clinical efficiency of drugs: orally administered drugs efficiency depends on their Bioavailability

- Bioavailability absolutely determined in vivo test but is not suitable in terms of ethical consideration, biological difference, cost etc
- Most of the time it is determined using in-vitro method

- Bioavailability difference caused by a number of formulation variables, namely:
  - Particle size
  - Crystalline size,
  - Binding or disintegration agents or
  - Other excipients that has role on the release pattern of the DF

b) Drug adverse reaction

II-Chemical purity:

- This can be ascertained through chemical analysis such as:

➢ Analytical techniques:

  - TLC, HPLC, IR, UV-Visible spectrophotometry, titration, MS etc

➢ Determination of physical constant and chemical properties

  - MP, BP, RI, optical rotation etc

➢ Miscellaneous characteristics need to be monitored

  - Sulphated ash value for organic cpd
  - Loss on drying for hydroscopic cpd
  - Clarity & color of solution
  - Heavy metal determination

Stability Indicating Studies

- **Stability** of a drug defined as:
  - The time from the date of manufacture until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.
- Stability testing:
  - The assessment of a pharmaceutical dosage form under stressful condition for a change in terms of physical or chemical properties or both to ensure the product desirable biological effect and stability for the claimed shelf life (expiry date).

- Stability test data is very important for both manufacturers and regulatory bodies.
- It is useful for:
  - Anticipating the rate of decomposition thereby ensure that no toxic substances are produced to significant amount.
  - Ensuring that there is no significant reduction in the potency of the drug.

Factors Contributing to Instability of a Pharmaceutical Product

a) Incompatibility:

- Due to undesired reaction b/n two or more components of a drug.
- This may lead to:

i. Physical incompatibility:

- Leads to physical change that is recognizable by unusual odor change, color change, gross precipitate.

ii. Chemical incompatibility:

- This is a reaction in which a visible change may not occur and an experiment is required to identify the cause.

iii. Therapeutic incompatibility:

➢ Therapeutic Incompatibility

- This is an undesired pharmacological interaction between two or more ingredients which may lead to:
  - Potentiation of therapeutic effects,
  - Destruction of the effectiveness of one or more of the ingredients or the occurrence of toxic manifestations.

b) Oxidation & reduction reaction:

- Many oxidative reactions are first order type.
- When molecular oxygen is involved, the reaction is known as auto oxidation (occurs spontaneously at room temp).
- N_2 or CO_2 are frequently used to displace the head space air in pharmaceuticals in order to minimize deterioration by oxidation.
- In many oxidation reaction, the reaction rate is dependent on:
  - The concentration of oxidizing species
  - Not on the concentration of oxygen present.

- The rate of oxidation is influenced by:
  - Increase in temperature,
  - Radiation
  - The presence of catalysts
    - trace of heavy metals, hydronium & hydroxyl ions
- Oxidation can be inhibited by the use of antioxidants (negative catalysts).
  - E.g. sodium bisulfite, sodium thiosulfate, ascorbic acid, ascorbyl palmitate, hydroquinone, etc.

c) Hydrolysis:

- Drugs possessing an ester or an amide linkage are susceptible to hydrolysis.
  - E.g. physostgmine, procaine, benzyl pencilline etc.
- Rate of hydrolysis depends up on T^0 & pH of the solution.
- The reaction order for hydrolytic reaction follows zero & first types.
- The rate of hydrolysis doubles for every 1^0C rise in storage T^0.

- Many oxidative hydrolytic reactions are catalyzed by both [H^+] or [OH^-],
  - The pH range of minimum decomposition or
  - Maximum stability depends up on
    - The ions having greatest effect on the reaction
- In general, [OH-] has stronger catalytic effect & the maximum stability is often found between pH 3 & 4.
- Sometimes it is necessary to compromise b/n the optimum pH for stability & that of pharmacologic activity,
  - e.g. several local anesthetics are most stable at acidic pH where as the desired biological activity is possible at neutral or slightly alkaline conditions.

- The amount of water present in a given sample have also a profound effect on the rate of hydrolysis,
  - And when hydrolytic reactions takes place fairly rapidly in water, other solvents should be used.

