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

CHAPTER 6 - PRODUCTION

Prepared by:

Malaysia

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.

Muhammad Lukmani Ibrahim	Chair of ASEAN GMP TF
Quitevis, Ludivina Fama	Co-Chair of ASEAN GMP TF
Mega Valentine	ASEAN Secretariat
Hasmilawaty Mohammad Taib	Brunei Darussalam
Jamilah Metusin	Brunei Darussalam
Hean Kimseat	Cambodia
Som Samnang	Cambodia
Kristiana Haryati	Indonesia
Widiastuti Adiputra	Indonesia
Bounleuane Douangdeuane	Lao PDR
Solivanh Sengchanh	Lao PDR
Sivong Sengaloundeth	Lao PDR
Mohd Nasrul Mohamad Noor	Malaysia
Sharifah Mastura Ahmad Fuad	Malaysia
Thiri Kyaw Soe	Myanmar
Wah Wah Aung	Myanmar
Mary Angeline V. Francisco	Philippines
Ms. Rochel Averion Francisco	Philippines
Ong Hai Ann, Terrance	Singapore
Pinpong Intarapanich	Thailand
Thida Thaveerit	Thailand
Lam Quoc Hung	Vietnam
Luu Duc Du	Vietnam
Mak Sum Shing, Andrew	AAHSA
Tamotsu Iwai	AAHSA
Robles, Frances Evelyn	AATMI

OUTLINE

1. Objectives
2. Principle
3. General
4. Verification
5. Prevention of Cross Contamination in Production
6. Starting Materials
7. Dispensing/ Weighing of Starting Materials
8. Water
9. Processing Operations: Intermediate and Bulk Products
10. Packaging Materials
11. Packaging Operations
12. Finished Products
13. Rejected, Recovered and Returned Materials

OBJECTIVES

- To ensure consistency of production activities by following established procedures
- To ensure consistency of finished products quality and safety in accordance to specification
- To ensure traceability of production activities with good documentation practice
- To avoid risk of contamination, cross-contamination, and mix-ups during storage and production
- To avoid error in production

PRINCIPLE

- **Processes** used **in production shall be capable of yielding finished products** which **conform to** their **specifications**.
- **Defined manufacturing procedures** are necessary to ensure that production, quality control and other relevant personnel are instructed on the details of the processes concerned.

GENERAL

- Production shall be performed and supervised by competent personnel
- Handling of materials and products, such as:
  - receipt and quarantine,
  - sampling,
  - storage,
  - labelling,
  - dispensing,
  - processing,
  - packaging and
  - distribution

  shall be in accordance with written procedures and recorded

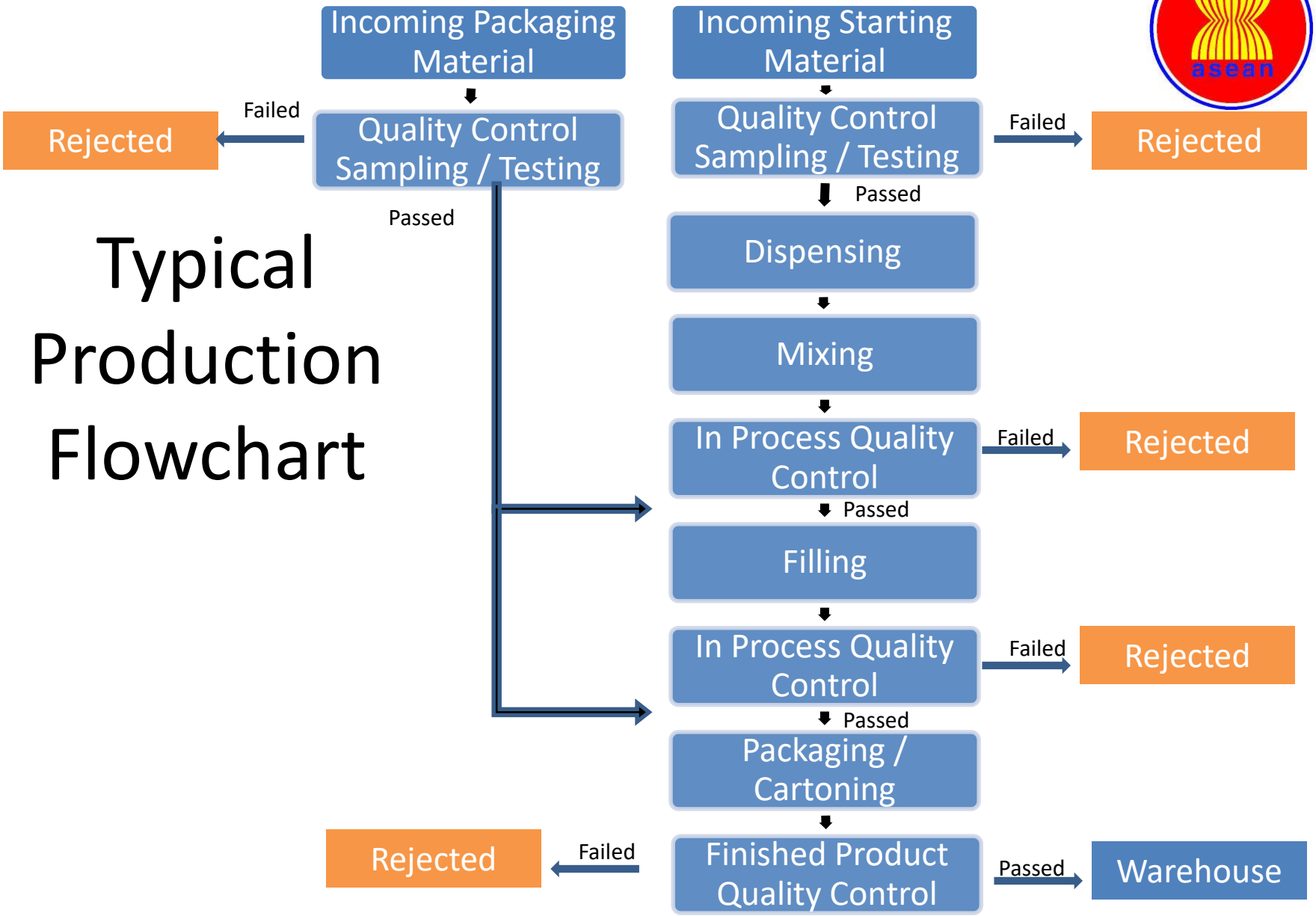
GENERAL

- All incoming materials shall be checked to ensure that the consignment corresponds to the order. Containers shall be cleaned where necessary and labelled with the prescribed data.
- Checks on yields and reconciliation of quantities shall be carried out to ensure there are no discrepancies outside defined/acceptable limits.
- Operations on different products shall not be carried out simultaneously/consecutively in the same room to prevent the risk of mix-up or cross-contamination.

