ASEAN Guidelines on GMP for Traditional Medicines / Health Supplements (TM/HS)

CHAPTER 1 – QUALITY MANAGEMENT

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OUTLINE

- **Introduction**
- **Objectives**
- **Principles**
- **Quality Assurance (QA)**
- **Good Manufacturing Practice (GMP)**
- **Quality Control (QC)**
- **Product Quality Review (PQR)**

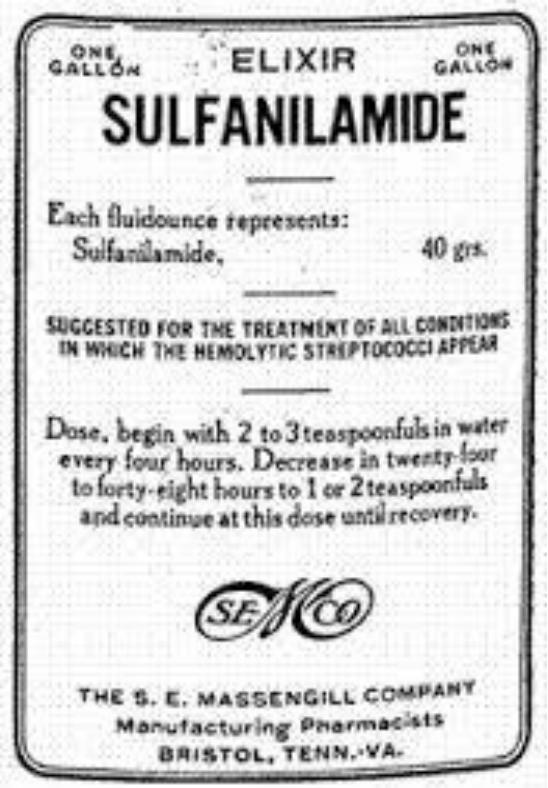
INTRODUCTION

- **Some examples happened in the world-wide history:**

Year	Event	Non conformance/issue
1935	Elixir Sulfanilamide made with poisonous solvent (Contamination of Glycerine contaminated with Di ethylene glycol diethylene glycol) caused 107 deaths	correct starting and packaging materials
1941	Nearly 300 people were killed or injured by sulfathiazole tablets-, a sulfa drug tainted with the sedative, phenobarbital (Winthrop Chemical Co.)	Manufacturing and quality control requirements

INTRODUCTION

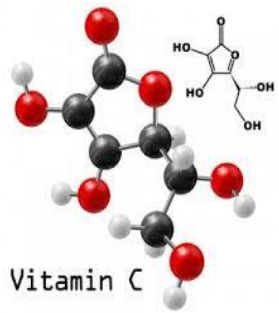
- **Some examples happened in the world-wide history:**



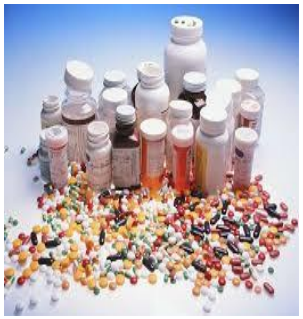
The birth of GMP

INTRODUCTION

INDUSTRIES/SME ➔ TM/HS PRODUCTS



Starting Material / Crude plant



TM/HS Products

INTRODUCTION

TM/HS PRODUCTS ➔ CONSUMERS

Receive product with assured Quality & Safety

INTRODUCTION

FUNCTION OF TM/HS PRODUCTS TO CONSUMERS

- enhance
- improve

QUALITY OF LIVES

INTRODUCTION

- Poor quality products ➔ risk to consumers
  - Receive
    - wrong drug/dosage
  - Contaminated / degraded
  - Products packaged with wrong label / brochure
  - Non conformance of storage/distribution

INTRODUCTION

CONSUMERS believe that they:

buy and receive a good product and consume it

INTRODUCTION

Who is responsible for the quality of products?

Whether :

- QUALITY CONTROL
- QUALITY ASSURANCE
- QUALITY UNIT

MANAGEMENT should be responsible to assure the quality of products

INTRODUCTION

MANAGEMENT should be responsible to assure the quality of products

MANAGEMENT RESPONSIBILITY, shall :

- In accordance with the indication/usage products
- Consistently meet the quality requirements
- Do not pose a risk to consumer in safety and quality

➢ **Protection to consumer**

INTRODUCTION

Not every single product can be tested so the quality of the products should be designed and built into the process/production.

