CHAPTER 7 - QUALITY CONTROL

Prepared by:
Indonesia and Myanmar

Approved by:
ASEAN TMHS GMP Task Force
30 November 2016

Endorsed by:
ASEAN TMHS Product Working Group
# ACKNOWLEDGEMENT

We would like to thank the following review team for their input to this training module.

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<th>Name</th>
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<tr>
<td>Muhammad Lukmani Ibrahim</td>
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<td>Lao PDR</td>
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OUTLINE

• General
• Principle
• Quality Relationship: Differences between QC and QA
• Basic Principles of Good Quality Control Laboratory Practices
  • Personnel
  • Premises
  • Equipment
  • Material
  • Documentation
• Sampling
• Testing
• On-going Stability Programme
• Contract Analysis
GENERAL

Quality Control is part of Good Manufacturing Practice which is concerned with:

- sampling,
- specifications and testing, and
- the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.
PRINCIPLE

• Manufacturers of TM/HS shall have a quality control systems which is designed to ensure that products are manufactured under adequate conditions and in accordance with procedures so as to meet established specifications,

• Quality control is not confined to laboratory operations, but must involve in all decisions which may concern the quality of the product.

• To meet this purpose, Quality Control Department should be appropriate and independent
QUALITY RELATIONSHIP:
DIFFERENCES BETWEEN QC AND QA
QUALITY RELATIONSHIPS

Quality Management

Production & Quality Control

Quality Assurance

Good Manufacturing Practises
QUALITY RELATIONSHIPS

Quality Management

Quality Assurance

Good Manufacturing Practises

Production & Quality Control
QUALITY RELATIONSHIPS

Quality Assurance

- A wide-ranging concept which covers all matters which individually or collectively influence the quality of a product
- Appropriate infrastructure or “quality system” consists of organisation structure, procedures, processes and resources
- The sum total of the organized arrangements to ensure that the products are of the quality required for their intended use
- Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of these Guidelines, such as product design and development
## QUALITY RELATIONSHIPS

### Differences Between QC – QA

<table>
<thead>
<tr>
<th>Quality Control</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product approach</td>
<td>Process approach</td>
</tr>
<tr>
<td>Reactive</td>
<td>Proactive</td>
</tr>
<tr>
<td>Corrective tools</td>
<td>Preventive tools</td>
</tr>
<tr>
<td>Testing and Controlling</td>
<td>Develop and Assuring</td>
</tr>
<tr>
<td>Identification and Defect correction</td>
<td>Defect avoiding</td>
</tr>
</tbody>
</table>
QUALITY CONTROL

BASIC PRINCIPLES OF GOOD QUALITY CONTROL LABORATORY PRACTICES
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Personnel

Document

Premises

Materials

Equipment

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Personnel

QC Personnel shall comply with requirements as stipulated in Chapter 2 – Personnel:

– Qualification and competency of QC Personnel
– Responsibilities
– Joint responsibility of the Heads of Production and QC department
Personnel

Qualification and competency of QC personnel

- Quality Control personnel shall have particular expertise in products, in order,
  - to be able to carry out identification tests and
  - to detect adulteration,
  - to detect the presence of fungal growth, infestations, and
  - to identify non-uniformity when receiving and checking crude materials

Competent personnel with specific expertise on natural products should be an advantage, since crude material can be an aggregate of an individual natural material which contain an element of heterogeneity.
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Personnel

Qualification and competency of Microbiology Analyst:

• Microbiological testing shall be performed and supervised by an experienced person, qualified in microbiology or equivalent.

• Analyst should have basic training in microbiology and relevant practical experience before being allowed to perform work covered by the scope of testing.

• Shall understand:
  – procedures for containment of microorganisms within the laboratory facility
  – In safe handling of microorganisms
Personnel

Training for Microbiology Analyst shall cover:

• basic technique of:
  – plate pouring,
  – counting of colonies,
  – aseptic technique,
  – media preparation,
  – serial dilutions, and
  – techniques in identification, with acceptability determined using objective criteria where relevant.
  – procedures for containment of microorganisms
  – safe handling of microorganisms

• interpretations of test results
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Personnel
Example of QC Organisation chart

Quality control

Testing of Starting Matl incl Natural Matl & Packaging Matl

Finished product testing

Microbiological testing

Quality Compliance

Documentation

Released product for sale/ GMP compliance

Verification
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Personnel

Training

• The head of Quality Control Department shall have adequate training (such as knowledge of Good Quality Control Laboratory Practice and TM/HS analysis) and practical experience, which can enable the person to perform the functions effectively.
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Premises

The Quality Control Department shall have a designated area with sufficient to perform any required analysis before, during and after manufacture.