GENERAL

- Protection from microbial and other contamination at every stage of processing
- Requirement of labelling of all materials, bulk containers, major equipment and rooms (where appropriate)
- At every stage of processing, products and materials shall be protected from microbial and other contamination / cross contamination. Any treatment used to reduce fungal / microbial contamination or other infestation shall be documented.

Typical Production Flowchart



VERIFICATION

According to ASEAN Guideline on GMP for Health Supplements and ASEAN Guideline on GMP for Traditional Medicines

Para 6.17;

Verification *work that is needed* ***to prove control of critical aspects of particular operations*** *shall be identified and documented.* ***Significant changes*** *to the* ***facilities, equipment, testing*** *and the* ***processes*** *which* ***may affect*** *the* ***quality of the product*** *shall be verified. A* ***risk assessment approach*** *shall be used to determine the scope and extent of verification.*

for details please refer to the module on Appendix 2 - Verification

SCOPE OF VERIFICATION

- Equipment
- Utilities
- Processes
- Manufacturing Process (demonstration, in-process control)
- Supplier
- Cleaning of product contact equipment
- Electronic data processing system, where applicable (clause 5.11)

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

- **Contamination**

  The undesired introduction of impurities of a chemical or microbiological in nature, or foreign matter into or onto a starting material or intermediate/bulk products during production, sampling, packaging or repackaging, storage or transport.

- **Cross-contamination**

  The contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

  (WHO Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues)

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

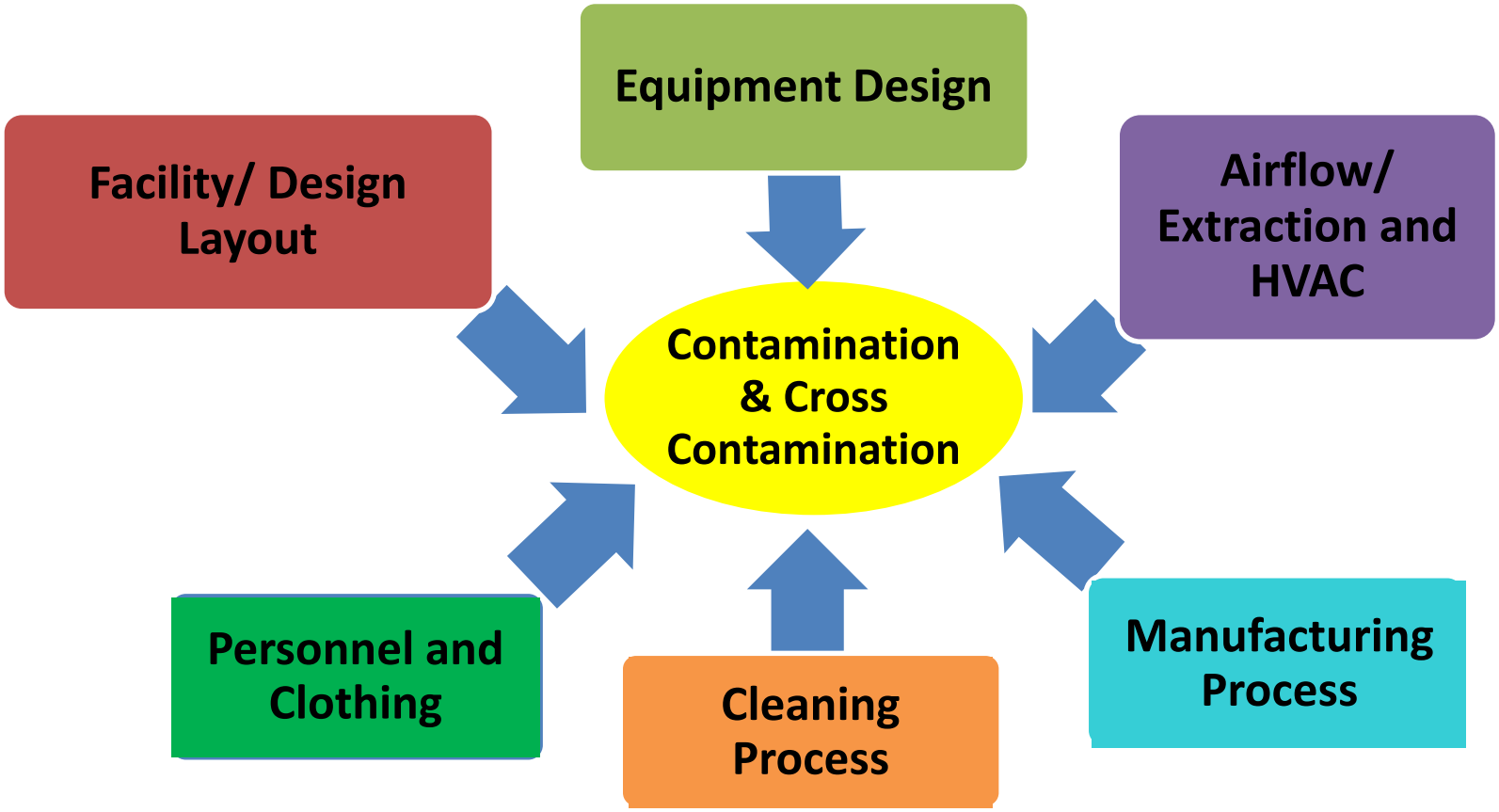
Each step/equipment/system can pose a risk of contamination.

– Manufacturing of TM/HS products involve a series of processing steps and use of various equipment. Equipment and ancillary systems may be used for manufacturing multiple products or single product.

