Regulatory Expectations & Challenges-Risk Assessment, Confirmatory Testing and Control Strategy for Drug Products

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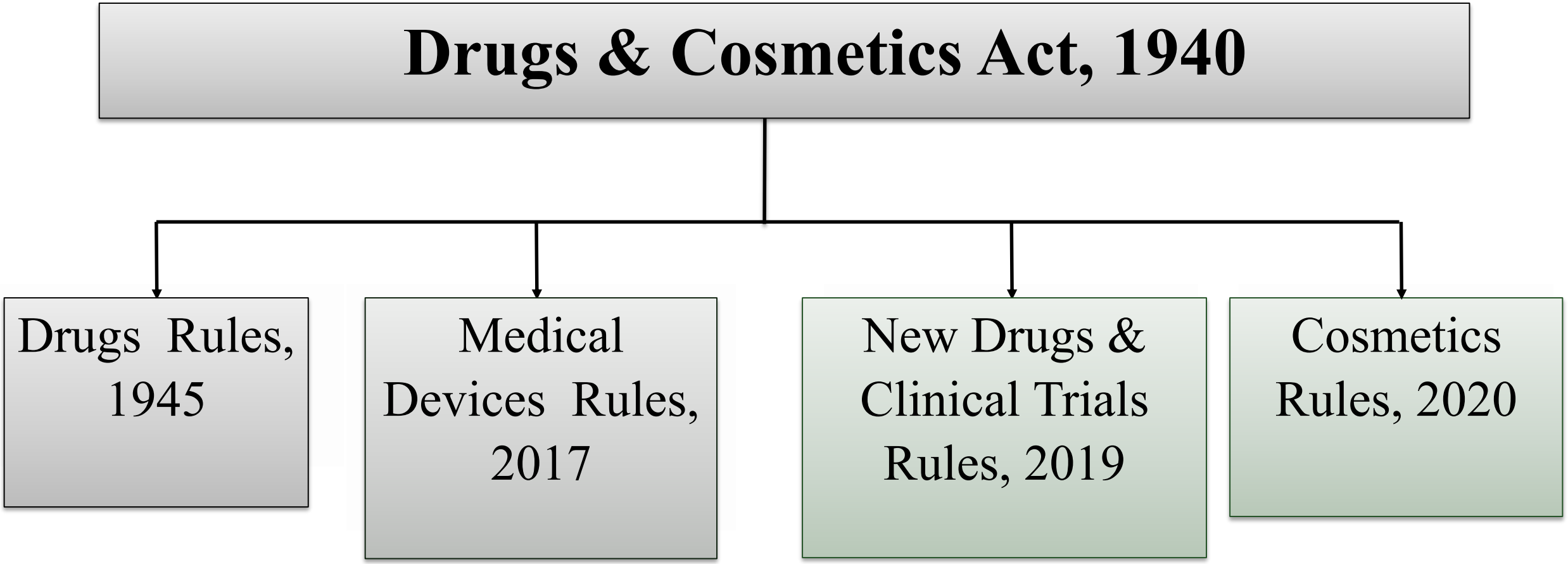
15.09.2023

Drugs Regulatory System :India

- Drugs fall under the **Concurrent list** of the Constitution of India.
- The Drugs and Cosmetics Act, 1940 is a **Central Act**, enforced by both Central and State Govt. through a system of licensing
- Extended to Whole of India

REGULATORY FRAMEWORK



DRUG REGULATORY SYSTEM

- D&C Act 1940 and Rules 1945: Legal framework
- A Legislation to regulate manufacturing and sale/stock /distribution of Drugs, Cosmetics, Devices
- Includes Legislation to regulate Imports
- Defines Quality standards for Drugs, Cosmetics & Devices etc
- Well established and Robust Drug Regulatory System

Administration of the Drugs &Cosmetics Act &Rules

- The Drugs & Cosmetics Act, 1940 and Rules thereunder have entrusted various responsibilities to Central & State regulators for regulation of Drugs, Cosmetics and medical devices in India.

