SECTION – I: Quality Assurance

1. Introduction, Sources of Quality Variation, Control of Quality Variation
2. Concept of Statistical Quality Control
3. Validation Methods- Quality of Equipment, Validation of Equipment, and Validation of Analytical Instruments and Calibration
4. GLP, ISO 9000
5. Total Quality Management, Quality Review, and Documentation
6. ICH - International Conference on Harmonisation- Guidelines
7. Regulatory Control

CHAPTER 1

Introduction, Sources of Quality Variation, Control of Quality Variation

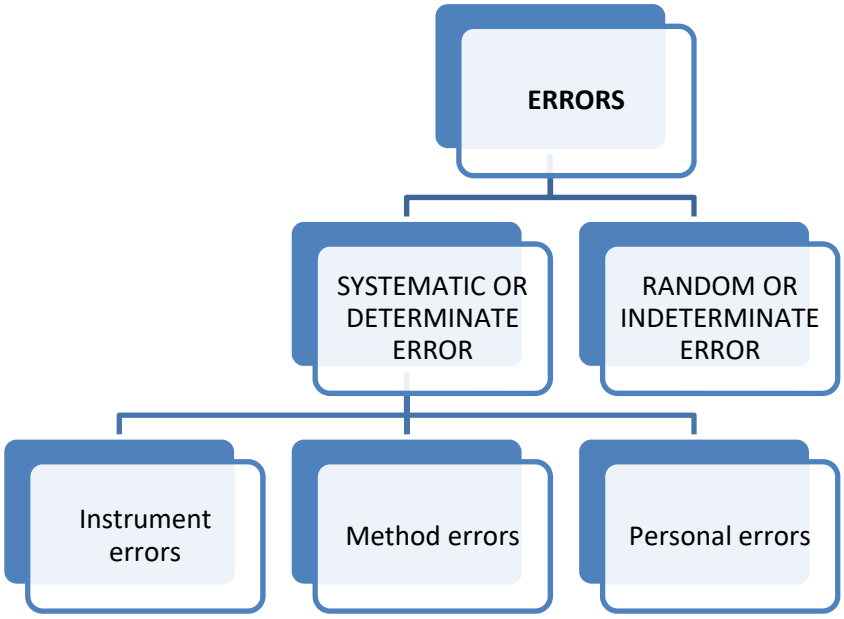
INTRODUCTION

Quality can be characterized in a variety of ways, such as "fitness for use" or "conformance to criteria". Quality assurance is a systematic procedure through which a product or service's compliance with predetermined specifications is determined. QA defines and upholds standards for developing or producing dependable products.

According to WHO, quality assurance in the pharmaceutical industry is a broad concept that encompasses all factors that either individually or collectively affect a product's quality. It is the totality of all the plans put in place to guarantee that pharmaceutical products are of the quality needed for their intended usage. GMP and other criteria like product design and development are thus included in quality assurance. Quality assurance, therefore, incorporates GMP and also other factors like product design and development.

Variation is the difference between the actual assessment of a product characteristic and the desired value. When the industry specifies the quality of a drug, any deviation from the norm is its fault. Any error made from the time the raw materials are received until the finished product is packaged can result in a quality variation. As the amount of material and the complexity of the process increase, the threat of error also rises.

TYPES OF ERRORS



Systematic/Determinate Errors

The error is reproducible and can be discovered and corrected.

(a) Instrument errors

- ✓ Failure to calibrate, degradation of parts in the instrument, power fluctuations, variation in temperature, etc.,
- ✓ Can be corrected by calibration or proper instrumentation maintenance

(b) Method errors

- ✓ Errors due to no ideal physical or chemical behavior completeness and speed of reaction, interfering side reactions, sampling problems
- ✓ Can be corrected with proper method development

(c) Personal errors

- ✓ Occur where measurements require judgment, result from prejudice, color acuity problems

Random error/Indeterminate errors

Caused by uncontrollable variables, which cannot be defined/eliminated

1. Sources of Quality Variation

(i) Materials

(ii) Machines
(iii) Methods
(iv) Men
(v) Milieu (Environment or Premises)

(i) Materials

- Variations among suppliers of the same substances
- Variations among batches from the same suppliers
- Variations within a batch

(ii) Machines

- Variation of equipment of the same process
- Differences in adjustments of equipment
- Aging of machines and improper care

(iii) Methods

- Wrong procedure
- Inadequate procedure
- Negligence in the procedure by chance

(iv) Men

- Improper working conditions
- Inadequate training and understanding
- Lack of interest and emotional upheavals
- Dishonesty, fatigue, and carelessness

(v) Milieu (Environment or premises)

- The environment must be clean, dust-free, spacious, and properly designed to minimize the risk of errors and permit effective cleaning and maintenance to avoid cross-contamination.
- It must be suitable for the purpose for which it is used.

2. Control of Quality Variation

The variations in quality can be controlled by managing the mistakes and GMP variations. The mistakes can be minimized or eliminated by material control, and packaging control. GMP variations can be managed when Quality Control and Quality Assurance work side by side.