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

- Contamination of a starting material or of a product by another material or product shall be avoided.
- The common causes of contamination are identified below:
  - Poor Facility/ Design Layout
  - Poor Equipment Design
    - residues on equipment
  - Poor Airflow Extraction and HVAC
  - Poor Manufacturing Process
    - dust, gases, vapours, sprays or organisms
  - Inadequate Personnel Hygiene and Clothing
  - Inadequate Cleaning Process
- The significance of this risk varies with the type of contaminant and of product being contaminated.

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION



PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

The design of facility, Air Handling Unit (AHU) or Heating Ventilation and Air Conditioning system (HVAC) and equipment is the first and crucial step in preventing contamination and cross-contamination.

Cross-contaminations shall be avoided by appropriate technical or organization measures such as those shown in the following slides:

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Facility/ design Layout

- Suitable size, construction and location: to facilitate suitable cleaning, maintenance & appropriate operation
- Smooth surfaces (no cracks, crevices or shedding) which are easily cleaned
- Adequate space for placement of equipment, production & packaging materials

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Facility/ design Layout

- Adequate segregation of materials & components to further reduce the risk of cross-contamination
- Consider the sequence of operation during the design phase; with particular attention to space & location of the equipment & removal of unnecessary traffic
- Adequate internal temperature, ventilation & lighting

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Equipment Design

- Smooth inert surfaces which are not adsorptive
- Designed and installed in areas that are easily cleaned
- If the equipment is difficult to clean, may consider using for dedicated purpose.

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Air Flow/ Extraction & HVAC System

- Dedicated HVAC System with appropriate filters in all process areas.
- **Suitable air locks** with pressure differentials.
- **Dust extraction system** (wherever applicable)
- **Risk of contaminants caused by re-circulation or re-entry of untreated or insufficiently treated air should be minimized.**
  - Air intakes should not be situated near wet drains, air exhaust or sources of dust.
  - Separate area for cleaning of filters away from AHU.
  - Air showers to ensure personnel is free from adherence of powder.

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Manufac-turing Processes

- **Campaign manufacturing, with verified cleaning processes & checks performed in-between batches**
- **Specific provisions for sampling, weighing, mixing & processing operations of crude plants whenever dust is generated.**
- **Closed manufacturing system.**
- Perform line clearance according to procedures and appropriate checklist.
- Zone the facility. E.g.: Powder vs. Liquid, internal Vs external dosage form
- Cleaning Status labeling on all equipment & materials.

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Cleaning Process

- Approved cleaning procedures of known effectiveness (verified cleaning process)
- Operators trained in the relevant cleaning procedures
- Utilities (such as water & HVAC) and services tested and monitored routinely for any microbial growth and cleanliness of supply
- Document the cleaning status of each equipment in logbooks
- Labels attached to each piece of equipment to clearly state the cleaning status

PREVENTION OF CROSS CONTAMINATION IN PRODUCTION

Personnel & Clothing

- Trained operators
  - Understanding principle of GMP)
  - Requirements for cleanliness, hygiene, control of entry.
- Changing before entry to production areas
- Personnel protective equipment (PPE)
  - Clean body coverings
  - Appropriate footwear
  - **Wearing protective clothing inside areas where products with special risk of cross-contamination are processed**
- Direct contact should be avoided between the operator and starting materials, primary packing materials and intermediate and finished products. (gloves)

STARTING MATERIALS

- Personnel in charge of starting material purchase should have sufficient knowledge of the suppliers.
- **Starting materials** shall **only** be **purchased from approved suppliers** named in the relevant specification and, where possible, directly from the producer.
- **Specifications established by the manufacturer** for the starting materials are discussed with the suppliers including:
  - all aspects of the production and control of the starting material
  - handling, labelling and packaging requirements,
  - complaints and rejection procedures etc.

STARTING MATERIALS - SUPPLIER

- Procedure or flow chart that describes methods to qualify your suppliers of each active ingredients. (Screen→ Audit→ Evaluate→ Approve→ Monitor)

- Prepare the information regarding natural ingredients (herbal) supplied, e.g.: Latin Binomial, part of ingredients used, country of origin, harvest age and common adulterants.

- Information about supplier: location, company QMS, accreditation or certification from any authorized body & etc.

STARTING MATERIALS - SUPPLIER

- Supplier Assessment
  - Supplier Audit: Conduct yourself (Inspection frequency), 3rd party (report needed)
  - Quality of materials supplied : complied with specification, duration delivery
  - Financial : pricing

- Periodic supplier assessment needed to ensure the quality of materials supplied.

STARTING MATERIALS

- The **supplier of the materials shall be** adequately **assessed** and the assessment shall be recorded.
- The **Supplier Assessment Programme** shall include:
  - The establishment of an approved supplier list which may include alternative supplier,
  - Initial assessment before placing the supplier on the approved supplier list ,
  - Periodic assessment thereafter,
  - Provision for on-site audit of the supplier premises, etc

STARTING MATERIALS

- For each delivery, the containers shall be checked for **integrity of package and seal** and for correspondence between the delivery note and the supplier's labels.

- If one material delivery is made up of different batches, **each batch shall be considered as separate for sampling, testing and release**.

STARTING MATERIALS

- Starting materials in the storage areas shall be appropriately labelled. Labels shall bear at least the following information:
  - The designated **name of the product** and the **internal code reference** where applicable
  - A **batch number** given at receipt
  - Where appropriate, the **status of the contents** (e.g. In quarantine, released, rejected)

STARTING MATERIALS

Examples of labels

(can consider using different coloured labels to facilitate easy identification of different status)

QUARANTINE			
Name of Material			
Internal Code			
Batch No. / Receiving No.			
Expiry Date			
Received Date		**Signature**	

RELEASED			
Name of Material			
Internal Code			
Batch No. / Receiving No.			
Expiry Date		**Released Date**	
Retest Date		**Released by**	

REJECTED			
Name of Material			
Internal Code			
Batch No. / Receiving No.			
Expiry Date			
Date of Reject		**Signature**	

STARTING MATERIALS

- There should be **appropriate procedures** or measures **to assure the identity** of the contents **of each container** of starting material.
- **Bulk containers** from **which samples** have been **drawn should be identified** by using labels or etc.

Sample taken
by ____ date____
Container no. __ of __

STARTING MATERIALS

Only starting materials which **have been released by** the **Quality Control Department** and which are **within their shelf life/expiry date** can be used for production.