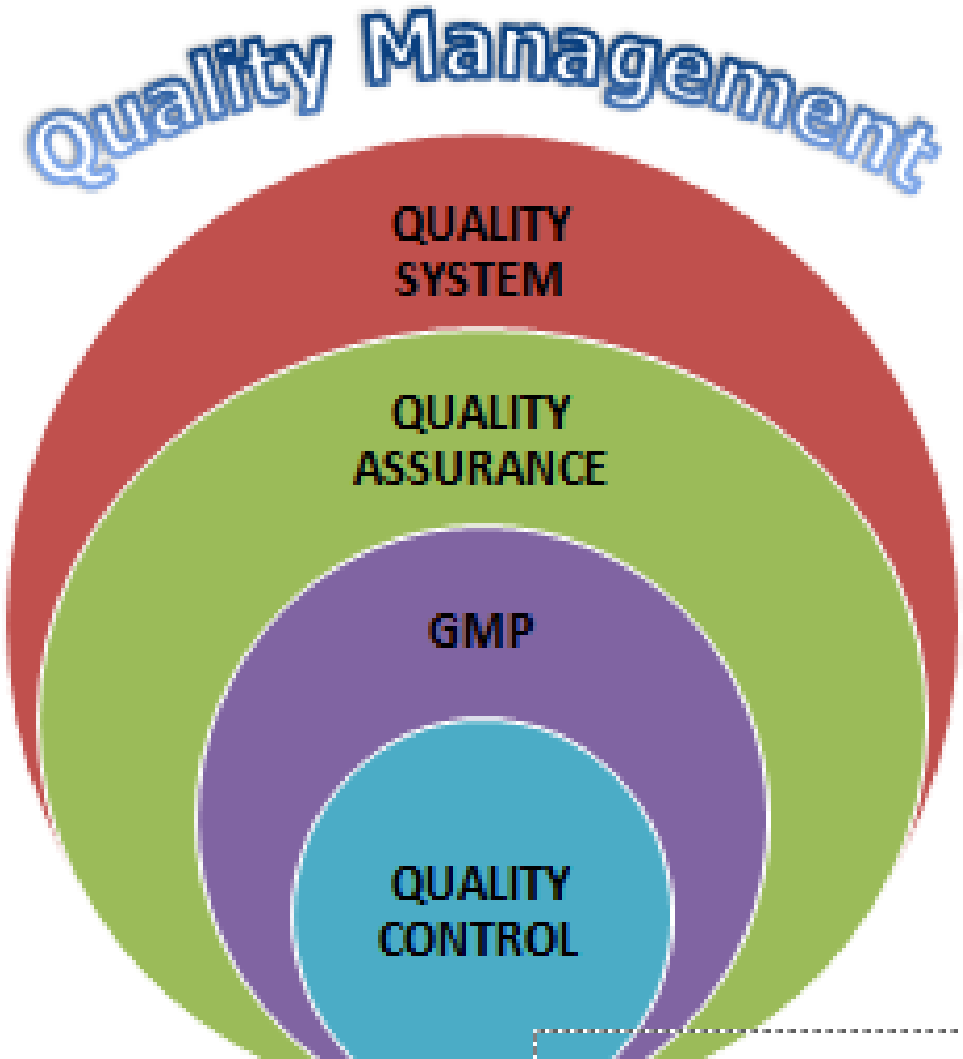
INTRODUCTION

- **Quality management** is established and enforced with the aim of the quality requirements of all products are met and consistently maintained to safeguard consumers.

- **Quality management** is overall control encompassing Quality Assurance, GMP and Quality Control to ensure the consumer receives good quality of product for its intended use and do not place the health of the patients or consumers at risk due to inadequate safety and quality.

- Quality management shall develop and maintain controlled condition
  - using established monitoring and evaluation system
  - performing product quality review
  - to attain continual improvement

PRINCIPLES



- **Quality Management** is a management function which is established and implementing company's Quality Policy.
- **Quality System** is an infrastructure consist of organization structure and responsibilities, procedures, processes and resources.
- **Quality Assurance** is systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality
- **GMP** is that part of quality assurance which ensures that product are consistently produced and controlled to quality standard appropriate to their intended use and as required by product specification.
- **Quality Control** is the part of GMP focusing on sampling, specification, testing, documentation and release of product.

