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

CHAPTER 7 - QUALITY CONTROL

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Approved by:
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ASEAN TMHS Product Working Group

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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 CONTROL

QUALITY RELATIONSHIP: DIFFERENCES BETWEEN QC AND QA

QUALITY RELATIONSHIPS

QUALITY RELATIONSHIPS

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, processess 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

Quality Control	Quality Assurance
Product approach	Process approach
Reactive	Proactive
Corrective tools	Preventive tools
Testing and Controlling	Develop and Assuring
Identification and Defect correction	Defect avoiding

QUALITY CONTROL

BASIC PRINCIPLES OF GOOD QUALITY CONTROL LABORATORY PRACTICES

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Personnel

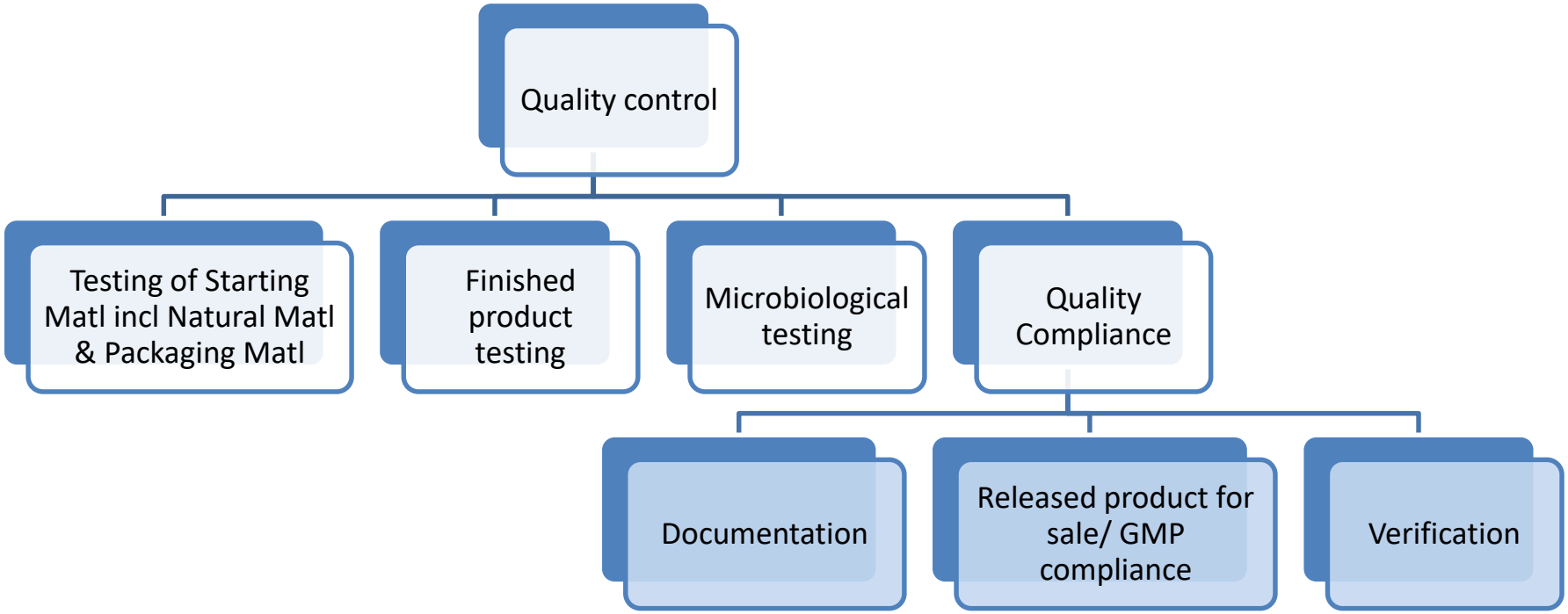
Training for Microbiology Analyst shall cover :