Either 'Released' labels and/or segregated area for released starting materials could be used.

QUARANTINE				
Name of M	RELEASED			
Internal C	Name of Material			
Batch No. / Receiving	Internal Code			
Expiry Dat	Batch No. / Receiving No.			
Received	Expiry Date		Released Date	
	Retest Date		Released by	

DISPENSING/ WEIGHING OF STARTING MATERIALS

- Weighing should be carried out
  - in defined areas
  - using calibrated equipment.
  - by designated, trained personnel
  - following a written procedure

- All weighing and measurement carried out should be
  - recorded
  - independently checked by a second person

- Materials dispensed for each batch shall be kept together and conspicuously labelled as such.

DISPENSING/ WEIGHING OF STARTING MATERIALS

WEIGHING

- correct material
- correct quantity of material

DISPENSING/ WEIGHING OF STARTING MATERIALS

The weighing room/area should be:

- separated from activities of mixing, filling and warehouse
- clean, dry, well maintained and line clearance should be performed to make sure there is no unrelated material and documents

The weighing device and utensils should be:

- appropriate range and precision, and well calibrated
- appropriately verified/checked prior to use and documented at log book
- clean (balances, pails, scoops, pumps, etc.). Use of stainless steel utensils (pails, scoops, spatulas, etc.) are highly recommended because they are easier to clean, non-reactive, non-adsorptive, non-breakable.
- Clean equipment should be well identified

DISPENSING/ WEIGHING OF STARTING MATERIALS

Issuance of materials (starting and packaging) from warehouse to production :

- material request should use a dedicated documents.
- request and delivery of material should be acknowledged by supervisor of production and warehouse
- The quantity of materials released from store to production department shall be captured in warehouse documents (e.g. in the stock card), any materials returned from production department to warehouse shall be also verified (correct materials and the quantity) and duly recorded before placing back into stock.

DISPENSING/ WEIGHING OF STARTING MATERIALS

Prior the weighing process

- Check starting material name/starting material code
- Check of approved label and verify the lot number and other information (Expiry/Retest date, etc.)
- Check temperature, humidity as required
- Verify the quantity of starting materials to be weighed
- Use appropriate weighing equipment (e.g. capacity) and utensils (balance, spoon and pails)

DISPENSING/ WEIGHING OF STARTING MATERIALS

During weighing process :

- Finish one batch before weighing other batches of same material. Must perform proper cleaning and verification before weighing another type of material.
- **Weighing same starting material for different production batches/runs should be avoided.**
- Employ/use dust extractor/collector or weighing booth during weighing and dispensing operation.
- Gather and place all starting material for production of one batch of product in the same area/pallet and clearly label them with product batch identification tags.

IDENTIFICATION TAG FOR DISPENSE MATERIAL

Example for Identification tag

Name of Material				
Material Code				
Lot No. of Material				
Weight	g / kg / mL / L			
Weighed by		Date		
Checked by		Date		
Product Name		Product Batch No.		
*Crossed if not required				

WATER

- Water used as an ingredient or for final rinsing of production equipment shall be treated to minimise microbial contamination

- Why treatment is important:
  - Water quality may vary due to the source and regional/ seasonal changes e.g. rainfall, erosion, pollution, dissolution, sedimentation, decomposition
  - Must remove impurities and controlled microbes to avoid contamination to products
  - Treatment required on raw water is based on the quality of the source water

THE USE OF WATER IN PRODUCTION

- Should be treated to minimize impurities:
  - physical,
  - chemical,
  - microbiological and
  - radioactive contaminants.
- May require purification of potable water to eliminate chemicals, tastes or odors that could affect product quality
- Examples where water is used as a starting material include:
  - To produce Liquid dosage form product (e.g. Syrups, Suspension, Solution)
  - To formulate/make coating solution for other dosage forms (e.g. tablets)
  - To prepare solution to be used for granulation step
- Also used for final rinsing of equipment

THE USE OF WATER IN PRODUCTION

Treatment of water to remove physical, chemical, microbiological contaminants:

- Removal of residual particles and solids
- Optimise the pH
- Removal of metals, minerals, salts, fertilizers, contaminants
- Effectively killing or removal of biological contaminants

THE USE OF WATER IN PRODUCTION

Treated water supply to manufacturing unit should be monitored and maintained regularly to ensure consistency of quality by sample testing. An SOP should be established to describe the following:

- Water system schematic
- Labeled points of use and sampling
- Sampling technique
- Testing frequency
- Specification with limits (alert and action)
- Handling Out of Specifications (OOS)
- Corrective Actions
- Maintenance and sanitation

WATER SPECIFICATIONS

Specifications for water used in production should include (authorised and dated, specifications, including tests, content, purity and quality), but not limited to, the following:

- pH
- Conductivity
- Turbidity
- Total Organic Carbon (TOC)
- Chemical parameters
- Microbiological parameters (Total Plate Count, Yeast & Mold, Total Coliforms, E. coli, Salmonella, Staphylococcus, Listeria, Pseudomonas)

  Eg: WHO Guideline on Drinking Water Standard; ISO and national or regional agencies – regular testing needed

PROCESSING OPERATIONS

Processing procedure should describe:

- operations (such as drying, crushing, sifting etc.) carried out upon crude materials
- methods used to control particle size and remove foreign materials when necessary

PROCESSING OPERATIONS
INTERMEDIATE AND BULK PRODUCTS

Master Formula should be evaluated sufficiently (before being used) to determine its suitability for routine processing operations and the ability of the process to be reproducible.

PROCESSING OPERATIONS
INTERMEDIATE AND BULK PRODUCTS

- Production personnel should follow **defined & authorised procedures** for **every stage of** each **manufacturing process**.
- **Any deviation** from defined procedures **must be recorded & agreed upon** between the Heads of **Production Dept and QC Dept**.