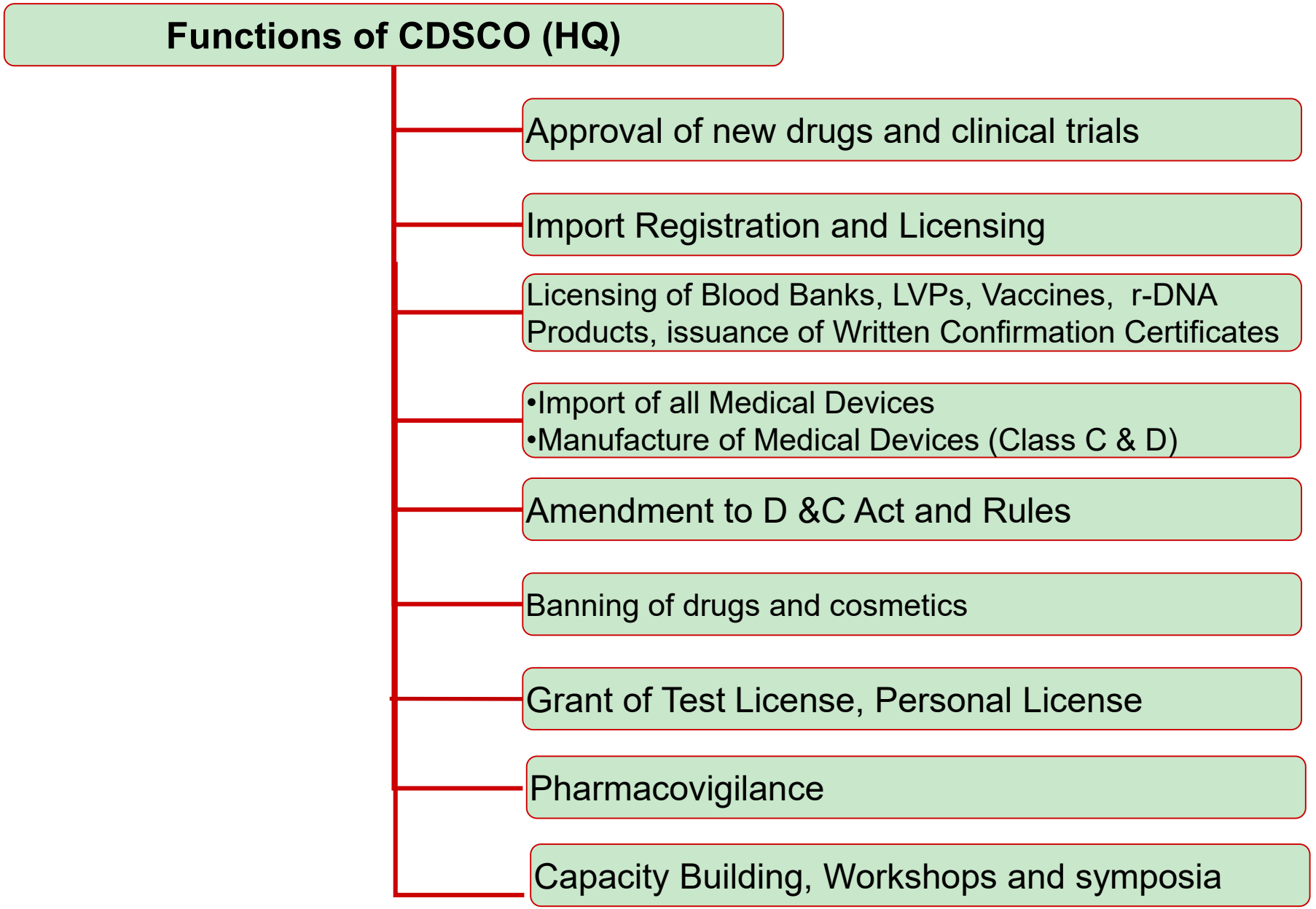
- It envisages uniform implementation of the provisions of the Act & Rules made thereunder for ensuring the safety, rights and well being of the patients by regulating the Drugs, Cosmetics and Medical Devices.