PRINCIPLES

- **Quality Management:**
  - **Requires the responsibility of senior management**
    - To establish and maintain a companywide commitment to quality and the performance of the quality system
    - To ensure an effective quality system to achieve quality objectives
    - To define and communicate roles, responsibilities, authorities throughout the company
  - **Requires participation and commitment of**
    - staff in all departments and all levels within the company
    - the company's suppliers and distributors
  - **A comprehensively designed and correctly implemented system of QA incorporating GMP and QC**

PRINCIPLES

- **Quality Management**

  - **All parts of Quality Assurance system:**
    - adequately resourced with competent personnel
    - suitable and sufficient premises, equipment and facilities

QUALITY ASSURANCE

- **A wide-ranging concept**

  → covers all matters which individually or collectively influence the quality of a product.

- **Total of the organized arrangements**

  → ensuring the quality required for their intended use.

- **QA incorporates GMP plus other factors outside the scope of these guidelines.**

QUALITY ASSURANCE

Quality Assurance (QA) System should ensure that:

- Traditional Medicine and Health Supplements are designed and developed in a way that its encompasses **the requirements of GMP**;
- **Production and control operations** are clearly specified and GMP adopted;
- **Managerial responsibilities** are clearly specified

QUALITY ASSURANCE

QA System should ensure that (cont.):

- Arrangements are made for the manufacture, supply and use of **the correct starting and packaging materials**

QUALITY ASSURANCE

QA System should ensure that (cont.):

- **All necessary controls** on intermediate products, and any other in-process controls (IPC) are carried out;
- **The finished product is correctly processed and checked, according to the defined procedure**;
  - Prior to release for sale, finished product must be tested and complied with the specifications *(see next slide for details)*
  - The specifications: must be in writing, approved by the authorized QC/QA, comply with NRA

STATEMENT OF RIGHTS & RESPONSIBILITIES

QUALITY ASSURANCE

QA System should ensure that (cont.):

- **Satisfactory arrangements to ensure, that TM & HS are not sold or supplied before the authorised person has certified** that each production batch has been produced and controlled in accordance with the requirements of the NRA and any other procedures relevant to the production, control and release;
  - **Batch certificate with the statement**:
  - ✓ This batch of product has been manufactured, including packaging include labelling and quality control in full compliance with GMP requirements of NRA and with registered specifications .
  - ✓ The batch processing, packing and analysis records were reviewed and found to be in compliance with GMP
  - ✓ Approved by the authorised person

STATEMENT OF RIGHTS & RESPONSIBILITIES

QUALITY ASSURANCE

QA System should ensure that (cont.):

- **TM & HS products are stored, distributed & subsequently handled appropriately** so that quality is maintained throughout their shelf life

QUALITY ASSURANCE

QA System should ensure that (cont.):

- **There is a procedure for self-inspection and/or quality audit**, which regularly appraises the effectiveness and applicability of the QA system
- Self inspection should be performed with the view to improve the system

GOOD MANUFACTURING PRACTICE

Good Manufacturing Practices (GMP) is:

- Part of Quality Assurance which ensures that
  - products are consistently manufactured and
  - Controlled to the **quality standards** appropriate to their intended use and as required by **the NRA or product specification**

- concerned with both production and quali

GOOD MANUFACTURING PRACTICE

The basic requirements of GMP

- **All manufacturing process are：**
  - clearly defined and systematically reviewed
  - shown to be capable of consistently manufacturing TM & HS of the required quality and complying with their specifications

GOOD MANUFACTURING PRACTICE

The basic requirements of GMP are:

→ **Manufacturing processes should be clearly defined and systematically reviewed**

- ✓Performed by trained and qualified personnel,
- ✓Handling of starting/packaging materials and products, are done in accordance with approved written procedures or instructions, and recorded,
- ✓Establish and implement in-process control,
- ✓Manage deviation and changes,
- ✓Verify yield at various production steps and perform reconciliation of materials,
- ✓Perform process and equipment verification

GOOD MANUFACTURING PRACTICE

The basic requirements of GMP

- **Critical steps** of manufacturing processes **and significant changes** to the process **are assessed for impact and documented** *(refer to presentation slide: Verification)*

GOOD MANUFACTURING PRACTICE

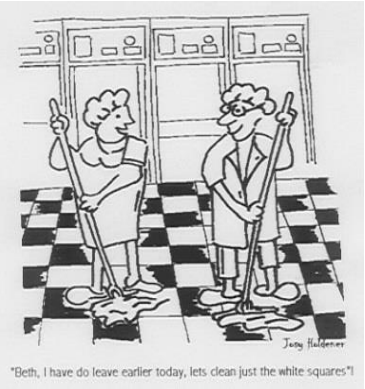
Change Control

- Change control is a system designed to ensure that all changes which have potential impact to product quality are evaluated before they are implemented.
- Type of changes not limited to:
  - Product formulation
  - Production process
  - Batch size
  - Equipment
  - Material
  - Test Method
  - Supplier, etc
- Changes should be proposed, evaluated, implemented, reviewed and approved by QA. Re-verification shall be performed when necessary.
- Changes related to manufacturing and product license shall follow related NRA regulation.