PROCESSING OPERATIONS
INTERMEDIATE AND BULK PRODUCTS

Before starting any processing operation, steps should be taken to **ensure that the work area and equipment are clean and free** from **any materials, products, product residues/ documents** not required for the current operation. (Line clearance)

SAMPLE LINE CLEARANCE CHECKLIST

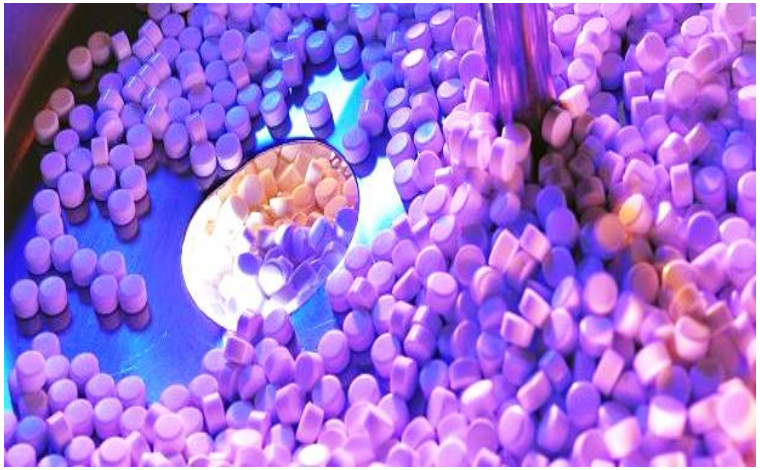
No	CHECK POINT	Yes/No	Checked by	Remark
1	Ensure that area is clean	Yes/ No		
2	Ensure that all starting and packing materials that were previously dispensed for the production of another product/batch are removed from the area	Yes/ No		
3	Ensure production equipment is clean, check for zero error and is calibrated as per SOP No. __	Yes/ No		
4	Ensure that environmental condition are maintained and recorded.	Yes/ No		Temp:_____ % RH:_____

PROCESSING OPERATIONS
INTERMEDIATE AND BULK PRODUCTS

- **All materials, bulk containers** and **major equipment** used **should be labelled/identified** with name of product/material being processed, its strength (if applicable), quantity and Batch No. **at all times.**
- All irrelevant labels/marks previously used should be removed before new labels/marks are applied to the materials/equipment.

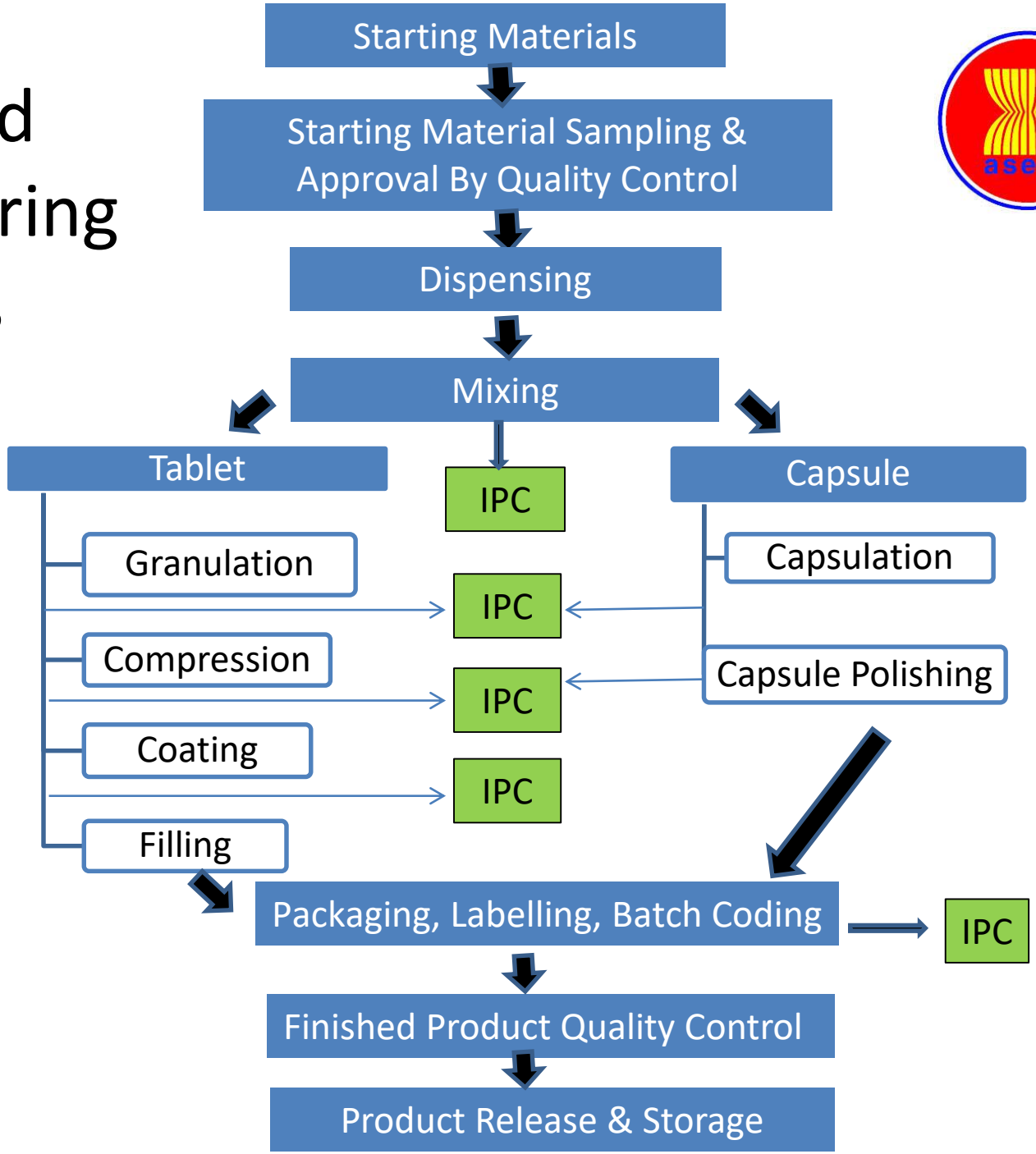
PROCESSING OPERATIONS
INTERMEDIATE AND BULK PRODUCTS

- The final yield of each production batch should be recorded and checked against the theoretical yield. Any event of significant deviation from the expected yield should be investigated before release/ further processing of the batch.