Administration of the Drugs &Cosmetics Act &Rules

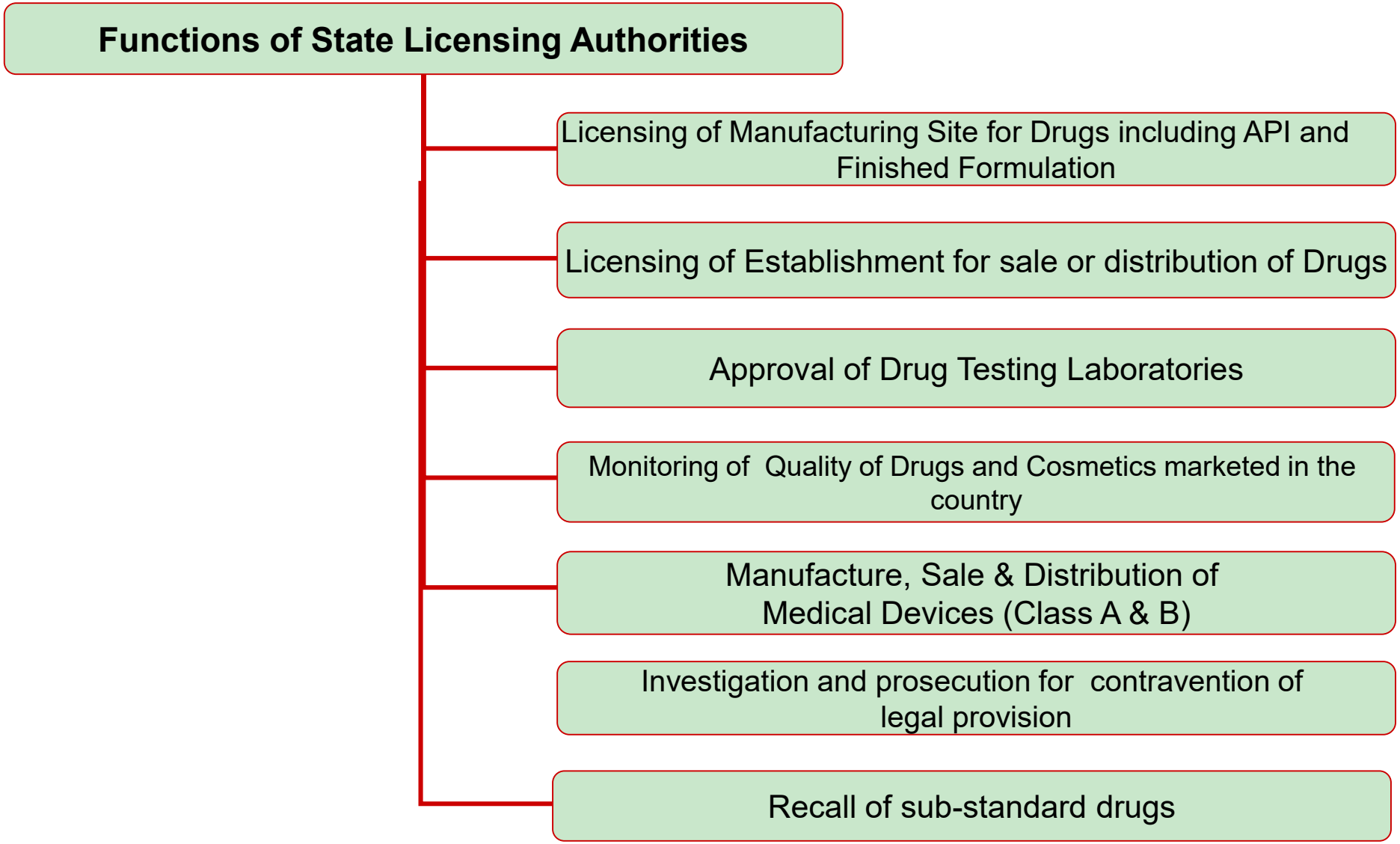
- CDSCO is the central regulatory authority under the Ministry of Health & Family Welfare, Govt. of India to safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices under the provisions of Drugs and Cosmetics Act, 1940 and Rules made thereunder.