- Hydrolysis can be prevented by structural modification of the active substance like:
  - Adding constituents like alkyl, acyl chain of aliphatic & aromatic ester
    - Reduce the solubility of the compound there by preventing hydrolysis
  - Steric & polar complexation
    - e.g. caffeine complexes of local anesthetics such as procaine, benzocaine, etc, reduce hydrolytic reactions
  - Addition of a surfactant to facilitate stabilization,
    - e.g. the half life of benzocaine is increased by 18 times by the addition of sodium lauryl sulfate.

d) Decarboxylation:

- Protolytic solid state degradation through decarboxylation is less common
  - Due to high heat of activation requirement to favor the reaction (25-30 Kcal).
- However, first order reaction catalyzed by $[H^+]$ at high temperature can take place for P-aminosalicylic acid to under go protolytic degradation to M-aminophenol & CO_2.

e) Racemiazation:

- The process of changing from an optically active compound into optically inactive (racemic) mixtures of corresponding dextro & levo forms.
- It follows first order reaction that is dependent on temperature, solvent, catalysts and the presence of light.
- It is a major factor of pharmaceutical stability,
  - e.g. l-epinephrine - 15 to 20 times more active than the d-form.
- It depend up on a functional group
  - Bound to the asymmetric carbon atom, with the aromatic substituent group at the asymmetric carbon tending to accelerate the process.

f) Photochemical:

- Photolytic degradation is an important limiting factor in the stability of pharmaceuticals.
- A drug can be chemically affected by the radiation of a particular wave length,
  - If it absorbs radiation at that wave length and the energy absorbed exceeds the threshold limit.
  - UV-radiation has a large energy level hence it is the cause for many degradation reactions.

- If the absorbing molecules react, the reaction is said to be photochemical.
- If the absorbing molecule passes the energy to the other reacting molecule (do not participate directly), the absorbing substance is called photosensitizer.
- Variables such as intensity and wave length of the light, size, shape, composition & color of the container containing the pharmaceutical may affect the reaction velocity.
  - Considerable protection from UV radiation and little form IR is required.

- The kinetics is very complex, in most cases zero & first order reactions are followed.
- Colored glass containers are most commonly used to protect light sensitive formulations,
  - e.g. yellow-green glass give best protection in UV region while amber colored glass confer

g) Radiation used for sterilization

➢ Ultrasonic energy:

- Consists of vibrations & wave with frequencies greater than 20,000/sec.
- It is used for sterilization of pharmaceuticals.
- It promote the formation of free radicals & alter drug molecules hence, abandoned as a means of sterilizing medicaments.
- Degradation increase linearly with increase in power of radiation.

➢ Ionizing radiation:

- Ionizing radiation especially γ-rays was used for sterilization of products.
- The usual sterilizing dose 2.5 mrad causes appreciable chemical degradation of drugs.
- In general, in most formulations which are in the solid or frozen state are more resistant to degradation from ionizing radiation than those in liquid form.

Reaction kinetics

- The study of rate of chemical change and the way in which this rate is influenced by conditions of concentration of reactants, products, other chemical species and factors such as solvents, pressure and temperature.
  - It permits a rational approach for the stabilization of pharmaceuticals.
  - It facilities the prediction of shelf life and optimum storage conditions.
  - It is useful for the elucidation of mechanisms by which chemical reactions proceeds and formulation of a model for the conversion of reactants to products.

Rate of reaction & order of reaction

- Rate of reaction is the velocity with which reactants under go chemical reaction towards a product.

  E.g. Hydrolysis of sucrose;

  $C_{12}H_{22}O_{11} + H_2O \rightleftharpoons C_6H_{12}O_6\,(Glu) + C_6H_{12}O_6\,(Fru)$

  - The rate at which conc of sucrose decrease with time, 't' is proportional to the unhydrolyzed sucrose (C).

    i.e. – dC /dt = K.C

    - Where, K is velocity or rate constant and - dC/dt is decrease in conc of sucrose with time.

- Reaction order refers to the way in which the conc of a reactant influences the rate of chemical reaction.

Zero order of reaction:

- The rate of reaction is independent of the conc of reactants.
- Mathematical expression for the general reaction:

A $\longrightarrow$ Product (P) in zero order is given by:

$$-dC_A/dt = K$$

- Plot of Concentration Vs time will give straight line.

- The following examples demonstrate zero order of reaction.
  - Photochemical reaction in which the rate determining factor is the light intensity rather than the concentration of reactants.
  - Decomposition through hydrolysis, weakly concentrated solutions tends to decompose at higher percentage ratio than the concentrated one if the reaction is zero order kinetics.

- If a compound for which decomposition in solution is first order is present in excess of its maximum solubility (a suspension),
  - The concentration of the reactant in solution will be invariant (constant) as long as there is excess solid reactant present, such a reaction is called apparent zero order or pseudo zero order. i.e. the observed reaction rate will be: **-dC /dt = KCo,** where Co is constant.