- basic tehnique 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



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

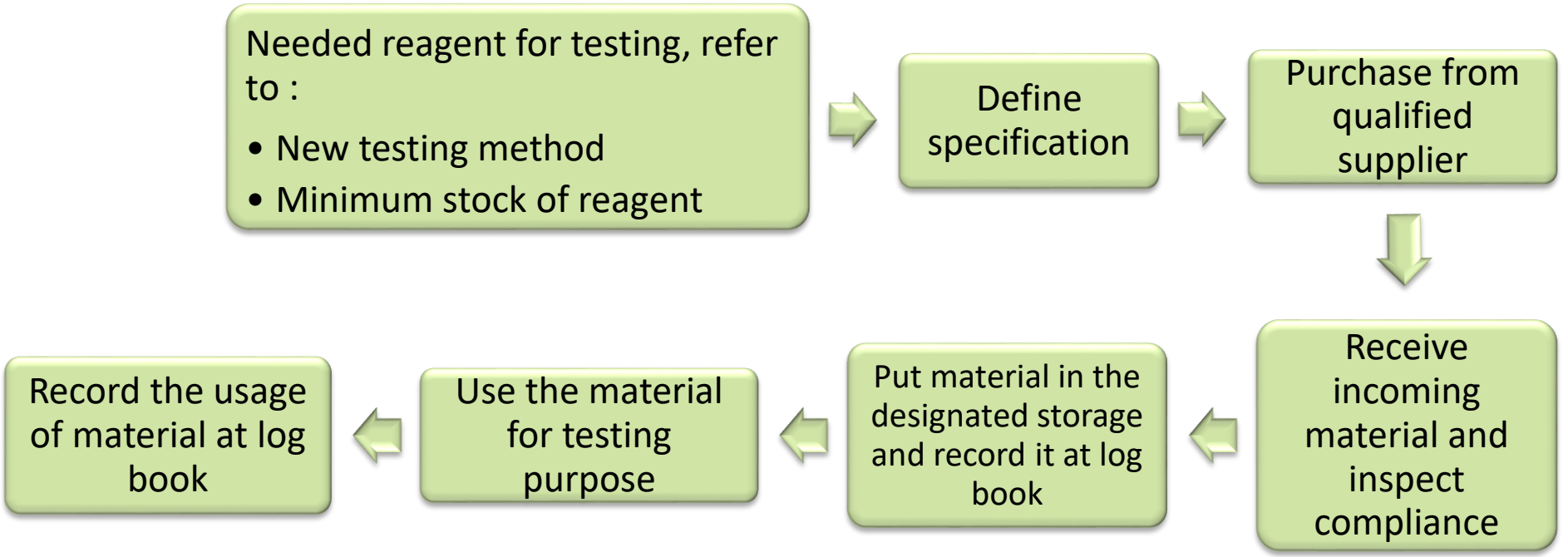
Materials

- 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



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

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.)

Adequate stock should be available for operation and documented

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

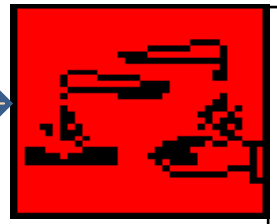
Materials

- 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



Corosive

Company Name
Dept. Quality Control

Name	: HCl 1N Solution
Lot No.	: 01AA
Preparation date	: 30-04-2015
Expiry Date	: 30-07-2015
Prepared by	: WA

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 ⇨ flamable storage
      - poison or toxic reagent ⇨ stored in a locked or secured cabinet

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Materials

- Reference Substances and Reference Materials -1

  - **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 -2

  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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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 *Apii* 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.

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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 :

(a) the identification number	(f) the location of storage and condition
(b) a precise description of the substance or material	(g) purity
(c) the source;	(h) expiry or retest date
(d) the date of receipt	(j) batch validity statement (CoA)
e) the intended use	

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

→ ***Working culture***
Specified conditions and recommended storage times
Routine use

