

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

## APPENDIX 2 – VERIFICATION



Prepared by:  
AAHSA AND INDONESIA

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



# OUTLINE

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## 1. Principles of Verification

- Definition
- Need
- Scope
- Risk Management
- Trend Analysis

## 2. Documentation

- Verification Programme
- Verification Protocol
- Verification Report



# OUTLINE

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## 3. Verification of Utilities

- Water system
- Heating, Ventilation and Air Conditioning (HVAC)
- Compressed Gases

## 4. Verification of Equipment and Machinery



# OUTLINE

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## 5. Verification of Process

- Production Processes
- Process Conditions and Equipment Setting and In-Process Controls
- Packaging
- Equipment Cleaning and Sanitising
- Testing & Analysis

## 6. Change Control



# Principles of Verification



# VERIFICATION DEFINITION

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ASEAN Guideline on GMP for Health Supplements and ASEAN Guideline on GMP for Traditional Medicines – Glossary

***“Confirmation, through the provision of objective evidence, that the requirements for any procedure, process, equipment, material, activity or system have been fulfilled.”***

In other words, ‘Verification’ means CHECKING that the procedure, process, equipment, material, activity or systems are consistently working, delivering results in accordance with the requirements.



# VERIFICATION

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ASEAN Guideline on GMP for Health Supplements and ASEAN Guideline on GMP for Traditional Medicines – Appendix 2 para 1.0

***“Verification shall refer to the documented act or conduct of confirmation that the control or procedure required in a particular critical aspect of manufacturing operation has been complied with or satisfactorily implemented by the manufacturer based on risk assessment and risk management”***





# VERIFICATION

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.”***



# NEED FOR VERIFICATION

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- To ensure that critical utilities, equipment, processes and control which is critical to the safety and quality of the manufactured product are consistently operating within their prescribed limits or ranges.
- It is essential that all test methods are individually verified before the product and process verification begins.



# NEED FOR VERIFICATION

ASEAN Guideline on GMP for Health Supplements and ASEAN Guideline on GMP for Traditional Medicines – Appendix 2 para 1.0

- **“Re-verification** *shall be performed:*
  - *if there are any significant changes to the facilities, systems, processes and equipment that may have impact on the quality of the finished products, and*
  - *the changes would require regulatory approval or impact on the regulatory status of the product.”*
- *“If there are no significant changes, **Periodic Review** shall be performed to show that all the aspects continue to meet the prescribed requirements.”*



# NEED FOR VERIFICATION

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- Risk assessment is one of the methods used when undertaking verification.
- A risk assessment is used to determine those areas for which greater control and regular reviews or re-verification will be most required.



# RISK ASSESSMENT AND MANAGEMENT

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- Risk Management is where the outcomes of the risk assessment are reviewed and appropriate controls are determined.
- Various tools are available to assist with risk assessment and risk management, e.g.
  - Hazard Analysis Critical Control Point (HACCP),
  - Failure modes and effects analysis (FMEA),

ICH guideline Q9 on Quality Risk Management can be used as a reference.



# SCOPE OF VERIFICATION

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- Verification of the process should cover all aspects of production and quality control, including ancillary operations (storage and distribution) of starting material and finished product, in particular ensuring that all aspects consistently achieve expected results.
- Verification of critical utilities, equipment, and machinery should be carried out prior to the verification of production process and analytical method.