First order of reaction

- When the rate of a reaction is proportional to the first power of conc of a reactant.
  - Mathematical expression for the general reaction:

$$A \longrightarrow B$$

In first order, $\boldsymbol{-dC_A/dt = K.C_A}$

  - The above expression can be written as

$$dC_A/C_A = -k\,dt$$

- On integration: $\boldsymbol{-\ln C_A = kt + constant}$
- In common logarithm, $\boldsymbol{\log. C_A = -kt/2.303 + constant.}$

- If ‘a’ is the initial conc of the reactant & ‘x’ is the amount that has been reacted at time t, then ***K = 2.303 / t x log (a / a-x).***
- When the concentration at Co and elapsed time, t are known then, the conc C_1 at time t_1 and C_2 at later time t_2 are used to calculate ‘k’ by the following equation,

$$k = 2.303 / t_2 - t_1 \times \log C_1 / C_2$$

- A more useful expression of reaction rate in terms of half-life of a reaction ($t_{1/2}$),
  - Which is the time required for half of the reactant to under go reaction, and given by the expression $t_{1/2} = 0.693 / K$.
- This showed that $t_{1/2}$ value for the first order reaction is constant & which explains that,
  - The time interval required for the disappearance of any specified fraction of the reactant will be constant irrespective of the conc of the reactant.
- Thus in studies of drug stability the time required for the loss of 10% of the original conc or time required for the 90% of the conc to remain is the commonly employed term to calculate shelf life.

- It is also apparent that an infinite period of time would be required for all the substance to undergo reaction,
  - Hence it is impossible to measure first order reaction rate to completion and the log. Conc Vs time plot cannot be extrapolated to zero.
  - Plotting log C Vs time will give straight line & the rate constant,
    - k can be calculated from the slope of the line.
  - E.g. for fist order reaction that are shown to occur at rates proportional to the conc of drugs:
    - The passive diffusion of drugs across biological membrane, distribution, metabolism and excretion.
    - Rate of growth of microorganisms and rate of killing or inactivation of microorganisms by heat or chemical agents.

Second Order Reaction

- The experimentally determined rate of reaction is found to be proportional to the conc of each of the two reactants or to the second power of the conc of one reactant.
  - Mathematical expression: For a general reaction,

$$A + B \longrightarrow C$$

$$-dC_A/dt = -d\,C_B/dt = K\,C_A\,C_B$$

  - If ‘a’ and ‘b’ represent molar conc of ‘A’ and ‘B’ at t = 0 & the number of moles of each reacted at time t = t considered as ‘x’, then the number of molecules unreacted will be (a-x) and (b-x), then

$$dx/dt = K\ (a-x)\ (b-x) \qquad dx/\ (a-x)\ (b-x) = K\ dt$$

  - Integration and converting to logarithmic form will give the mathematical expression,

$$K = 2.303 / t(a-b)^{x} \log b\ (a-x)\ /a\ (b-x)$$

  - A plot of logb(a-x)/a(b-x) Vs t (when ‘a’ & ‘b’ are not equal) will give straight line

Note:

- Zero, first & second order rate processes are by far the most common type of rate process encountered in consideration of drug stability.
- If a reaction is a higher order, it is often convenient to adjust the experimental conditions by keeping the conc of one of the reactant to remain constant through out the experiment.
- e.g. $CH_3COOC_2H_5 + NaOH \rightleftharpoons CH_3COONa + C_2H_5OH$, if the base is in great excess or if a buffer system is employed then the observed reaction rate will depend on changing the conc of the ester, the reaction is then said to be apparent 1^{st} order or pseudo 1^{st} order.
- In complex reactions it is often desirable to use this approach of maintaining the conc of all but one of the reactants constant in order to facilitate determination of the dependency of reaction rate on each of the reactants in turn.

Third order rate of reaction

- The experimentally determined rate of reaction is found to be proportional to:
  - The concentration of each of the three reactants.
  - Or the conc of one of the reactant & the second power of the conc of the other.
  - Or the third power of the conc of a single reactant.
    - Mathematical expression: For a general reaction,

      $A + B + C \longrightarrow D$ at molar conc of ‘a’, ‘b’ & ‘c’.