- Respective State Drugs Licensing Authorities are responsible for licensing, approvals and recalls of drugs & cosmetics manufactured within their domain.

Functions of CDSCO (HQ)



Functions of State Licensing Authorities



GMP REGULATION IN INDIA

GMP Regulation

- GMP regulation is an integral part of Drugs & Cosmetics Act & Rules
- The Schedule M (for Manufacturing) was introduced under the Rules in the year 1988
- Subsequent amendments made in the year 2001 and 2005 to align with the International standards, particularly WHO –TRS
- Draft Revised Schedule M published by the MoH&FW on 05 Oct 2018 (vide G.S.R. 999)
- Other Schedules applicable : Schedule L1 (GLP)

REGULATORY EXPECTATIONS

GMP Compliant Quality System

- **The overall objective of a Drug Regulatory Authority (DRA) is to ensure that medicinal products are manufactured and distributed of acceptable quality, safety and efficacy in ways to ensure their quality till the products reach to the end user i.e. patient/consumer.**
- **Consumer have the right to expect that Drug Administration not just protect the public health by keeping unsafe drug off the market but facilitate the availability of safe and effective drug.**

REGULATORY EXPECTATIONS

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Regulatory Expectations- Quality Compliance

- **Quality focus is on medicinal products meeting the pre-defined specifications (e.g., physical, chemical and microbiological specifications) throughout the shelf life.**

- **To achieve the above, health authorities, together with professional organisations (e.g., ISO/WHO/BIS), have been developing requirements, guidance and standards to regulate and guide the industry.**

Regulatory Expectations- Quality Compliance

- The regulatory requirements often lay down the minimum requirements in order to achieve product quality, but without implementing those measures you can hardly achieve product quality consistently.
- It is important to recognize that quality cannot be tested into products; however it should be built in the product by in-house quality design.
- Quality is beyond Compliance – if we aim to achieve product quality, compliance comes naturally.

Regulatory Expectation- Quality Compliance

Guidelines of the Pharmaceutical Quality:

SCHEDULE M "Good Manufacturing Practices"	Provides Mandatory Principles and Requirements for manufacturing of pharmaceuticals products
WHO Guidelines	Provides Voluntary Guiding Principles and requirements in the firm of Technical Report Series for manufacturing of pharmaceuticals products
ICH Guidelines	Provides different voluntary Guidelines like Quality, Safety, Efficacy and Multi displinary guidelines for pharmaceuticals products

Regulatory Expectation- Quality Compliance

General Practices Recently Applied in the Pharmaceutical Industry:-

Regulatory Expectation- Quality Compliance

What is GMP Non-Compliant Quality System ?

GMP-Non-Compliant Quality System

- **The manufacturing process not operated in a State of Control i.e., no control on speed of blender,**

- **The firm has an inadequate system for managing changes- e.g., no documented procedure for change control, no impact assessment before initiating a major change like change in AHU etc.**

- **The process is not monitored for process performance and product quality to maintain a state of control. Instead, the manufacturer routinely reacts to problems (i.e., rejections, complaints, returns, and other quality problems are the principal quality measures.)**

GMP-Non-Compliant Quality System

- Responsible officials not aware of major product quality problems (e.g., complaints, returns) to enable appropriate management review
- The manufacturer routinely reacts to production failures by making corrective actions, but does not take any preventive actions (inadequate CAPA program)
- Management does not provide adequate and appropriate resources (human, financial, materials, facilities, and equipment) to sustainably meet GMP in order to maintain robust operations.
- Conditions of Licenses – Not Strictly implemented

Regulatory Challenges

- Inadequate Trained and Experienced Manpower
- Inadequate testing facilities (lack of sophisticated instruments, lack of trained analysts)
- Real time data and documentations/data integrity
- Non-validated methods and procedures
- No Reference/Working Standards, lack of chemicals & reagents
- NABL accreditation and GLP compliance as per Schedule L1
- IT services/data backup and archival
- Supply chain/Good distribution practices

Quality Risk Management Principles in Pharmaceutical Industry

Quality Risk Management Principles in Pharmaceutical Industry

- Quality Risk Management is the specific tool to assess the risk and mitigation associated with manufacturing of drug product and drug substance.
- Quality Risk Management should ensure the risk evaluation of manufacturing process with scientific knowledge, experience.