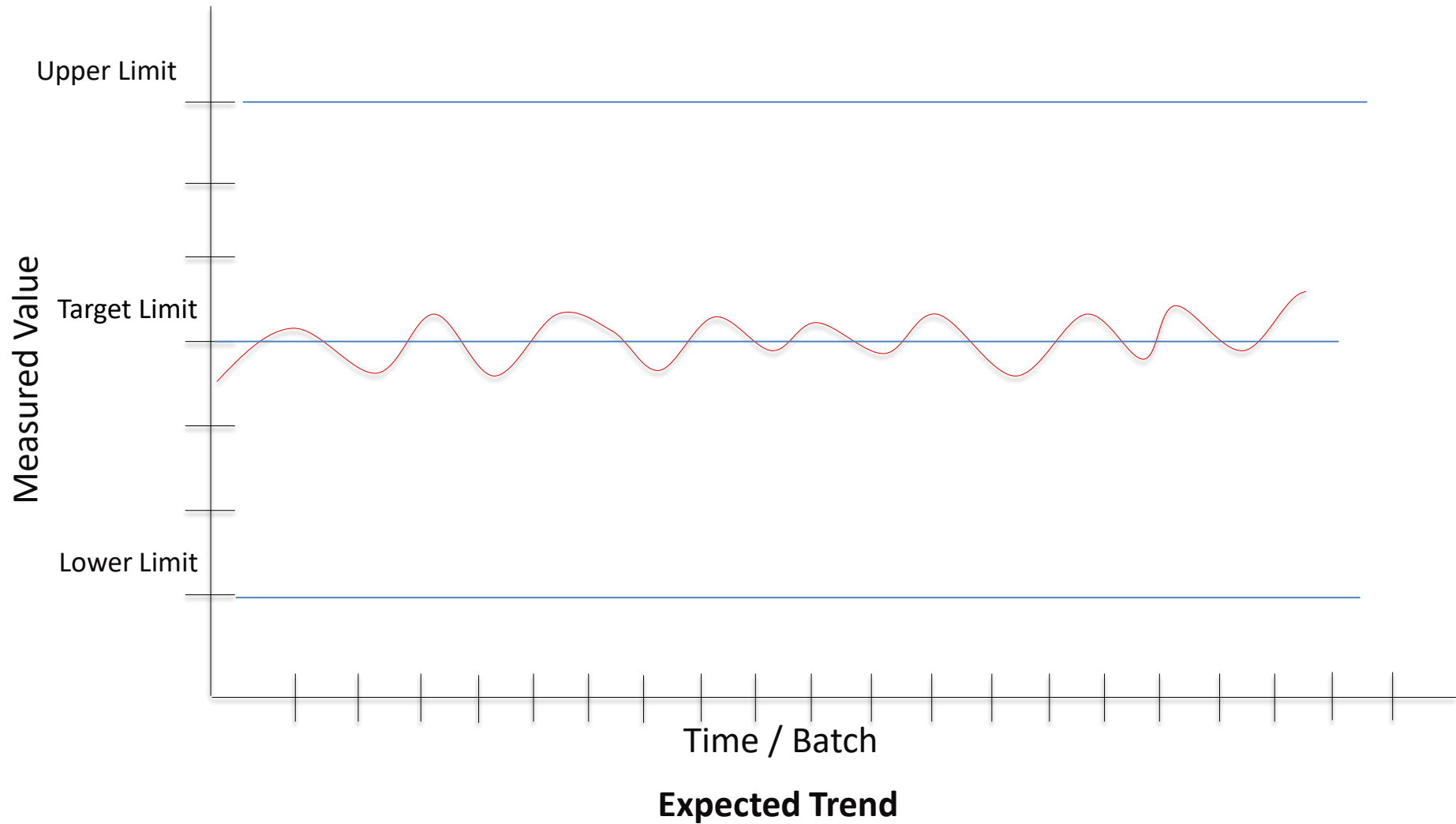


## SCOPE OF VERIFICATION (CONTINUED)

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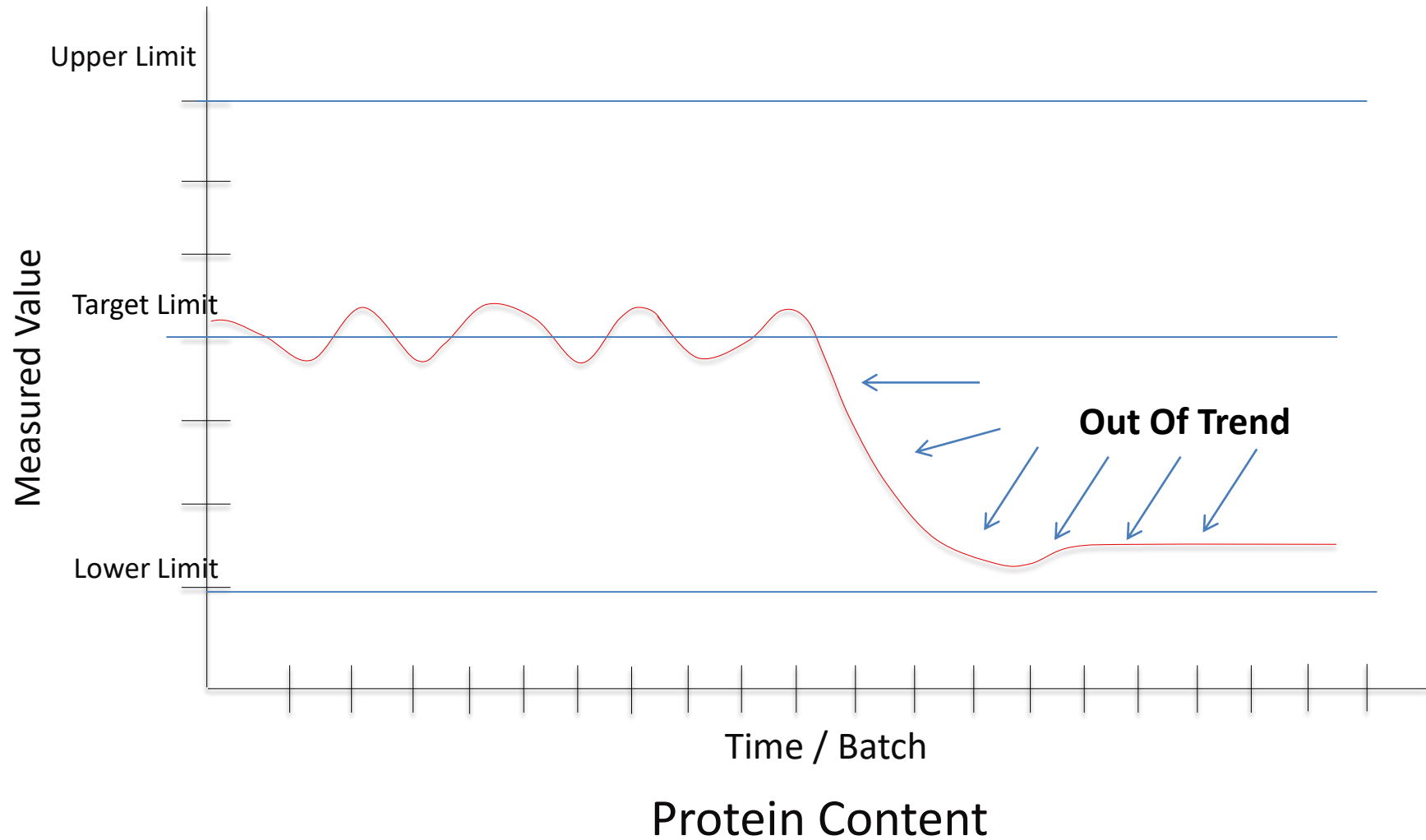
- Verification is ongoing and should constantly (periodically) review the results of the critical parameters to ensure that they consistently meet the prescribed requirements (trend analysis).
- Verification should also cover the various aspects of in-process control, product testing and analysis.