GOOD MANUFACTURING PRACTICE

The basic requirements of GMP

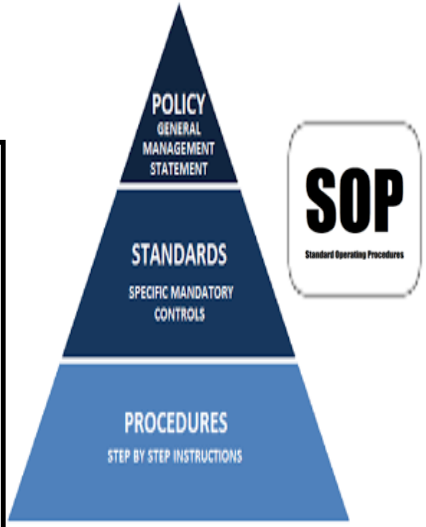
- **All necessary facilities/resources for GMP are provided:**
  - appropriate trained and qualified **personnel; see Chapter 2. Personnel**
  - adequate **premises and space**; **see Chapter 3 Premises & Equipment**
  - suitable **equipment and services**; **see Chapter 3 Premises & Equipment**
  - correct **materials, containers and labels**; **see Chapter 6 Production**
  - approved **procedures and instructions**; **see Chapter 5 Documentation**
  - suitable **storage and transportation, see Chapter 6 Production**



GOOD MANUFACTURING PRACTICE

The basic requirements of GMP:

- **Instructions and procedures are written** in
  - an instructional form in clear and
  - unambiguous language,
  - specifically applicable to the facilities provided;
- **Operators are trained** to carry out procedures correctly;



GOOD MANUFACTURING PRACTICE

The basic requirements of GMP:

- **Records are made**
  - Manually and/or recording instruments, during manufacture
  - Demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the products as expected
  - Any significant deviations are fully recorded and investigated

Batch records
Raw data records
Laboratory records
Distribution records
SOPs, manual
Specification & Test methods
Protocols
Form and formats
Log books
Recording instruments

GOOD MANUFACTURING PRACTICE

Deviation

- Deviation is a non compliance against GMP requirement, regulation, existing procedures which may:
  - ✓ lead to risk non-conformity of material, products and/or process
  - ✓ risk to consumers e.g. microbes contamination, cross contamination, mix-up, violation of SOP, out of specification (OOS) testing result
  - ✓ has an impact to product safety and quality
  - ✓ risk to business e.g. return, complaint product
- Deviation should be reported, investigated, recorded and followed up

GOOD MANUFACTURING PRACTICE

The basic requirements of GMP

- **Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained** in a comprehensible and accessible form.

Batch records
Raw data records
Laboratory records
Distribution records
SOPs, manual
Specification & Test methods
Protocols
Form and formats
Log books
Recording instruments

GOOD MANUFACTURING PRACTICE

The basic requirements of GMP

- **The distribution of the products** minimizes any risk to their quality;
  - storage and shipping condition
  - vehicles and equipment

GOOD MANUFACTURING PRACTICE

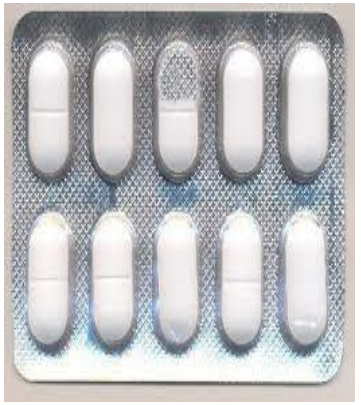
The basic requirements of GMP

- **A system is available to recall** any batch of product, from market/sale or supply
  - Recall handling shall comply to requirements in Chapter 9 - Complaint and Product Recall, ASEAN Guideline on GMP for TM/HS