Quality Control Laboratory/Premises shall comply with requirements as stipulated in Chapter 3 – Premises and Equipment.
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Equipment

• Availability of QC equipment shall be based on testing methods:
  • Balances
  • Measuring equipment of an appropriate range and precision shall be available for analytical test
  • Glassware
  • Analytical instrument/equipment
• For calibration and documentation regarding QC equipment refer to Chapter 3 – Premises and Equipment and Chapter 5 - Documentation
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Equipment

• Verification of equipment
  • Equipment shall be verified to determine if they are still operating in a valid state
  • Verification of equipment should be done prior to the testing method verification
  • For details, refer to Appendix 2- Verification
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

General Principles

– Reagent, media, culture, reference of substances, materials and culture used in tests and assays – of appropriate quality and should be accompanied by

• the certificate of analysis, and
• the material safety data sheet, if required
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Chemical testing
  • Reagents
  • Reference substances and reference materials
• Microbiological testing
  • Culture Media
  • Reference cultures
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

Flow of QC Logistics

Needed reagent for testing, refer to:
- New testing method
- Minimum stock of reagent

Define specification

Purchase from qualified supplier

Receive incoming material and inspect compliance

Put material in the designated storage and record it at log book

Use the material for testing purpose

Record the usage of material at log book
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

• Reagents
  
  • Type of reagents:
    – Directly used
    – Prepared in laboratory:
      Chemical substance, buffer solution, volumetric solution, solvent
  
  • Grade of reagent:
    (purity) should be appropriate for use as indicated in the testing procedure
    – Analytical
    – HPLC
    – USP, BP, EP, JP -grade, etc
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reagents
  Label of Reagents

The labels of reagents should specify:
- content;
- manufacturer;
- date received and date of opening of the container;
- concentration, if applicable;
- storage conditions; and
- lot no & expiry date

Adequate stock should be available for operation and documented

The labels of reagents / volumetric solutions prepared in the laboratory should specify:
- name;
- date of preparation and initials of analyst;
- assigned Lot No & expiry date;
- Concentration or molarity, ;
- date of standardization (for volumetric sol.)

Note: The laboratory should ensure that the volumetric solution is suitable for use at the time of use
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reagents

Preparation of reagent:
– Responsibility for this task should be assigned clearly specified in the job description of the assigned
– Prescribed procedures should be used which are in accordance with published pharmacopoeia or valid internal method/instruction
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

• Reagents

Preparation of reagent:

- Records such as log-book should be kept of the preparation and standardization of reagent/volumetric solutions.