Control Procedure:

Controlling every step of the process can control variations. Control can be divided into:

(i) Material Control
(ii) Manufacturing practices control
(iii) Packing control
(iv) Distribution control

(i) Material Control

- It starts just after the reception of materials. Most of the materials that are: active substances, excipients, packaging, and printed materials are received by the industry from suppliers.
- Thus there should be an adequate established system for the receipt, testing, and storage of all these supplies. There should be a complete record of all the procedures and tests.
- In materials, the following things are included:
  - Drug substances.
  - Excipients.
  - Packaging and printed materials.
- After the reception of the material, it is kept in a definite area. Thus before laboratory testing, proper containers, labels, lot numbers, expiry dates, etc, all are checked.
- The material is stored properly, either they are arranged alphabetically or they are differentiated depending upon physical nature. Then samples are taken for laboratory testing and a label (Sampled) is fixed on the material.
- In the case of active constituents, percentage purity, adulteration, expiry date, lot number, exact packing, etc are checked.

(ii) Manufacturing Practices Control

Successful GMP is difficult to attain but to some extent, it can be modified and controlled. Specific procedures can be applied to attain the best quality. In the case of manufacturing, the following controls are important:

A. Personnel.

B. Equipment and building.

C. Control of record.

D. Production procedure control.

A. Personnel

Usually properly educated and well-trained persons should be in the industry.

(a) There should be proper selection and training in all departments i.e. production, packaging, labeling, etc.

(b) There should be general lectures for less educated persons who work in the labeling or packaging section in an understandable language.

(c) They should be made aware of the importance of life-saving.

(d) They should be warned about all the dangers of their mistakes and errors.

(e) There should be properly educated supervisors working above the workers.

(f) The supervisors should always be there so that in case of any trouble or question, they must be available.

B. Equipment and building

(a) The equipment and building used in storage, processing, checking, and packaging should be of a suitable design, size, construction, and location.

(b) In the case of equipment, these should be constructed in the proper size and proper way. The size should be such that the complete batch can be processed all at once.

(c) The surfaces of equipment should be non-reactive, non-absorptive, and non-additive.

C. Control of records

The records such as master formula records and batch production records must be maintained.

1. Master Formula Record:

(a) The master formula record must be prepared for each product.

(b) It must be signed by a competent and responsible person.

(c) The language must be simple and easy to understand so that it may not be misinterpreted.

(d) It should be checked by another competent person and must be countersigned.

(e) Master formula record includes the following information:

- ✓ Name of the product, dosage form, and strength.
- ✓ Complete list of ingredients including excipients.
- ✓ Quality by weight or volume of every ingredient.
- ✓ Standards or specifications of each ingredient.
- ✓ Any calculated excess of an ingredient.
- ✓ Theoretical yield and termination of the process.
- ✓ Manufacturing and control instructions, specifications, and precautions.
- ✓ Complete description of closures, containers, labeling, packaging, and other finishing material.

2. Batch Production Record:

(a) Batch production record must be prepared, maintained, and controlled for each batch of a product.

(b) It must be retained for about 5 years after product distribution.

(c) Batch production record should have the following information in addition to the master formula record:

- ✓ Batch number.
- ✓ Code number.
- ✓ Manufacturing date.
- ✓ Expiry date.

D. Production procedure control

The processes of manufacturing are operated according to the established rules from the reception of material up to the delivery of the final product.

(a) In the production procedure control, some tests are done during the process, which is called "In Process Quality Control (IPQC)"

(b) The IPQC is under Quality Control Department.

(c) Both the Quality Control and Production Departments are responsible for the production procedure control.

IPQC Tests for Different Dosage Forms are as Under:

1. ***IPQC tests for tablets:***

(a) Drug contents determination.

(b) Moisture, contents of granules.

(c) Assay of active ingredients.

(d) Weight variation of uncoated tablets.

(e) Hardness test.

(f) Disintegration test

2. ***IPQC tests for syrups and suspensions:***

(a) Drug contents determination.

(b) Assay of active ingredients.

(c) pH.

(d) Weight per ml.

(e) Particle size

3. ***IPQC tests for semi-solids:***

(a) Drug contents determination.

(b) Assay of active ingredients.

(c) Uniformity and homogeneity test.

(d) Viscosity and specific gravity test
(e) Filling test.
(f) Leakage test

4. ***IPQC tests for injectables:***

(a) Drug contents determination.
(b) Assay of active ingredients.
(c) pH
(d) Pyrogen test.
(e) Stability test.
(f) Leakage test.
(g) Check up of particulate matters.

(iii) Packing Control

The packaging control is usually completed before manufacturing the product.

(a) When the product comes in the packaging section, it should be packed in recommended containers and there should not be any mistakes in the case of labelling and writing of batch number, etc.
(b) The packaging material is used according to the nature and distribution of the product.

(iv) Distribution Control

The responsibilities of the Quality Control Department are not finished even after the distribution of finished dosage forms in the market.

(a) The samples of each batch are kept in record and these samples are selected during packaging and are in the same packs as they are marketed.

These are kept for years to examine or test the material for any purpose or necessary demand.