↓

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

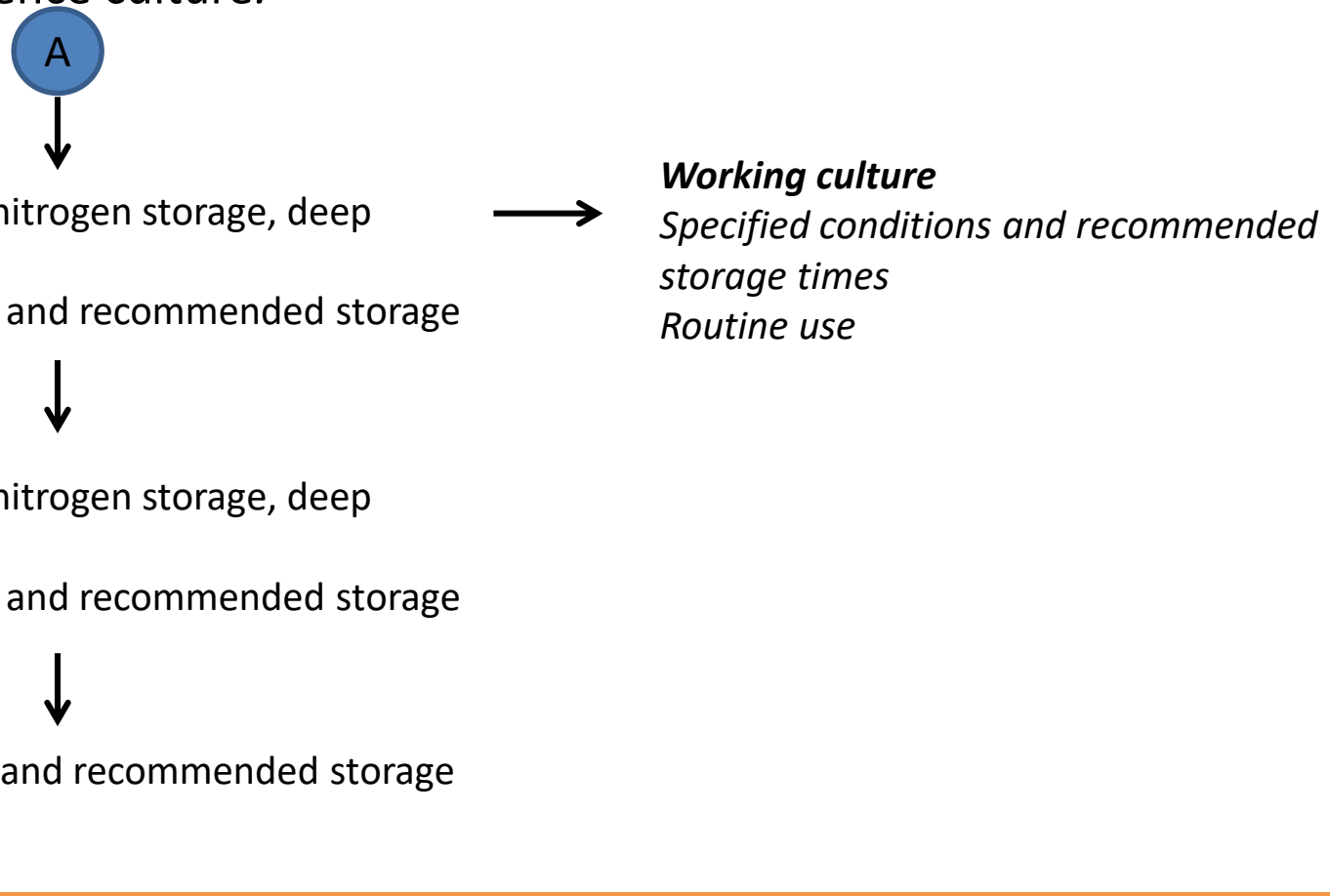
↓

A

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Handling of QC Materials

- Passage of reference culture*:*



BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

SPECIFICATIONS AND TESTING PROCEDURES	SOURCE OF DEVELOPMENT
Starting and Natural Material	•Pharmacopoeia or other international accepted references • Manufacturer Technical Data for specific paramaters (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. Intermediatte product)	•Pharmacopoeia or other international accepted references •Product trial during development (e.g. appearance and non-chemical requirement)

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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.

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Document

- Quality control records
  - Quality control data documentation shall implement good documentation practices (ALCOA Principles):

A
L
C
O
A

  - **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)

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Document

- Quality control records
  - DATA INTEGRITY is the assurance that data records are accurate, complete, intake and maintained within there 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)

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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.