- Label:
  Refer to: International Hazard Label

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<table>
<thead>
<tr>
<th>Company Name</th>
<th>Name</th>
<th>HCl 1N Solution</th>
</tr>
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<tbody>
<tr>
<td>Dept. Quality Control</td>
<td>Lot No.</td>
<td>01AA</td>
</tr>
<tr>
<td></td>
<td>Preparation date</td>
<td>30-04-2015</td>
</tr>
<tr>
<td></td>
<td>Expiry Date</td>
<td>30-07-2015</td>
</tr>
<tr>
<td></td>
<td>Prepared by</td>
<td>WA</td>
</tr>
</tbody>
</table>
```

Corrosive
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reagents
  • Visual inspection
    – Delivered reagent containers should be visually inspected to ensure that the seals are intact.
  • Water as reagent
    – The appropriate grade for testing as described in the pharmacopoeias
    – The quality of the water should be verified regularly to ensure that water meet the specifications.
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

− Reagents
  
  • Storage
    − reagent/volumetric solution should be kept in reagent bottle and put it on the shelf
    − stored under the designated storage conditions (ambient temperature, under refrigeration, with proper dessication).
    − note:
      • flamable reagent \(\Rightarrow\) flamable storage
      • poison or toxic reagent \(\Rightarrow\) stored in a locked or secured cabinet
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reference Substances and Reference Materials

  • **Reference substances** are intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses an adequate degree of purity

  • **Reference materials** are intended for calibration and/or qualification of equipment, instruments or other devices, e.g. pH buffer for pH-meter standardisation

Note: the above are not Reference Sample which are mentioned in Slide 71
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reference Substances and Reference Materials

  Reference Substances
  – Markers
    » Markers are chemically constituents of a herbal material for control purposes. They may or may not contribute to the clinical efficacy.
    » Markers are generally employed when constituents of known therapeutic activity are not known or are not clearly identified, and may be used to identify the herbal material or preparation or calculate their quantity in the finished product.
      e.g.: flavonoid, total alkaloid
Materials

• Reference Substances and Reference Materials

Reference Substances:

» Active ingredients for herbal material(s) or preparation(s)

Constituent with known therapeutic activities are known, the active ingredients should be standardized to contain a defined amount of this/these constituent(s)

e.g.: Piperine originated from *Piper retrofractum* extract, Apigenin originated from *Apici* herbal extract
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reference Substances and Reference Materials

Reference Substances:

— The reference standard may be a botanical sample of the herbal material

— If the herbal medicine is not described in a recognized pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant may be used for macroscopic identification
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

• Reference Substances and Reference Materials
  – Reference Substances:
    • Primary reference substance
      – A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance.
      – Note: Pharmacopoeia chemical reference substances are considered to be primary reference substances.
Materials

• Reference Substances and Reference Materials
  – Reference Substances:

• Primary reference substance (cont.)
  – In the absence of a pharmacopoeia reference substance, a manufacturer should establish a primary reference substance
  – Active ingredients for health supplement material(s) or preparation(s)

Constituent with known therapeutic activities are known, the active ingredients should be standardized to contain a defined amount of this/these constituent(s)

  e.g.: Ascorbic acid
BASIC PRINCIPLES OF GOOD QC
LABORATORY PRACTICES

Materials

• Reference Substances and Reference Materials
  – Reference Substances:
    – Secondary reference substance (working standard)
      • A substance whose characteristics are assigned and/or calibrated by comparison with a primary reference substance.
    • Preparation of Working Standard
      – The information shall include the results of all tests and verifications used to establish the reference substances and expiry date or retest date; signed by the responsible analyst
      – All preparation shall be performed in accordance to instruction and duly recorded
### BASIC PRINCIPLES OF GOOD QC

#### LABORATORY PRACTICES

**Materials**

- **Reference Substances and Reference Materials**
  - **Handling**
    - A person should be nominated to manage reference substances and reference materials.
    - Registration of material should be maintained in log book, at least containing information of:

<table>
<thead>
<tr>
<th>Information</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) the identification number</td>
<td>(f) the location of storage and condition</td>
</tr>
<tr>
<td>(b) a precise description of the substance or material</td>
<td>(g) purity</td>
</tr>
<tr>
<td>(c) the source;</td>
<td>(h) expiry or retest date</td>
</tr>
<tr>