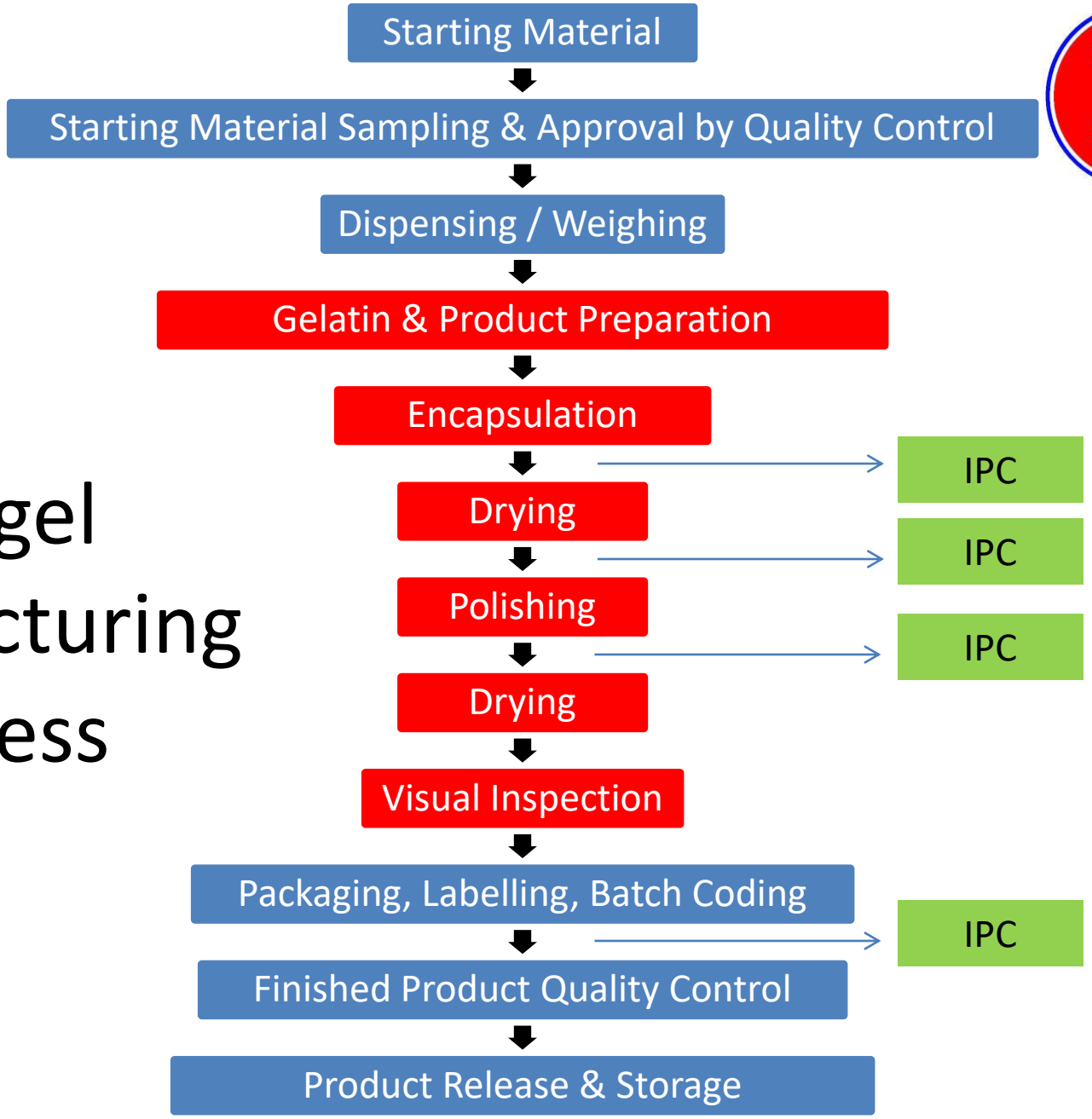


- Storage of intermediate materials and bulk products must be under controlled condition.