- Rate equation, $-dC_A/dt = -dC_B/dt = -dC_C/dt = KC_AC_BC_C$

  $dx/dt = K(a-x)(b-x)(c-x)$, when a = b = c then,

  $dx/dt = K(a-x)^3$, on integration

  $1/2(a-x)^2 = Kt + \text{constant}$

  - Evaluating the constant by substituting zero for ‘x’ at t = 0 will give the expression

$K = 1/2t\,[1/(a-x)^2 - 1/a2\,]$

Complex reactions

- Many chemical reactions are not simple reaction like zero, first, second or third order often consists of a combination of two or more reaction.
  - The rate equations in such cases become a complicated function involving 1^{st}, 2^{nd} or 3^{rd} order intermediate steps.
  - A reaction order which is not integral or fractional are considered to be complex.
  - The complex nature of a reaction is converted to integral reaction order by controlling the concentration of various reactants to permit simplified form of order of reaction.
  - Complex reactions are classified as simultaneous, consecutive and opposing reactions.

Arrhenius equation & temperature effect on reaction rate

- **Temperature**: It increases the rate of chemical reaction because the number of collision per unit time becomes higher.
- **Vant-Hoff's rule:** Reaction rate is increased 2 to 4 times when the temperature is increased by 10 ^{0}C in the vicinity.
- Hence, the importance of temperature on the chemical stability of a pharmaceutical product cannot be over-emphasized because reaction rate doubles for every 10 ^{0}C rise in temperature.

Arrhenius equation & temperature effect on reaction rate …

- Arrhneius equation: variation with temperature of rate constant of chemical reaction could be expressed by the equation,

$$K = A\, e^{-Ea/RT}$$

- Where K = temperature rate constant, Ea = Arrhenius activation energy

$e^{-Ea/RT}$ = Boltzmann factor

R = is gas constant (1.987 cal/K) & T is absolute temperature (273 K).

A = frequency factor

- Converting the equation to the logarithmic form will give,

$$\ln K = \ln A - \ln e^{-Ea/RT},$$

$$\text{Log } K = \text{Log } A - Ea / 2.303\ RT$$

- Integrating between limits K_1 and K_2 and T_1 and T_2 will give

$$\text{Log } K_2 / K_1 = Ea / 2.303R \times (T_2 - T_1 / T_1 T_2).$$

- Plotting Log K Vs 1/T yields straight line with intercept of Log A and Ea can be calculated from the slope of the line.
- This plot is known as Arrhenius plot.

Predicting the shelf life of a pharmaceutical product

- A number of factors should be considered during stability studies & accelerated testing procedures.
- The most important ones are the following.

a) Humidity (moisture): Medicaments may absorb or adsorb humidity that facilitate chemical reaction at faster rate leading to decompose product.

  - The saturation of the crystal structure of a solid with moisture follow zero order.

Predicting the shelf life of a pharmaceutical product …

- Adsorption and desorption phenomena varies with the type of crystal structure of the drug.
  - E.g. Phenobarbitone the phenomena give hysteresis loop (type of curve) while for procaine adsorption/desorption process will not occur until certain specific relative humidity.
- A set of relative humidity is used for accelerated testing of sample, these include 75% RH, 80% RH and 90% RH (note ambient humidity without stress condition is 40 to 60% RH).

- The product is kept with or without its final container in a cabinet (adjusted with different stressed RH) for specified period.
  - The samples are then analyzed for the set different RH conditions.
- A graphical plot of the % potency of the drug Vs % relative humidity is done for the stressed sample.
  - The plot will be subsequently used to determine the critical humidity (the point beyond which the drug is unstable).
- The critical humidity value is very important in giving information regarding the storage and protection needed for the sample.
- The potency of the drug should be above 90%.

b) Light: It is one of the factors that bring photochemical reaction since UV radient energy can enhance certain type of reaction.

- Light enhance activation energy there by increase reaction rate.
- For specific kinetic study of a reaction, the λmax and intensity of the radiant energy should be known because the type of energy responsible for the reaction can be identified. E.g.
  - ✓oxidation: adrenaline;
  - ✓auto oxidation: oil rancidity, color fading.

- Type of radient energy that influence photochemical reaction:

  sunlight > day light >>artificial light or a combination of these.

- Colored bottles are used for the protection of light reactions because they prevent the passage of certain wave length of the light.

- Accelerated testing: a more intense source of radient energy is used for kinetic studies.