<td>(d) the date of receipt</td>
<td>(j) batch validity statement (CoA)</td>
</tr>
<tr>
<td>e) the intended use</td>
<td></td>
</tr>
</tbody>
</table>
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials
• Reference Substances and Reference Materials
  – Handling
    • Identification number should be:
      – Marked on each vial/container
      – Quoted on the analytical worksheet when used
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

• Media
  • Media shall be obtained from qualified supplier
  • Growth promotion test should be done on each prepared media
  • Positive and Negative control should be carried out on every test
  • Records such as log-book should be kept for the preparation of media (incl. expired date of media)
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

- Reference Cultures
  - Reference cultures should be obtained from recognized source which have WHO International Biological Standards Category (status and traceable),
    - e.g. *Eschericia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027
  - Subcultured not more than 5 generations (passages)
  - Provided with CoA
Handling of QC Materials

- Passage of reference culture:
  - **Reference strain**
    - From source recognized by accreditation body
  - **Reference stock G1**
    - Freeze-dried, liquid nitrogen storage, deep frozen, etc.
    - Specified conditions and recommended storage times
  - **Reference stock G2**
    - Freeze-dried, liquid nitrogen storage, deep frozen, etc.
    - Specified conditions and recommended storage times
  - **Working culture**
    - Specified conditions and recommended storage times
    - Routine use
  - **A**
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Handling of QC Materials

- Passage of reference culture:

  Reference stock G3
  Freeze dried, liquid nitrogen storage, deep frozen, etc.
  Specified conditions and recommended storage times

  Reference stock G4
  Freeze dried, liquid nitrogen storage, deep frozen, etc.
  Specified conditions and recommended storage times

  Working culture
  Specified conditions and recommended storage times
  Routine use
Document

Type of Document

• Specifications (refer to Chapter 5)
• Testing Procedures
  – Approved testing procedures shall refer to testing method described in specifications, and Internationally accepted method
• SOPs related to QC activities
• Records including Analysis worksheets and/or laboratory notebooks
• Analysis reports and/or certificates
## BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

### Document

<table>
<thead>
<tr>
<th>SPECIFICATIONS AND TESTING PROCEDURES</th>
<th>SOURCE OF DEVELOPMENT</th>
</tr>
</thead>
</table>
| Starting and Natural Material         | • Pharmacopoeia or other international accepted references  
                                      | • Manufacturer Technical Data for specific parameters (e.g. particle size, moisture content, etc) |
| Primary Packaging Material            | • Manufacturer Technical Data and  
                                      | • Based on stability study during product development |
| Secondary Packaging Material          | • Manufacturer Technical Data and  
                                      | • Refer to approved labelling, strength, product protection and commercial aspect |
| Finished Products (incl. Intermediate product) | • Pharmacopoeia or other international accepted references  
                                                      | • Product trial during development (e.g. appearance and non-chemical requirement) |
Document
– SOPs related to QC activities
• Sampling Procedure
• Testing and Release
• Handling Reagent, Media and References
• Calibration of equipment
• Handling Out Of Specification and Deviation
• Corrective Action and Preventive Action
• Handling Complaint and Product Recall
• Change Control
• Product Quality Review

• Training
• Self Inspection and Quality Audit
• Supplier qualification
• Labelling
• Verification of equipment, system and process
• Environmental Monitoring
• Safety measures (for hazardous materials)
• Sanitation and Personnel Hygiene
• Handling Quality Control Waste
• Disposal/Destruction of The Rejected Product
Document

- Quality control records
  - records are made, manually and/or by recording instruments, during testing/analysis which demonstrate required steps by the defined procedures
  - laboratory should establish and maintain procedures for
    - identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records
  - data recorded in the analytical worksheet by the technician or analyst on consecutively numbered pages.
Document

- Quality control records
  - The records should include information of:
    - sample, instruments, equipment, reagent/media/column, reference standard, refer to testing method
    - identity of the personnel involved in the sampling, preparation and testing of the samples.
    - appendices containing the relevant recordings, e.g. chromatograms and spectra.

  to ascertain traceability
Document

- Quality control records
  - Quality control data documentation shall implement good documentation practices (ALCOA Principles):
    - **Attributable** – data are identified with a specific subject and a specific observer and recorder. (Password, audit trail, e-signature and name & authentic signature)