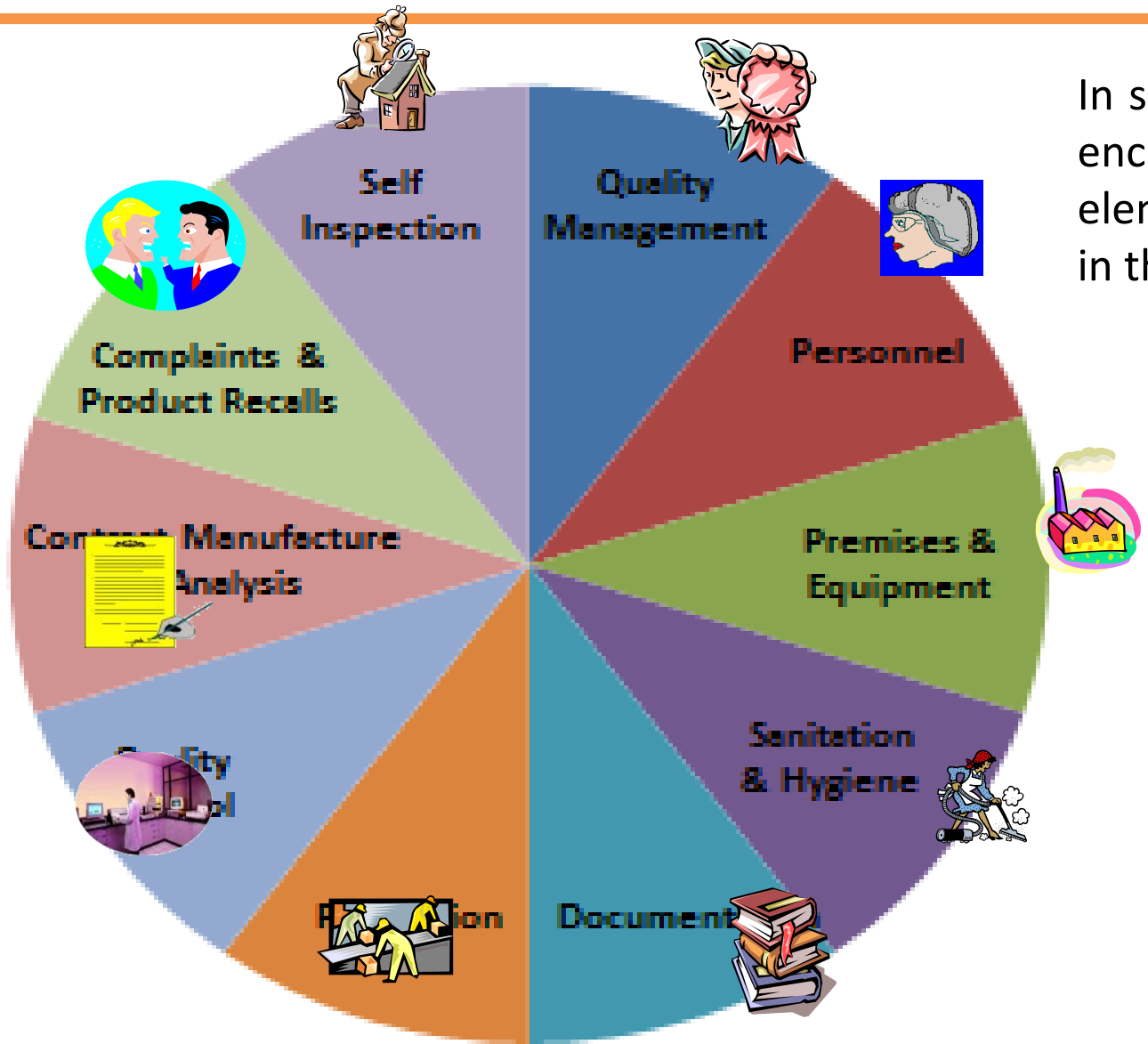
GOOD MANUFACTURING PRACTICE

The basic requirements of GMP

- **Complaints about marketed products**
  - are examined
  - the causes of quality defects should be investigated
  - appropriate measures taken in respect of the defective products and to prevent recurrences.
- Complaints handling shall comply to Chapter 9 - Complaint and Product Recall, ASEAN Guideline on GMP for TM/HS



GOOD MANUFACTURING PRACTICE



In summary, GMP encompass all the elements shown in this chart

QUALITY CONTROL

QUALITY CONTROL

A part of GMP which is concerned with:

- Sampling,
- Specification and testing,
- Organisation,
- Documentation,
- Release procedures