Quality Risk Management Principles in Pharmaceutical Industry

Two primary principles:

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient

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

Quality Risk Management Principles in Pharmaceutical Industry

How can risk be assessed if the manufacturing process is not defined, and the critical aspects are not identified?

Quality Risk Management Principles in Pharmaceutical Industry

What is risk assessment?

During the risk assessment process, one should review and evaluate their premises to:

•Identify processes and situations that may cause harm, particularly to people (**hazard identification**).

•Determine how likely it is that each hazard will occur and how severe the consequences would be (**risk analysis and evaluation**).

•Decide what steps the organization can take to stop these hazards from occurring or to control the risk when the hazard can't be eliminated (**risk control**).

Quality Risk Management Principles in Pharmaceutical Industry

Identification of Key Parameters for risk assessment :-

– Key Manufacturing/Process stages e.g., the manufacturing of tablet involves numerous unit processes, including:-Particle size reduction, Blending, Granulation, Drying, Compression, Testing of physical properties, Coating and packing

– Key in-process Critical Quality Attributes e. g. physical, chemical, biological or microbiological characteristics that should be within appropriate limit or range to ensure desired product quality

Quality Risk Management Principles in Pharmaceutical Industry

Common Causes & Risk Reduction Opportunities:-

- Unpredictable manufacturing can lead to quality problems, defects, and supply shortfalls
- Many firms do not take advantage of contemporary technology
- Many processing lines require frequent starts and stops to correct problems and to pull samples e.g., Tablet, Sterile manufacturing lines
- Open vs. Closed Processes (Also, Unit Operations vs. Integrated)
- Manually Intensive Operations vs. Automation–
- Use of Quality Risk Management Principles for supplier selection, monitoring, and management

Quality Control Strategy for Drugs

Quality Control Strategy for Drugs

- **Quality control is a "part of quality management system focused on fulfilling quality requirements."**

- **It can be defined broadly as the regular control of quality within a company,**
  - **department equipped with trained and qualified staff responsible for the acceptance or rejection of incoming raw materials and packaging components, in- process test and inspections to assure that systems are being controlled and monitored and finally, for the approval or rejection of finished dosage form.**