    - **Legible** – data are readable and understandable by humans (reports, tables, and listings)
    - **Contemporaneous** - data are recorded at the time they are generated or observed. (Time stamps and time-limited entry)
    - **Original** – data are recorded for the first time. (Source data and meta data)
    - **Accurate** – data are correct (data can be verified)
Document

- Quality control records

  - DATA INTEGRITY is the assurance that data records are accurate, complete, intake and maintained within their original context including traceability to other data/records

  - Data integrity: ALCOA ++ principles

    - **Complete**: all data including repeat or reanalysis perform from the sample
    - **Consistent**: consistent application of data time stamps in the expected sequence
    - **Enduring**: recorded on controlled worksheets, laboratory logbook or electronic media
      - **Available**: available, accessible for review/audit for the lifetime of the record

  - Data integrity applies to data recorded in:

    - electronic and
    - paper format or
    - a hybrid of both (paper and electronic)
Document

- Quality control records
  - stored and retained in a manner that prevents modification, damage or deterioration and/or loss
  - held secure and in confidence
  - retained for an appropriate period of time, generally shelf-life plus one year for finished product is recommended, unless national regulations are more stringent or contractual arrangements
  - electronic data shall be backed-up regularly and stored in secured place
Document

- Data processing equipment
  - Data may be recorded by:
    - electronic data processing systems,
    - photographic,
    - manual or other reliable means,
  - Detailed procedure relating to the system in use shall be available and the accuracy of the records shall be checked and verified.
Document

• Data processing equipment
  • If documentation is handled by electronic data processing methods
    ▪ only personnel who have been authorised shall be able to enter or modify data in the computer and there shall be a record of changes and deletions i.e. must have audit trail;
    ▪ access shall be restricted by passwords or other means and the result of entry of critical data shall be independently checked and verified
QUALITY CONTROL

SAMPLING
SAMPLING

Samples received by QC laboratory:

• routine for control: natural, starting, packaging materials and finished products
• on going stability samples
• environmental monitoring: cleanliness of production area, water as starting material and final rinsing for equipment cleaning
• investigative testing: complaint, recall, deviation, reprocessing
BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Samples

• must be taken from each batch and
• well documented in:
  – Sampling form
  – Sample Log book
• Due to herbal materials are an aggregate of individual plants and/or different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out
  – by personnel with the necessary expertise
Sampling procedure shall describe:

- method of sampling
- sampling tools, to include instruction for cleaning and storage of sampling equipment
- sampling facility
- amount of the sample to be taken must be in accordance with sampling plan
- instructions for any required subdivision of the sample
- type and condition of the sample container to be used
- identification of containers sampled (label)
- the storage conditions
- sampling forms to be used
Sampling PLAN

- Definition of Sampling Plan:
  - description of the location, number of units and/or quantity of material that should be collected, and associated acceptance criteria.

An example of sampling plan for starting materials

- n plan
- p plan
- r plan
### Basic Principles of Good QC Laboratory Practices

#### Sampling Plan for Starting Materials

**Explanation of sampling plan**

<table>
<thead>
<tr>
<th>‘n’ plan</th>
<th>‘p’ plan</th>
<th>‘r’ plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material is uniform</td>
<td>Material is uniform</td>
<td>Material is suspected to be non-uniform</td>
</tr>
<tr>
<td>Supplied from a recognized source</td>
<td>Supplied from a recognized source</td>
<td>Received from a source that is not well known</td>
</tr>
<tr>
<td>Drawn from any part of the container (usually from the top layer)</td>
<td>The main purpose is to test for identity</td>
<td></td>
</tr>
<tr>
<td>The formula:</td>
<td>The formula:</td>
<td>The formula:</td>
</tr>
<tr>
<td>( n = 1 + \sqrt{N} )</td>
<td>( p = 0.4\sqrt{N} )</td>
<td>( r = 1.5\sqrt{N} )</td>
</tr>
<tr>
<td>( N ) is the number of sampling units in the consignment.</td>
<td>( N ) is the number of sampling units in the consignment.</td>
<td>( N ) is the number of sampling units in the consignment.</td>
</tr>
<tr>
<td>The value of ( n ) is obtained by simple rounding</td>
<td>( p ) are obtained by rounding up to the next highest integer</td>
<td>( r ) are obtained by rounding up to the next highest integer</td>
</tr>
</tbody>
</table>
### Sampling PLAN for Starting Materials

**Explanation of sampling plan**

Values of \( n, p \) or \( r \) for the \( N \) (number of containers received) sampling units

<table>
<thead>
<tr>
<th>Value of ( n, p ) or ( r )</th>
<th>Values of ( N )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n ) plan</td>
</tr>
<tr>
<td>2</td>