➢ **Ensure that the defined test were carried out and materials are not released for use, products are not released for sale or supply until their quality has been judged to be satisfactory**

QUALITY CONTROL

- If the in-house Quality Control Department cannot perform certain specific analysis, **the services of accredited/ recognised external laboratory** can be used to conduct the tests
- External contract laboratory shall meet requirement in Chapter 8 - Contract Manufacture & Analysis, ASEAN Guideline on GMP for TM/HS

QUALITY CONTROL

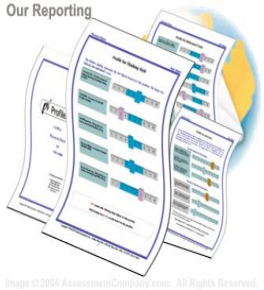
The basic requirements of QC :

- **Adequate facilities, trained personnel, approved procedures are available for sampling, inspecting and testing:**
  - Starting materials,
  - Packaging materials,
  - Intermediate, bulk products,
  - Finished products ,
  - Monitoring environmental conditions for GMP purposes where appropriate

QUALITY CONTROL

The basic requirements of QC :

- ❑ **QC Department shall have a designated area**
- ❑ **Adequate facilities included but not limited:**
  - **Premises**:
    - Analytical laboratory (physical and chemical)
    - Microbiological laboratory
  - **Equipment**:
  - **Materials:**
    - Reagent
    - Reference substance
    - Culture media
    - Reference culture

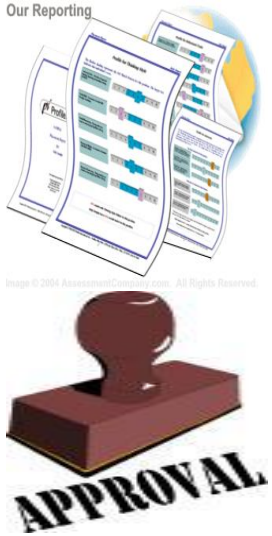


QUALITY CONTROL

The basic requirements of QC :

- **Samples of**
  - Starting materials,
  - Packaging materials,
  - Intermediate, bulk products,
  - Finished products

  are taken by personnel and by methods approved by QC



QUALITY CONTROL

The basic requirements of QC :

- **Records are made by manually and/ or by recording instruments**

→ demonstrate that all the required Sampling, Inspecting, Testing procedures were actually carried out.

→ raw data such as laboratory notebooks and/or reports shall be retained and readily available.

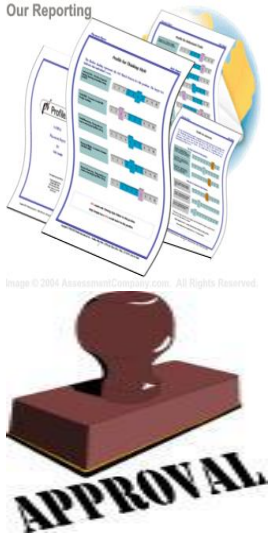
→ data (e.g. analytical test results, yields, environmental controls) it is recommended that records in a manner permitting trend evaluation be kept.

→ Any deviation are fully recorded and investigated.

QUALITY CONTROL

The basic requirements of QC :

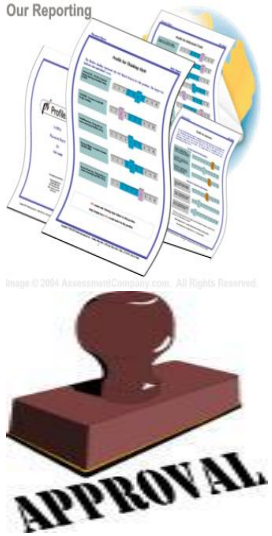
- **The finished products contain active materials complying with the qualitative and quantitative requirements of the NRA**
  - are of the quality required,
  - are enclosed within their proper containers and correctly labelled;



QUALITY CONTROL

The basic requirements of QC :

- **Records are made of the results of inspection and testing of material, intermediate, bulk and finished products is formally assessed against specification**



QUALITY CONTROL

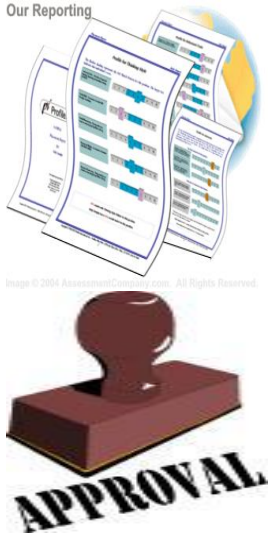
The basic requirements of QC :

- **Product assessment includes,**
  - a review and evaluation of relevant production documentation
  - an assessment of deviations from specified procedures.
- **Finished products assessment embraces all relevant factors:**
  - production condition
  - results of in-process testing
  - a review of manufacturing (including packaging) documentation
  - record of product testing is part of review prior to release for sale
  - compliance with Finished Product Specification
  - examination of final finished pack.