Quality Control Strategy for Drugs

METHODS USED FOR QUALITY CONTROL OF PHARMACEUTICALS

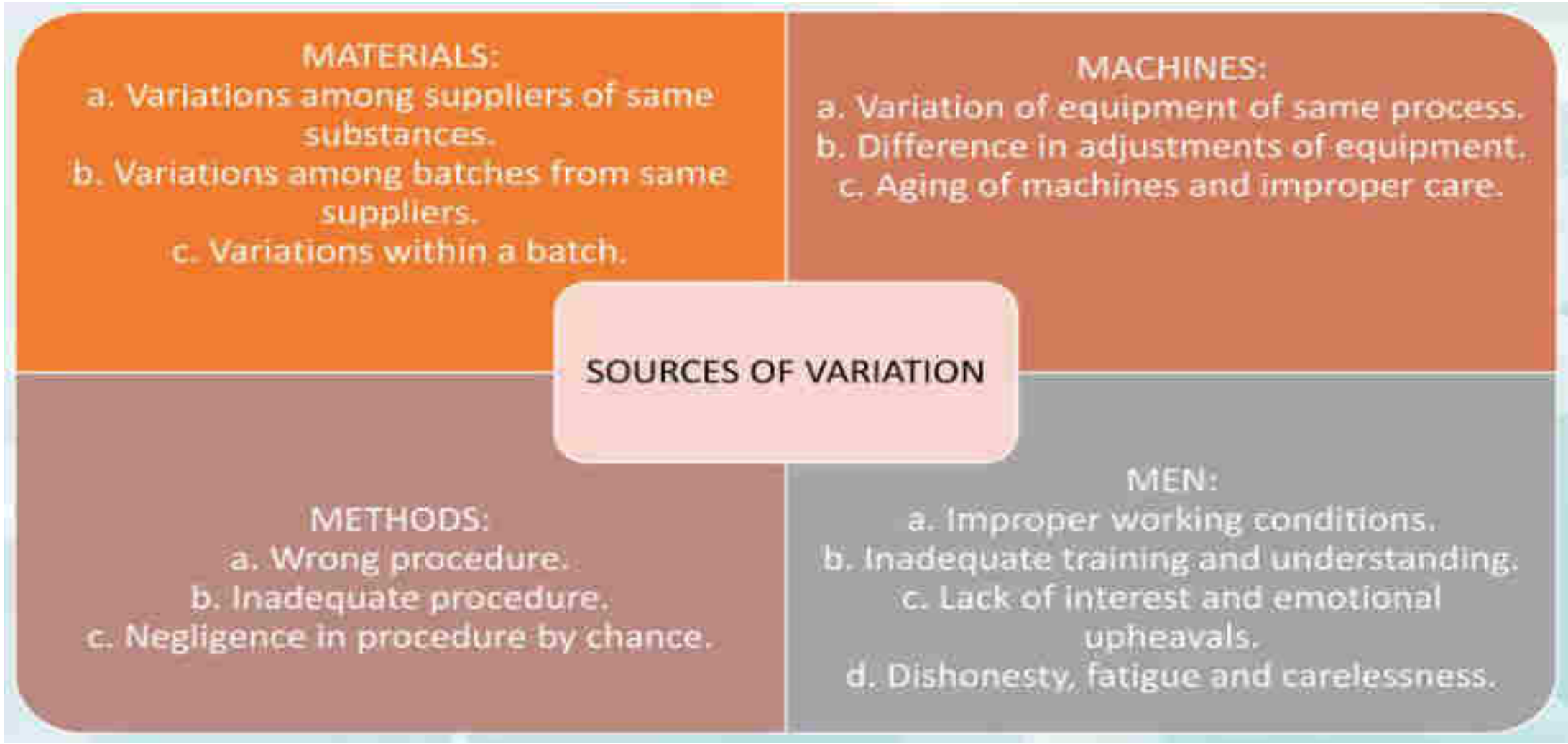
- **Various tests and procedures for analysis and determining impurities are given in official pharmacopoeias.**
- **In the pharmaceutical analysis, depending upon the characteristics of drugs and its formulation various analytical methods are followed.**

✓ **qualitative analysis [e.g., Physiochemical Methods]**

✓ **quantitative analysis [e.g., determination of the amount of the sample/assay]**

Quality Control Strategy for Drugs

Sources of Quality Control Variation



Quality Control Strategy for Drugs

1. Determinate Errors :-These are determinable and can be either avoided or corrected. For example:

- ❖ Weighing with un-calibrated weights,
- ❖ Measuring a volume using un-calibrated burette or pipette.

These are also called as systematic errors and they arise due to

a)Instrumental errors - by using un-calibrated equipment

b)Operative errors - by person operating or doing analysis (personal error)

c)Chemical error - due to impurities in chemicals solvents and reagents.

d)Errors in methodology: error due to un validated method Errors of above categories are usually detectable and can be eliminated to the large extent.

2. Indeterminate Errors

These are often called accidental or random errors. They are found by small differences in series of measurements made by the same analyst under identical conditions. They can not be predicted and hence cannot be eliminated.

Quality Control Strategy for Drugs

Sources of Impurities in Pharmaceuticals

The substances used in pharmaceutical field should be almost pure.

- The purity of the substances varies with different factors such as, their methods of manufacture, types of their purification etc.
- Impurity means presence of other materials than drug or presence of unwanted foreign particle other than active drugs.
- The impurities may be toxic or non-toxic even if it is non-toxic it may be used intentionally as adulterant to increase the weight of the active ingredient.
- Nontoxic impurities also reduce the activity of the drug, so that one must avoid/control impurities in pharmaceuticals, cannot eliminate all the impurities.
- The official pharmacopoeias prescribe limits for impurities like sulphate, chloride, iron, heavy metals and arsenic.