<td>up to 3</td>
</tr>
<tr>
<td>3</td>
<td>4 - 6</td>
</tr>
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<td>4</td>
<td>7 - 13</td>
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<td>9</td>
<td>57–72</td>
</tr>
<tr>
<td>10</td>
<td>73–90</td>
</tr>
</tbody>
</table>
Sampling PLAN for Starting Materials

- Examples of use of sampling plans \( n, p \) and \( r \) (Consider a consignment of 40 containers \( N \) of a starting material)

  - **\( n \) plan**: samples taken from 7 containers selected at random. The appearance and identity of each of these 7 samples is checked. If the results are concordant, the 7 samples are combined to produce a single, composite sample from which an analytical sample is prepared for full testing.

  - **\( p \) plan**, samples taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, the samples are appropriately combined to form 3 final, composite samples to be used for retention (or full testing if required).

  - **\( r \) plan**, samples taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, 10 samples are selected at random and individually subjected to full testing.
Sampling PLAN for Packaging materials

- Examples of sampling plan include:
  - Number of sample \(( n ) = 1 + \sqrt{N} \)
  - BS 6001-1, ISO 2859 or ANSI/ASQCZ1.4-1993.

  The objective is to ensure that there is a low probability of accepting material that does not comply with the predefined Acceptance Quality Level (AQL)
Sampling PLAN for Natural materials (medicinal plants)

- Initial inspection to each container shall indicate that the lot is uniform
- Sample taken

<table>
<thead>
<tr>
<th>Number of container</th>
<th>Sample taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5</td>
<td>All</td>
</tr>
<tr>
<td>6 - 50</td>
<td>10%</td>
</tr>
<tr>
<td>≥ 50</td>
<td>10% rounding up to the no unit to the nearest multiple of 10</td>
</tr>
</tbody>
</table>

- Samples should be taken from the top, middle and bottom of the container
- Dented containers must be subjected for sampling.
- Intermediate, bulk and finished products
  - Samples should be taken from the start, middle and end of the process
SAMPLING

Sampling Facility

• Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

• Where possible, sampling should be performed in an area or booth designed for this purpose, although this will not be possible where samples are required to be taken from a production line (e.g., in-process control samples).

• Cleanliness class of sampling facility should be the same as where the material is processed.

• The area in which the sample was taken should be recorded in the sampling form.
SAMPLING

- Reference samples shall be representative of the batch of materials or products from which they are taken.
- Sample containers shall bear a label indicating:
  - name of materials,
  - batch number (internal system),
  - date of sampling and
  - containers from which samples have been drawn.
- Containers from which samples have been drawn shall bear label “SAMPLE TAKEN”.
- Usage and cleaning status of sampling devices should be documented in log book.
## SAMPLING

### Example of Sampling tools

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Powder</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Liquid sample" /></td>
<td><img src="image2.png" alt="Powder sample" /></td>
</tr>
</tbody>
</table>

*Example of Sampling tools for Liquid and Powder samples.*

- **Liquid**: Needle for liquid samples.
- **Powder**: Spatula and pipette for powder samples.
SAMPLING

• Sample Registration
  – Samples should be registered / written in log book containing:
    – registration number
    – date of receipt
    – sample identification as described in sample’s label
    – specific chemistry/microbiology lab to which the sample is forwarded.

• Sample Storage
  – The sample prior to testing, the retained sample and any portions of the sample remaining after performance of all the required tests should be stored securely, taking into account the storage conditions specified for the sample.
Reference Sample

- Finished Products
  - Each batch shall be retained till one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions.

- Starting materials (other than natural materials, solvents, gases and water) shall be retained for at least two years after release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter.

- Reference samples of materials and products shall be of a size sufficient to permit at least a full re-examination.
QUALITY CONTROL

TESTING
TESTING

FLOW OF TESTING

- **Subject of testing**
  - Natural/starting/packaging materials and finished products
  - On going stability
  - Environmental Monitoring
  - Verification activities
  - Investigative testing due to noncompliance of quality

- **Sampling**
  - Refer to valid sampling procedure

- **Physical, chemical, microbial testing**

- **Testing**
  - Refer to valid and verified testing procedure
  - Implement Good Quality Control Laboratory Practices

- **Result and Decision**
  - Result evaluation
  - Release/reject
TESTING

• All testing operations described in the marketing authorisation shall be carried out according to
  – approved methods which shall be internationally accepted (Refer to Appendix 1: List of Internationally Accepted References for Test Methods) or