QUALITY CONTROL

The basic requirements of QC :

- **No batch of product is released for sale or supply prior to certification by an authorised person** that it is in accordance with the requirements of the NRA,
- **Sufficient reference samples of starting materials and products are retained** to permit future examination of the product if necessary,
  - **The product is retained in its final pack** unless exceptionally large packs are produced



PRODUCT QUALITY REVIEW (PQR)

Regular periodic or rolling quality reviews of all TM and HS, including export only products, shall be conducted with the objective verifying:

- the consistency of the existing process,
- the appropriateness of current specifications for both starting materials and finished product,

to

- highlight any trends
- identify product and process improvements.
- Such reviews shall normally be conducted and documented annually, taking into account previous reviews.

PRODUCT QUALITY REVIEW (PQR)

PQR should include at least a review of:

- **Starting materials and packaging materials** used for the product especially those from new sources,
- **Critical in-process controls and finished product results;**
- **All batches that failed to meet established specification(s) and their investigation;**

PRODUCT QUALITY REVIEW (PQR)

PQR should include at least a review of (cont.):

- **All significant deviations or non-conformances,** their related investigations, and the effectiveness of resultant CAPA taken;
- **All changes** carried out to
  - the processes
  - analytical methods;
- **Product authorization variations** submitted/granted/refused, including those for third country (export only) dossiers;

PRODUCT QUALITY REVIEW (PQR)

PQR should include at least a review of (cont.):

- **Results of the stability monitoring programme** and any adverse trends;
- **Quality-related returns, complaints and recalls and the investigations** performed at the time;
- **Effectiveness of corrective actions** on any other previous product process or equipment;

PRODUCT QUALITY REVIEW (PQR)

PQR should include at least a review of (cont.):

- **Verification status** of relevant equipment and utilities (HVAC, water, gas…);
- **Contractual Agreements** to ensure that they are up to date
- **Post-marketing commitment** for new product/ variation**;**

PRODUCT QUALITY REVIEW (PQR)

- **The manufacturer and manufacturing authorization holder shall evaluate the results of PQR**
  - An assessment shall be made, recommendation following the assessment result should be established.
  - Corrective and preventive action following recommendation shall be undertaken.
  - Reasons for such corrective actions shall be documented.
  - Agreed corrective and preventive actions shall be completed in a timely and effective manner.
  - There shall be management procedures for the ongoing management.
  - Review of these actions and the effectiveness of these procedures verified during self-inspection.

PRODUCT QUALITY REVIEW (PQR)

- **Quality reviews may be grouped by product type**, e.g. solid dosage forms, liquid dosage forms, etc. where scientifically justified.

PRODUCT QUALITY REVIEW (PQR)

- Corrective Action Preventive Action (CAPA) is a system of quality procedures required to eliminate the cause of existing of nonconformity and to prevent recurrence of nonconforming product, processes and other quality problem
- Source of CAPA:
  - Deviation
  - Customer complaint
  - Nonconforming product/process
  - Audit
  - Recall
  - Product Quality Review (PQR)
  - Verification

PRODUCT QUALITY REVIEW (PQR)

CAPA development:

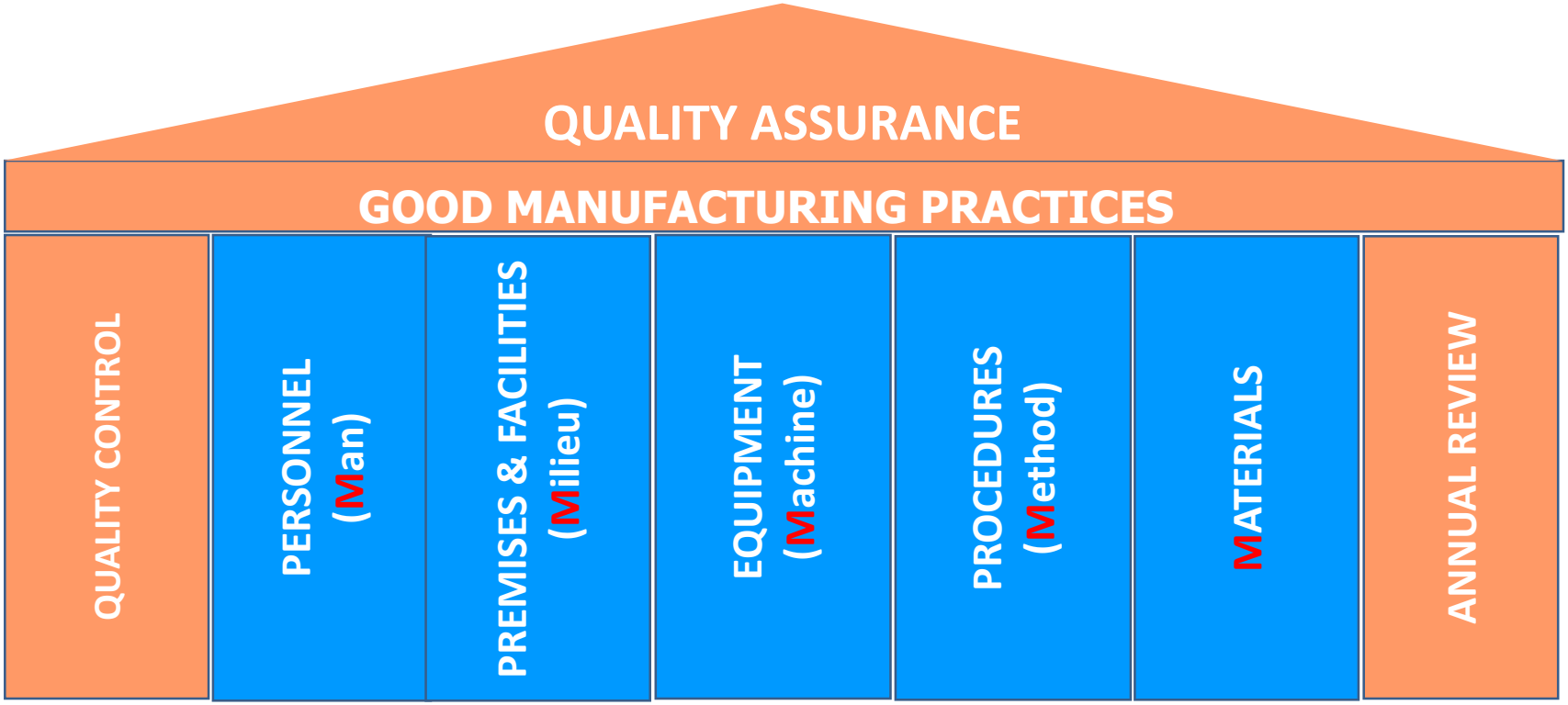
- ❑ Identification
  Clearly define the problem based on evidence and/or documented data
- ❑ Evaluation
  Appraise the magnitude and impact
- ❑ Investigation and analysis
  Perform root cause analysis
- ❑ Action plan
  Create a list of required plan/task (CAPA)
- ❑ Implementation
  Execute the action plan
- ❑ Follow up
  Verify and assess the effectiveness of CAPA

PRODUCT QUALITY REVIEW (PQR)

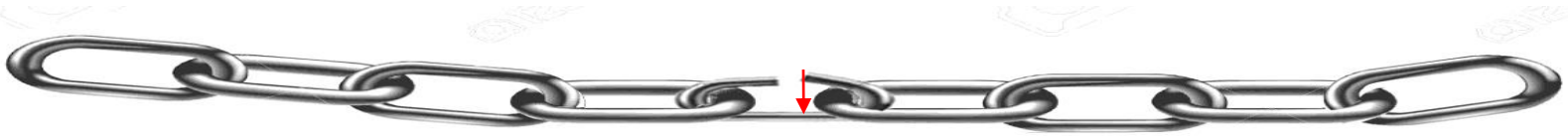
- **Technical agreement/ contract** in place between the various parties where the product owner is not the manufacturer

  - Defines their respective responsibilities in producing the quality review.
  - The authorised person responsible for final batch certification together with the product owner shall ensure that the quality review is performed in a timely manner and is accurate.

SUMMARY



SAY "NO"



THANK YOU!

ONE VISION, ONE IDENTITY, ONE COMMUNITY