Quality Control Strategy for Drugs

Some factors which are responsible for pharmaceutical impurities are:

1.Raw Material Employed in Manufacture

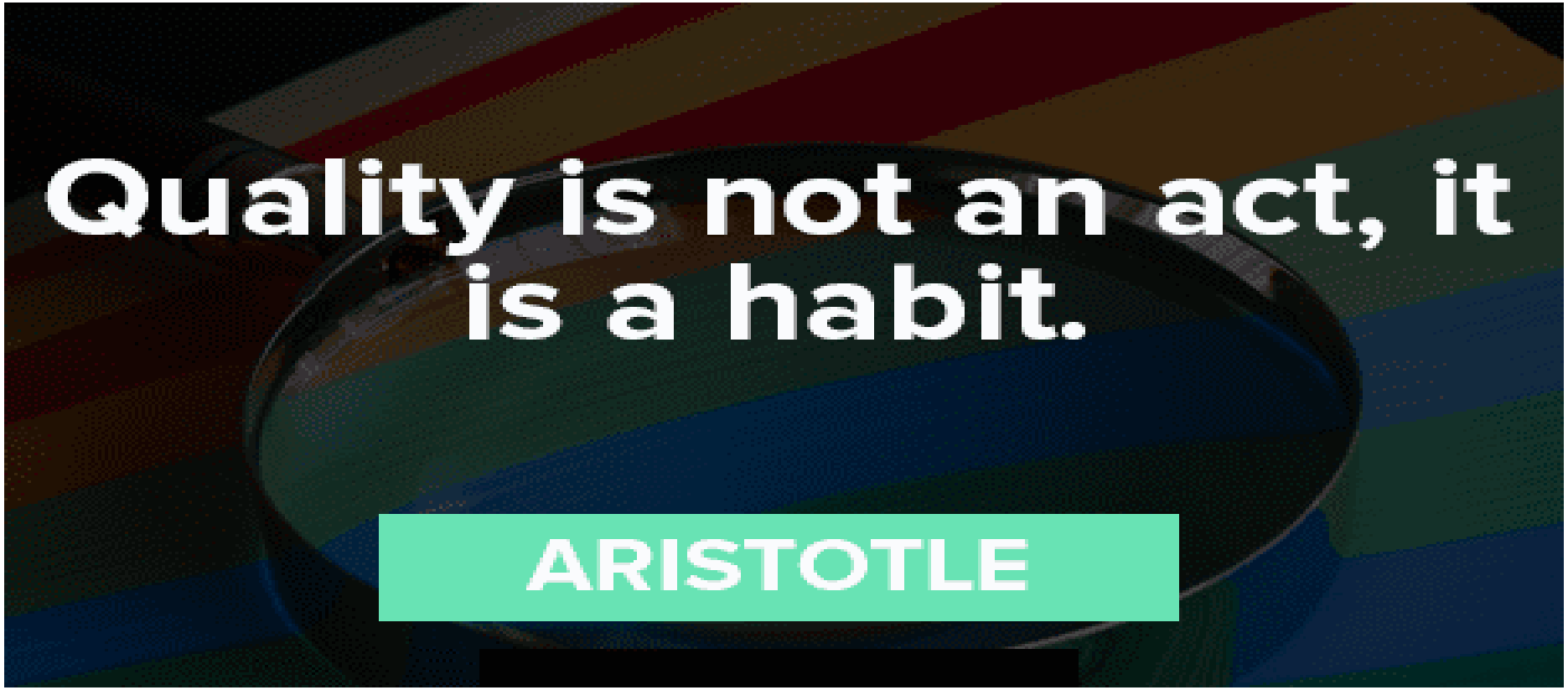
2.Method used in Manufacture Some impurities get incorporated into the materials during the manufacturing process

3. Reagents used in the Process,

4.Solvents for example Water is a common solvent in large scale manufacturing of pharmaceutical

5.The Reaction Vessels - The vessels used in manufacturing process are made of metals like copper, iron, aluminium, zinc, tin though these days many of these metals are replaced by stainless steel.

6.Atmospheric Contaminants- Manufacturing in Non GMP Compliant facility


Quality is not an act, it is a habit.
ARISTOTLE


THANK YOU !!!