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

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

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

'n' plan

- Material is uniform
- Supplied from a recognized source
- Drawn from any part of the container (usually from the top layer)
- The formula :
  - $n = 1 + \sqrt{N}$
  - N is the number of sampling units in the consignment.
  - The value of n is obtained by simple rounding

'p' plan

- Material is uniform
- Supplied from a recognized source
- The main purpose is to test for identity
- The formula :
  - $p = 0.4\sqrt{N}$
  - N is the number of sampling units in the consignment.
  - p are obtained by rounding up to the next highest integer

'r' plan

- Material is suspected to be *non-uniform*
- Received from a source that is not well known
- The formula :
  - $r = 1.5\sqrt{N}$
  - N is the number of sampling units in the consignment.
  - r are obtained by rounding up to the next highest integer

BASIC PRINCIPLES OF GOOD QC LABORATORY PRACTICES

Sampling PLAN for Starting Materials

Explanation of sampling plan

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

Value of n, p or r	Values of N		
	n plan	p plan	r plan
2	up to 3	up to 25	up to 2
3	4 - 6	26–56	3–4
4	7 - 13	57–100	5–7
5	14–20	101–156	8–11
6	21–30	157–225	12–16
7	31–42		17–22
8	43–56		23–28
9	57–72		29–36
10	73–90		37–44

SAMPLING

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

Sampling PLAN for Packaging materials

- Examples of sampling plan include:
  - Number of sample (n) = 1 + √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

Sampling PLAN for Natural materials (medicinal plants)

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

Number of container	Sample taken
≤ 5	All
6 - 50	10%
≥ 50	10% rounding up to the no unit to the nearest multiple of 10

- **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 processsed
- 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

Liquid	Powder
	  

SAMPLING

- Sample Registration
  - Samples should be registrated / 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.

SAMPLING

Reference Sample

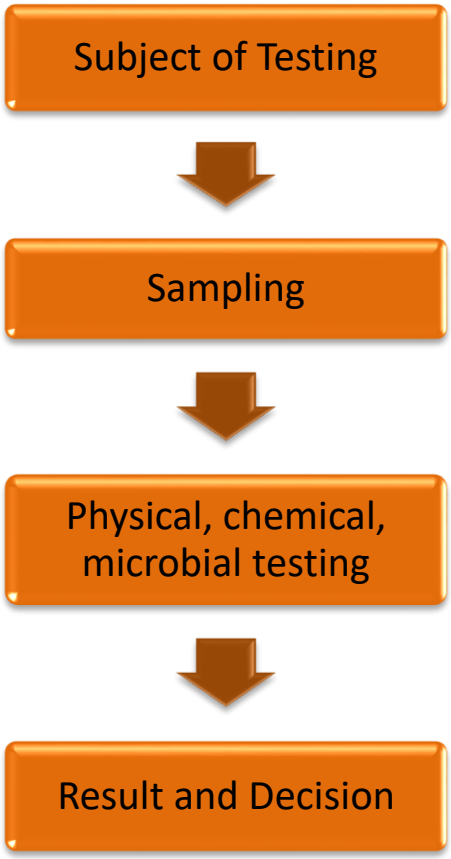
- Finished Products
  - Each batch shall be retained till one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions.
- Starting materials (other than natural materials, solvents, gases and water) shall be retained for 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

➢ **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 resuls 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