  – other validated test methods
TESTING

The test results shall be recorded in ANALYTICAL WORKSHEET and the records shall include at least:

- Name of the material or product and, where applicable, dosage form
- Batch number, expiry date and, where appropriate, the manufacturers and/or supplier
- References to the relevant specifications and testing procedures
- Test results, including observations and calculations, and reference to any certificates of analysis
- System Suitability Test (SST) shall be carried out where applicable
- Dates of testing, the name of the analyst and the name of the external laboratory, if applicable
- Date and signature of the persons who performed the testing and who verified the testing and the calculations, where appropriate
- A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person
TESTING

- Release/Reject
  - Release and rejection procedure shall be available for materials and products,
  - Release for sale of finished product shall be done by the QA / QC authorised person
  Finished product assessment shall include production condition, results of in-process testing, review of manufacturing (including packaging) documentation, in compliance with Finished Product Specification and examination of final finished pack.

- Contract analysis
  - Contract analysis can be performed
    » In case no availability of facilities for testing
    » Requirement of Contract Analysis should be comply
TESTING

• Out of specification (OOS) or significant atypical trends shall be investigated.

• FLOW OF OOS:

OOS TEST RESULTS

IDENTIFYING AND ASSESSING OOS TEST RESULTS
• PHASE I: LABORATORY INVESTIGATION

INVESTIGATING OOS TEST RESULTS
• PHASE II: FULL-SCALE OOS INVESTIGATION

Perform CAPA

Decisions should be made whether to reject or approve (with justification) the materials or product
Monitoring of Environment and Water Quality

- Data from environmental monitoring, where appropriate shall be available

- Program for monitoring should be available for
  - Water for production
  - Production environment
ON-GOING STABILITY PROGRAMME
ON-GOING STABILITY PROGRAMME

- **Purpose of the on-going stability program is**
  To monitor the product over its shelf life (in the market) and to determine that the product remains, within specifications under the labelled storage conditions

- **Selection of batches**
  Unless otherwise justified, at least one batch per year of product manufactured in every primary packaging type

- **Follow-up stability for risk product should be conducted:**
  - After any significant change or
  - Significant deviation to the process or package.
  - Any reworking, reprocessing or recovery operation
ON-GOING STABILITY PROGRAMME

Stability study requirements

- Refer to ASEAN Guidelines on Stability Study and Shelf Life TM and HS (Annex 5 of the ASEAN Agreements on TM and HS)
- Storage condition and testing frequency

<table>
<thead>
<tr>
<th>TYPE OF CONTAINER CLOSURE SYSTEM</th>
<th>STORAGE CONDITION</th>
<th>TESTING FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products in primary containers permeable to water vapour</td>
<td>30°C ± 2°C / 75% RH ± 5% RH</td>
<td>0, 3, 6, 9, 12, 18, 24 months and annually thereafter through the proposed shelf-life</td>
</tr>
<tr>
<td>Products in primary containers impermeable to water vapour</td>
<td>30°C ± 2°C</td>
<td></td>
</tr>
</tbody>
</table>
ON-GOING STABILITY PROGRAMME

Written PROTOCOL should be available and define:

• Number of batch(es) per strength and different batch sizes, where applicable
• Relevant physical, chemical, microbiological and biological test methods, stability indicating parameters, where applicable
• Acceptance criteria
• Reference to test methods
• Description of the container closure system(s)
• Testing intervals (time points)
• Description of the conditions of storage
• Other applicable parameters specific to the finished product
ON-GOING STABILITY PROGRAMME

Testing Parameters shall refer to ASEAN GUIDELINES ON STABILITY STUDY & SHELF-LIFE OF TRADITIONAL MEDICINES AND HEALTH SUPPLEMENTS

Annex 1 - Testing Parameters Stability Study
Annex 2 - On Going Stability Protocol
ON-GOING STABILITY PROGRAMME

• Stability chamber/room used to store the samples, should be verified/qualified, maintained and monitored

• A summary of all the data generated, including any interim conclusions on the programme, shall be written and maintained. This summary shall be subjected to periodic review.

• Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned.

• Results of on-going stability studies should be available at the site of manufacture for review by the competent authority
ON-GOING STABILITY PROGRAMME

• Out of specification or significant atypical trends shall be investigated.

• Any confirmed out of specification result, or significant negative trend, shall be reported to the relevant competent authorities.

• The possible impact on batches on the market shall be considered in accordance with Chapter 9 – Complaints and Product Recalls of the GMP Guide and in consultation with the relevant competent authorities.
REFERENCES

1. ASEAN Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements.
2. ASEAN Guidelines on Stability Study and Shelf-Life of Traditional Medicines and Health Supplements.
THANK YOU!

ONE VISION, ONE IDENTITY, ONE COMMUNITY