  - Fluorescent lamp is commonly used to produce decay of a product

c) Mechanical stress and gravity:

- Stress (vibration) and pressure brings breakage, abrasion and chipping of formulated product like tabs and suspensions.
- ***Solid sample***: the test performed are friability and hardness test
  - Friability test is associated with chipping and abrasion.
  - Hardness helps to anticipate the strength of tabs to withstand stress conditions during transportation, handling and usage.
- **Suspensions (liquids):** The mechanical stress is due to gravity during storage conditions and physical stability.
  - The degree of physical stability of a suspension is determined by:
    - ✓ Shaking: proof for homogenous re-distribution with moderate shaking.
    - ✓ Pourability: proof for easy pourability during its shelf life.

- Brook field viscometer is used for quantitative determination.
  - It gives idea about the particle size distribution in quantitative manner.
    - Emulsion (oil/water or water/oil): its instability is associated with creaming (due to gravity).
- The particle size distribution can be determined by:
    - Microscopy: globule particles observed are considered as particles.
    - Coulter counter method: the dimension and the No. of particles are determined, and a histogram is plotted (for frequency of particles Vs dimension range) to determine the homogeneity of the particle size.

d) Temperature

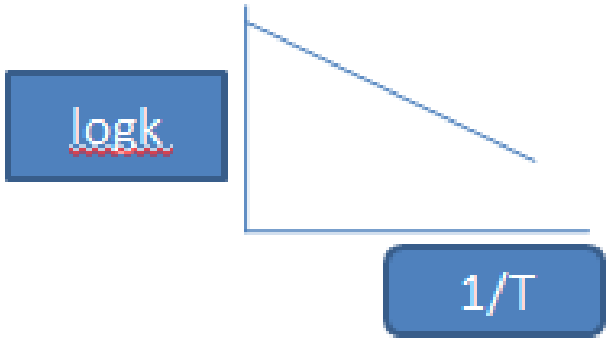
- It enhances the reaction rate because the number of collision per unit time become higher.
- The importance of temperature on the chemical stability of a pharmaceutical product cannot be over-emphasized because the rate of chemical reaction doubles for every 10 ^{0}C rise in temperature.
  - E.g. Reconstituted syrup preparation like amoxicillin syrup are stable:

d) Temperature …

- For 14 days if stored at room temperature.
- 3 weeks to 1 month if stored in refrigerator.
- The stability will be reduced to a week or less, if it stored in very hot and humid environment.

- Stability testing at controlled laboratory conditions (usually for samples used in clinical study) is usually performed at room temperature (15 to 25^0C) or 2.8^0C (refrigeration condition) and ambient humidity (40-60 %RH).

- The stability of a product can be predicted by testing at higher temp (accelerated testing).
- This facilitates the prediction of an expiry date by Arrhenius equation ($K = A e^{-E/RT} = \log K = -Ea/2.303 R \times 1/T + \log A$)
- The test is performed on at least three elevated temp conditions with identical relative humidity, i.e. 40 ^{0}C (75% RH), 50^{0}C (75% RH), 70^{0}C (75%RH), and higher temp.
- The value obtained at elevated temp is extrapolated to shelf life at room temp.
  - e.g. if the shelf life at 60^{0}C is 30 days the shelf life at room temp (15-20^{0}C) will be 8 to 9 months.
  - Taking log K = -Ea/2.303 Rx 1/T + log A and plotting log K Vs 1/T a straight line plot with a negative slope.



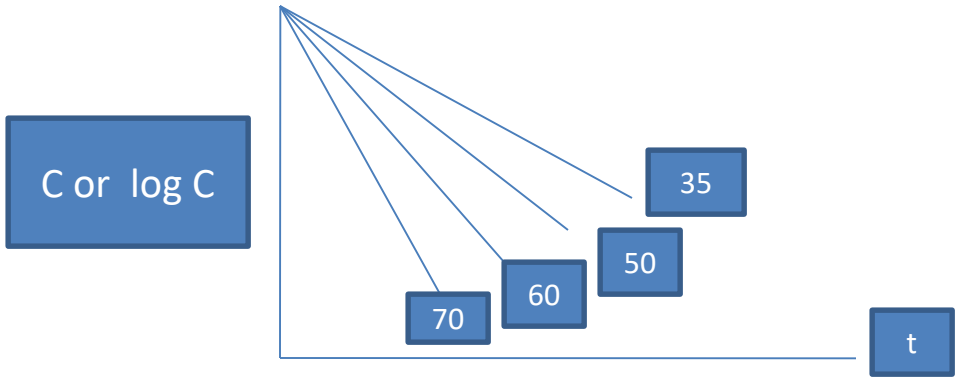
- Plotting either:
  - Conc Vs time for zero order (equation C = -Kt + Constant) or
  - log Conc Vs time for first order (equation log. (a-x) = -Kt /2.303 + log. A)
    - Yield straight line with a negative slopes in both case

- The $t_{½}$ for first order and second order given by $t_{½} = 0.693 / K$ and $t_{½} = 1 / Ka$, respectively.