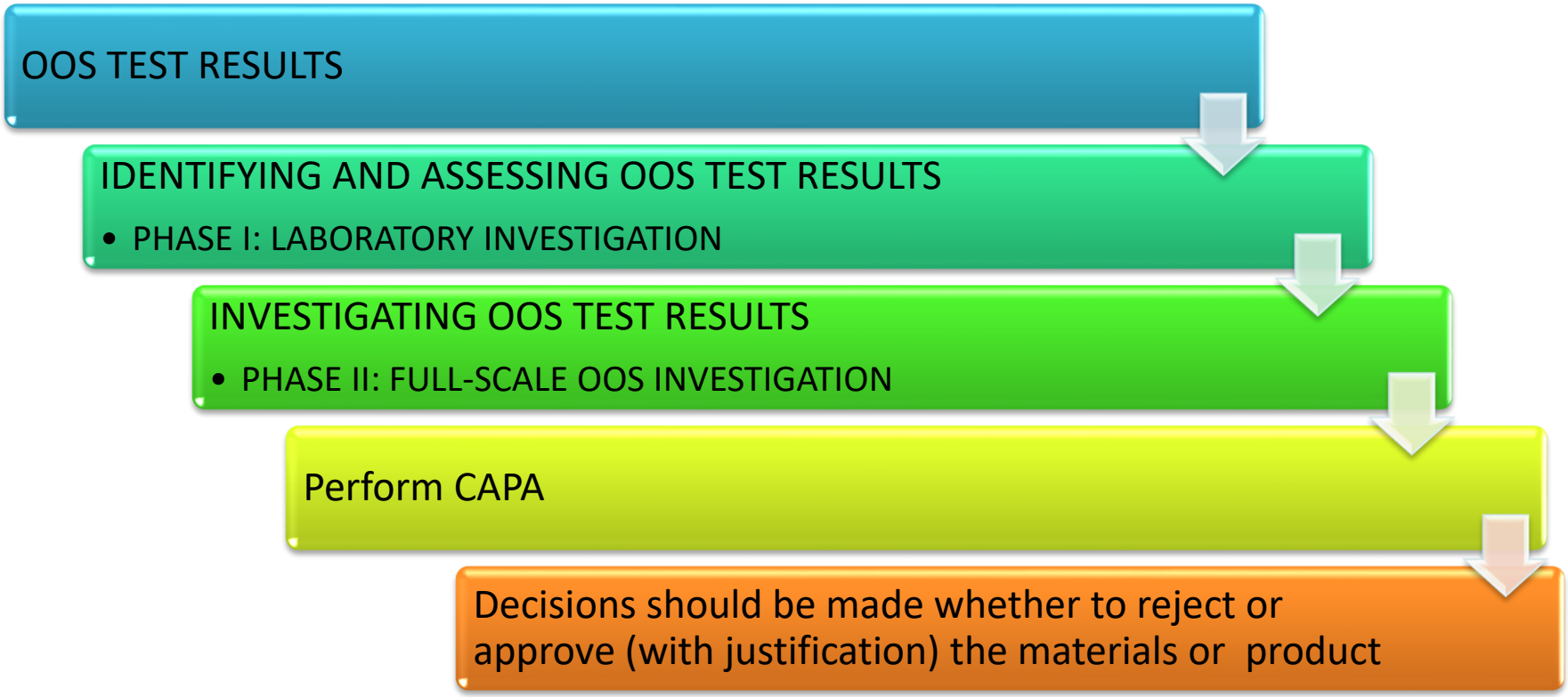
TESTING

- 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 shoud be comply

TESTING

- Out of specification (OOS) or significant atypical trends shall be investigated.
- FLOW OF OOS:



TESTING

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

QUALITY CONTROL

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

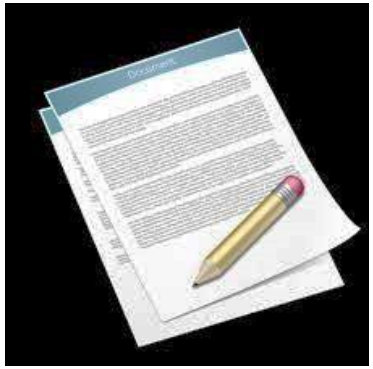
- Refer to ASEAN Guidelines on Stability Study and Shelf Life TM and HS (Annex 5 of the ASEAN Agreements on TM and HS)
- Storage condition and testing frequency

TYPE OF CONTAINER CLOSURE SYSTEM	STORAGE CONDITION	TESTING FREQUENCY
Products in primary containers permeable to water vapour	30° C ± 2° C/75% RH ± 5% RH	0, 3, 6, 9, 12, 18, 24 months and annually there after through the proposed shelf-life
Products in primary containers impermeable to water vapour	30° C ± 2° C	

ON-GOING STABILITY PROGRAMME

Written PROTOCOL should be availabe 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.
3. WHO TRS 937, 2006, Annex 3, Supplementary Guidelines on GMP for the Manufacture of Herbal Medicines.
4. WHO TRS 957, 2010, Annex 1, WHO Good Practices forPharmaceutical Quality Control Laboratories.
5. Quality Control Methods for Medicinal Plant Material, WHO Geneva 1998.
6. WHO TRS 961, 2011, Annex 2, WHO Good Practices for Pharmaceutical Microbiology Laboratories.
7. MHRA GMP Data Integrity Definitions and Guidance for Industry, March 2015.
8. WHO TRS 929, 2005, Annex 4, WHO Guidelines for Sampling of Pharmaceuticals Product and Related Materials.

THANK YOU!

ONE VISION, ONE IDENTITY, ONE COMMUNITY