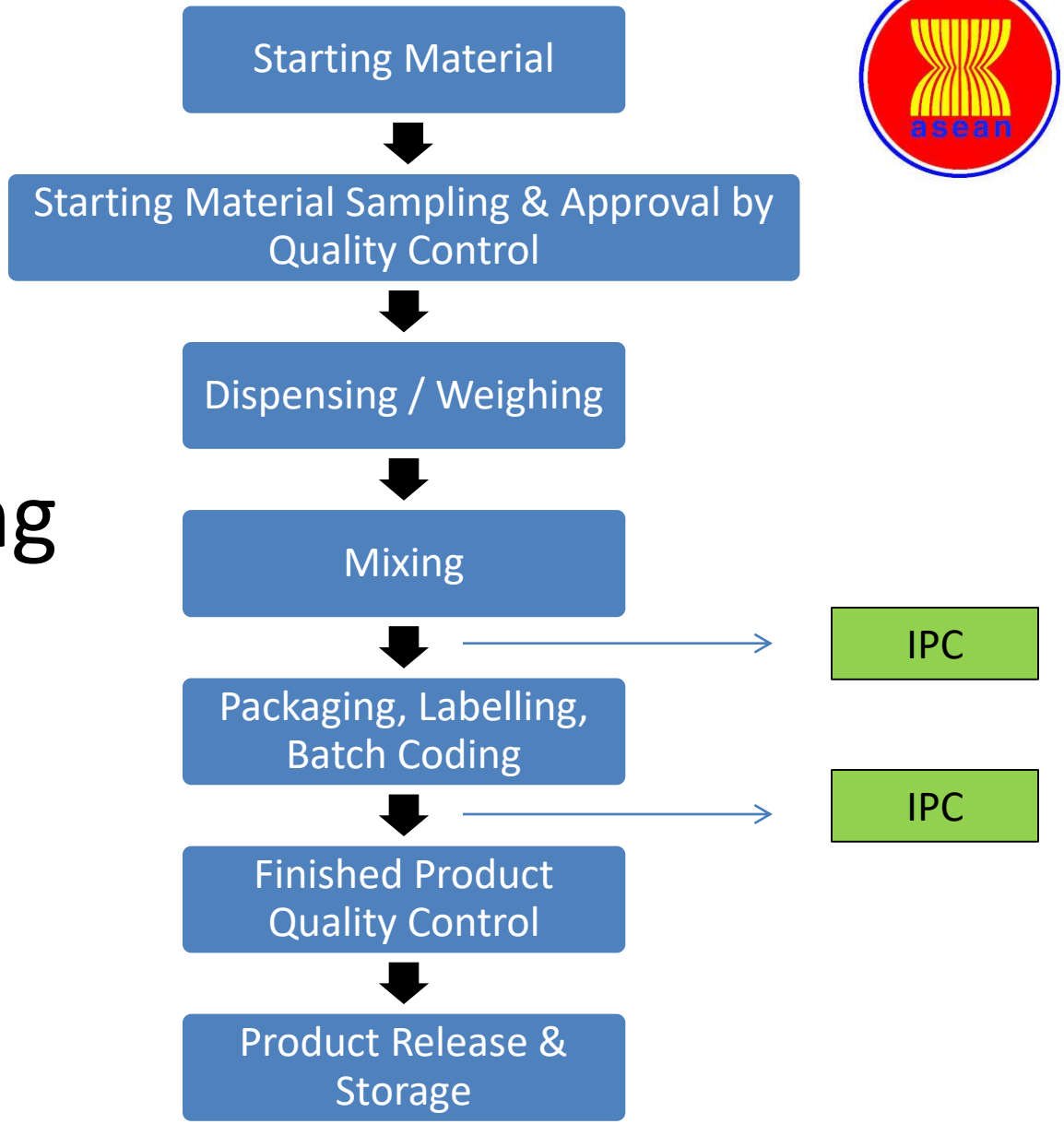
Oral Solid Manufacturing Process



Softgel Manufacturing Process



Liquid Manufacturing Process



IN-PROCESS CONTROL (IPC)

- Checks that are carried out DURING the manufacturing process.

- Includes control of
  - Equipment
  - Environment

IN-PROCESS CONTROL (IPC)

Written procedures should be established and approved by Quality Control, for example:

- Tablet or capsule weight variation
- Disintegration time
- Clarity, completeness or pH of solutions
- Moisture content
- Hardness
- Friability

IN-PROCESS CONTROL (IPC)

- Performed at **REGULAR INTERVALS**
  - **During** a process step (tableting, encapsulation)
  - **At the end** of process step (granulation, blending)

- Monitor:
  a) Critical Quality Attributes
  b) Critical Process Parameters

IN-PROCESS CONTROL (IPC)

a) Critical Quality Attributes

Performed by **documenting the following**:

- product attributes (e.g. Weight, Hardness, Friability)
- tests following completion of intermediate products

IN-PROCESS CONTROL (IPC)

b) Critical Process Parameters

Performed during **processing**, which includes:

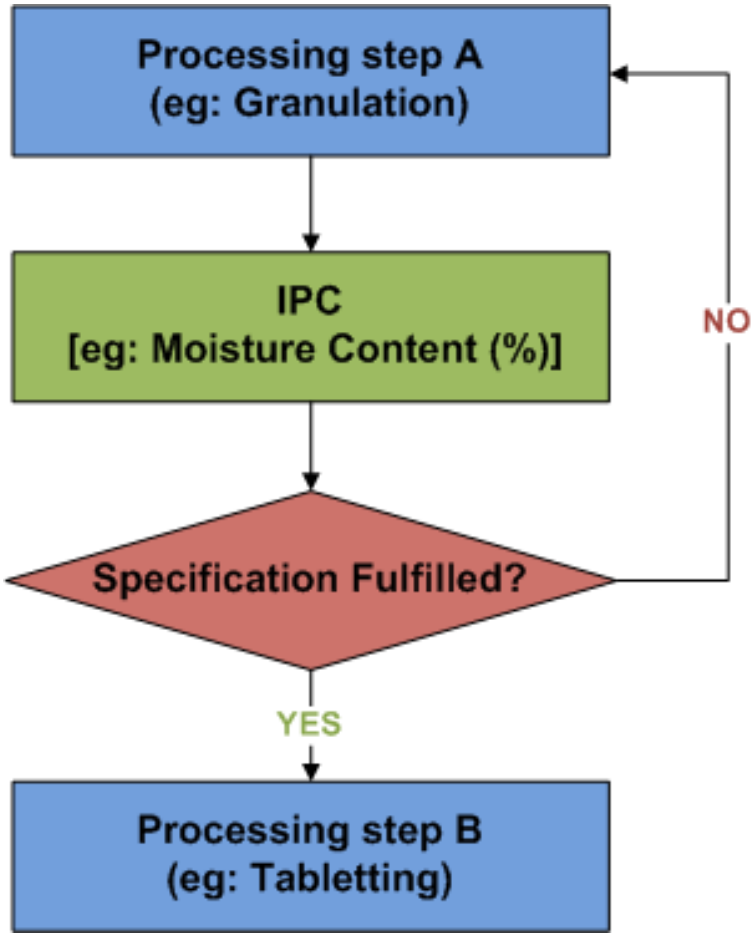
- Monitoring and recording of process parameters (e.g. time, temperature of oven/ fluid bed dryer)
- Environmental monitoring reading of the production (e.g. Temperature, Humidity)
- The results of the measurements may indicate that a corrective action is required to maintain the process and the product within the specified ranges.

IN-PROCESS CONTROL (IPC)

b) Critical Process Parameters

E.g.: Drying of granulate:

- Measurement of moisture content (to achieve specified range)
- If it is not achieved, should be handled as deviation since the process had been verified



Process control by means of In-process Control (IPC)

PACKAGING MATERIALS

- Packaging material shall only be purchased from **approved supplier**.
- Handling and control of primary and printed material shall be similar to that given to starting material.
- **Printed materials** should be **stored in secure condition** (authorise access).
- **Loose printed materials/ cut labels** stored and transported in a separate secured container to **avoid mix-up**.
- **Issuance** of packaging material only **by authorised personnel** in accordance to documented procedure.

PACKAGING MATERIALS

- Specific reference/ identification number given for each delivery or batch of printed or primary packaging material.
- **Expired/ Obsolete** packaging material should be **destroyed in accordance to procedure** and disposal **record** kept.
- Attention should be given to **minimize risk of cross-contamination, mix-ups** or substitutions.