Prediction of shelf life using Arrhenius equation & graphical plots following accelerated stability testing

Illustration-1: Using the plots of zero, first order reactions and Arrhenius equation:

- If given sample is kept under stressed conditions at different temp (e.g. 35, 50, 60 & 70 ^{0}C).
- The samples (that were under stressed conditions) are removed and analyzed at a fixed interval of time.
- A plot of conc Vs time (zero order) or log. Conc. Vs time (first order) is then made.
  - The value of 'K' at each temp can be obtained from both types of plots.
  - If log k Vs 1/T plot is drawn from the above plot (Arrhenius plot). The value for log K_{25} can be obtained by extrapolation.



- Given the value of K_{25} that was obtained by extrapolation, the t 10% (shelf life) for a sample that under go first order type of decomposition can be obtained from the equation. Let $K_{25} = 0.17x10^{-3}$ per days.

$$\text{i.e. } t = 2.303 /K \text{ x log } C_0/C_t$$

$$t10\% = 2.303/ 0.17 \text{ x } 10^{-3} \text{ x log } 100/90$$

$$= 619 \text{ days.}$$

* Hence the shelf life of the product will be about 20 months.

Guidelines or scheme for stability studies:

1. Pre-formulation stability studies on active ingredient:

- Include studies on the active ingredient at various stress conditions i.e. elevated temperature (the most important one), high relative humidity, the effect of acidic and alkaline solution, oxygen and artificial light exposure.
  - The testing interval is at most one month
  - It should give a good understanding of possible degradation route
  - If possible the degradation product should be isolated and characterized.
  - Compatibility of the active ingredient with the excipients relevant for intended dosage from.

2. *Accelerated stability studies on dosage form for clinical studies*

- This study is used to predict the expiry date of the specified dosage (the stability of the active ingredient is also studied at the same time as a control).
- At least three elevated temperature with identical relative humidity i.e. 40 ^{0}C (75% RH), 50 ^{0}C (75% RH) and 60 ^{0}C (75% RH) are used for two batches.
    - The testing interval are zero, one, two, three and six months.
    - Studies are carried out in open glass containers (tabs or caps) or in a clear glass ampoule or vials.

3. Stability studies on clinical supplies

- This study is used to assess the stability of clinical supplies that are stored in their primary pack at a controlled laboratory conditions i.e. 15-25 ^{0}C and ambient relative humidity (40-60%RH) or in a refrigerator (2 to 8 ^{0}C).
    - Testing interval: the samples are routinely analyzed at zero time and then at half yearly or yearly interval up to a final expiry date of 5 years.

4. Long term stability studies on the finished product and active ingredient

- The study is carried out both in the final packing and in open container (for solid dosages/ parenterals) or final packing and glass container to demonstrate the compatibility of the chosen pack with its content.
  - The testing intervals are zero time, three, six, nine, 12, 18, 24 months (optional testing period depending on the type of finished product are 30, 36, 48 and 60 months)
  - The study is carried out in order to choose long term storage condition and to compare the stability of the final dosage form with the dosage used in clinical studies.
  - The accelerated testing conditions are 40 ^{0}C (75% RH), 50 ^{0}C (75% RH) and 60 ^{0}C (75% RH) for three batches.

5. *Post-marketing on going stability studies*

- The stability of the first three production batches is performed after product is on the market.
    - The testing interval as of No. 4

6. *Post-marketing stability surveillance studies*

- This study is carried out to confirm for the claimed shelf life with respect to the recommended storage conditions.
    - The stability of the registered product is tested by analyzing a cluster of batches of finished product for the claimed shelf life.
    - The approach is a product oriented instead of batch oriented.
    - The study may facilitate in identifying change in product specification at early stage.

Analytical methods in stability studies

- The analytical methods used to assess the stability of active ingredient or dosage forms should be stability indicating and validated according to the requirements of GLP in QA program.
- A method is considered to be stability indicating when it differentiates between the active ingredient and its possible by products, decomposition products and other components.
- The stability of active ingredient can be assessed by different instrumental analytical technique. E.g. TLC, HPLC, GC, IR, NMR, measuring physical constants, etc.
- The stability of a dosage form should be characterized by considering its physical, chemical, biological effects and in some cases microbiological characteristics