RECAP ON KEY CONSIDERATIONS FOR STARTING AND PACKAGING MATERIALS

- Capability and responsibility of purchasing personnel
- Supplier credibility
- Checking of each consignment
- Clean and properly labeled outer packing
- Any damage on the containers
- Different batches in one consignment
- Material records and proper documentation
- Supply of correct and genuine material

RECAP ON KEY CONSIDERATIONS FOR STARTING AND PACKAGING MATERIALS

- Primary and printed materials control
- Handling of printed packaging materials (stored securely to exclude unauthorised access)
- Storage and transport to avoid mix-up
- Issued and returned packaging materials from production area
- Specific reference number for batch or consignment
- Checking and recording of packaging component
- Outdated or obsolete materials

PACKAGING OPERATIONS

- Attention should be given to **minimize risk of cross-contamination, mix-ups** or substitutions.
- **Packaging of different products in closed proximity is not permitted unless there is physical segregation.**
- **Each packaging station/lines** should be **clearly identified** (displaying name and batch number to avoid mix-ups).

PACKAGING OPERATIONS

- **Line clearance** should be done **before starting packaging operation** according to checklist.
  - All materials, products or documents from previous packaging operation should have been removed.
  - **Checks** performed **to ensure devices are clean and functional.**

- **Quantity, identity & conformity** of packaging material **upon delivery** should be **checked against the Packaging Instructions**.

PACKAGING OPERATIONS

- **Containers for filling** should be **clean before filling**. Measures shall be taken to prevent any contaminants such as glass fragments and metal particles

- Normally, filling and sealing shall be followed by labelling. If it is not the case, appropriate procedure in place **to avoid mislabelling or mix-ups**

PACKAGING OPERATIONS

- **Verification of correct performance** (code number, expiry date) **of any printing operations** done separately, checked and recorded.

- **Special precaution** must be taken **when using cut-labels and when over-printing is carried out off-line.**
  - Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups

- **Printed and embossed information** on packaging materials **should be distinct & resistant to fading or erasing.**

- Checks shall be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

PACKAGING OPERATIONS

- Samples should be **taken & checked at random** during packaging

- **Samples taken from packaging line should not be returned.**

- **Special inspection, investigation & approval** by authorized personnel required **in case reworked finished products** to be **reintroduced into the process** and detailed record kept.

- Any **unusual discrepancy during reconciliation should be investigated before product release**

PACKAGING OPERATIONS

- Any **unused batch-coded materials** should be **destroyed & recorded**.

- **Excess labels & packaging materials returned to store** should be **properly tagged/ labeled & recorded**.

- Any **rejected packaging materials** should be **disposed off accordingly and recorded.**

IN-PROCESS CONTROL – PACKAGING OPERATION

- Correct printing operation at regular intervals
  - Batch/ Lot Number
  - Expiry Date Coding

- On-line control of the product during packaging operation shall include at least
  - General Appearance of Packaging Materials (PM) and packages;
  - Whether the packages are complete;
  - Whether the correct products and packaging materials are used;
  - Whether any over-printing is correct;
  - Correct functioning of line monitors.

RECONCILIATION

- **Objective:** Ensure all materials have been accounted for and **no mix-up** occurred

- **Scope:**

  a) On printed/ coded components

  - Labels
  - Leaflets
  - Cartons

  b) Finished products

RECONCILIATION

- Calculation should be **based on ACTUAL figures**.
- **Tolerance** is allowed in relation to the materials that can be 'lost' during the process. Eg: Powder Mixing
- The finished product will be reconcile as % yield

$$\text{\% Yield} = \frac{\text{Actual Yield}}{\text{Theoretical yield}} \times 100\%$$

RECONCILIATION

- All components and product should be reconciled. However Tolerance/ Acceptable Limit can be set for finished products (taking into consideration on loss of production) but not for packaging materials.
- **Specification of Tolerance/ Acceptable Limit** should be established by the manufacturer (Process Verification)

  E.g.: Acceptable Limit for Finished Product= 90-100 %
- **ANY significant or unusual discrepancy SHALL be investigated before release.**

FINISHED PRODUCTS

Quarantine and Release

All finished products should be held in quarantine until the final release by the authorised person(s).

Evaluation

The evaluation of finished products and documentation (where applicable) before release of product for sale, not limited to:

1. Environmental monitoring result
2. Review of batch records
3. Retention samples are kept
4. Stability study samples are kept, where necessary
5. Review of test results to determine compliance with finished product specification

REJECTED COMPONENTS AND PRODUCTS

Identified and Segregated

Rejected components and products should be clearly identified and stored separately in restricted areas.

Fate of Components and Products

The rejected components and material may be returned to the suppliers, whereas rejected products may be reprocessed, where appropriate, or destroyed.

Approval and Record

Action taken should be approved and recorded by authorised personnel.

REPROCESSING/ RECOVERED PRODUCTS

Reprocessing

Only permitted if quality of final products not affected, the specification are met and if done accordance with defined and authorised procedure after evaluation of risk involved.

Recovery

- Recovery of earlier batches which met the required quality by incorporation into batch of same product at defined stage of manufacture should be authorised before hand.
- Should be carried out in accordance with defined procedure after involved risk evaluated.

REPROCESSING/ RECOVERED PRODUCTS

Records

Reprocessing and recovery should be recorded.

Additional Testing

The need of additional testing inclusive of follow-up stability for reprocessed and recovered products should be considered.

RETURNED PRODUCTS

Destroyed

Returned products which did not satisfy with the quality and specification should be destroyed.

Consideration

May be considered for re-sale, re-labeling or recovery in subsequent batch after been critically analysed by Quality Control Department accordance to written procedure.

Records

Records of action taken should be appropriately maintained.

REFERENCES

1. ASEAN Guidelines on Good Manufacturing Practice for Traditional Medicines
2. ASEAN Guidelines on Good Manufacturing Practice for Health Supplements
3. Supplementary Training Modules on Good Manufacturing Practice: Water for Pharmaceutical Use; Part 1: Introduction and treatment
4. WHO Expert Committee on Specifications for Pharmaceutical Preparations - WHO Technical Report Series, No. 908 - Thirty-seventh Report
5. PharmOut white paper: Prevention of Contamination and Cross-Contamination in Medicinal Manufacturing Facilities

REFERENCES

6. ICH Harmonised Tripatite Guideline; Quality Risk Management Q9; 9 November 2005
7. ASEAN-US Traditional Medicines and Health Supplements Good Manufacturing Practises Workshop, 18-20 November 2015

THANK YOU!

ONE VISION, ONE IDENTITY, ONE COMMUNITY