# TREND ANALYSIS

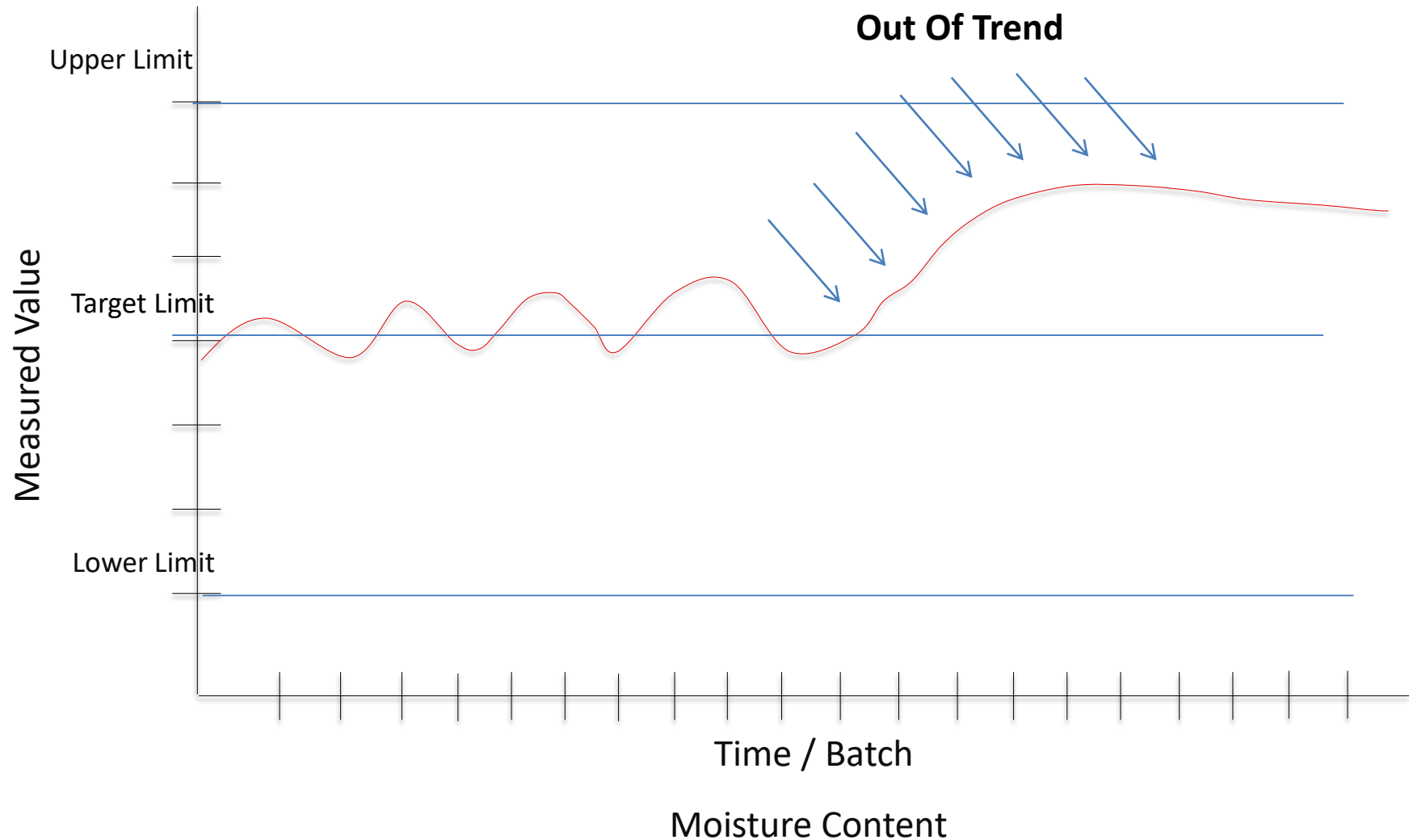




# TREND ANALYSIS



# TREND ANALYSIS





# Documentation



# DOCUMENTATION

The documents for the verification process must include:-

## 1. Verification Programme

- should include established written procedure(s) to specify how the verification activities will be carried out.
- The documentation provided will demonstrate the quality assurance (QA) systems needed to produce quality Traditional Medicines and Health Supplements.
- The documentation should state the responsibilities of the personnel undertaking the verification

## 2. Verification Protocol

- detailed written procedure for carrying out the verification;
- should include the test sample requirements, the tests to be used and acceptance criteria.
- It is essential that test protocol should be reviewed and approved by QC/QA head



# DOCUMENTATION

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## 3. Verification Report

- produced at the end of the process;
- should include:
  - confirmation that the verification protocol has been completed in full;
  - details of findings, including all analytical results;
  - details of any deviations from established procedures, investigation and CAPA(s)
  - conclusions and recommendations.



# VERIFICATION PROGRAMME

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- Issues to be addressed by the Programme include but not limited to:
  - the roles and responsibilities of personnel;
  - the training of personnel in the related procedures;
  - the management of documentation;
  - the maintenance and calibration of equipment;
  - manufacturing and laboratory control procedures.
- The organization should have a comprehensive Verification Programme.



# VERIFICATION PROTOCOL

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- Covers all the relevant aspects in written procedures;
- It specifies:
  - the responsibilities of the personnel involved in the verification;
  - the activities that are to be carried out.
  - acceptance criteria.



# VERIFICATION REPORT

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- There should be a detailed report at the end of the verification process that lists and cross-references the verification result towards protocol in detail.
- This report should evaluate and summarise all the results obtained from the cross references process.
- Any deviations or trends observed should be addressed.





# VERIFICATION REPORT (CONTINUED)

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- The conclusion(s) of verification should be made
  - Valid or not valid.
- If the conclusion is not valid, recommendations of changes (e.g. limit, process) to correct all deficiencies should be made after all deviations are thoroughly investigated and Re-verification should be carried out, in accordance to written procedure.



# DOCUMENTATION

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- It is important to verify and record that the test protocols and test methods are appropriate for:
  - the measurement of the parameters in the product and
  - for the processes being verified.



# DOCUMENTATION

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- Every aspect of the verification process must be evaluated and then documented in a systematic way to ensure that all the relevant data is retained in an appropriate manner.
- Documents should be retained in a form which:
  - allows rapid retrieval during subsequent verification exercises; and
  - permits ease of comparison of the data, between the current verification and previous ones.



# DOCUMENTATION

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- It is important that the full details of the protocol/procedure for each analytical or sensory test used in the verification process are retained in an accessible form.
- Any minor modifications or specific sample preparation procedures must be given in detail.



# EXAMPLE OF A VERIFICATION PROTOCOL

## 1. PURPOSE or OBJECTIVE

## 2. SCOPE

- Equipment or processes included
- Limits / Ranges

## 3. REFERENCES

- Regulations
- Internal documentation (SOPs *etc.*)

## 4. RESPONSIBILITIES

- Protocol leader / team (training confirmed as per verification programme)

## 5. VERIFICATION PLAN

*(for each piece of equipment or process)*

- Description of equipment or process
- Risk assessment (define criticality of systems or components)

- Pre-requisite programmes, as applicable (cleaning, operational SOPs *etc.*)

As applicable:

- Installation verification
- Operational verification
- Performance verification
- Cleaning verification

## 6. VERIFICATION SUMMARY

*(for each piece of equipment or system)*

- Corrective actions taken

## 7. PERIODIC REVIEW or RE-VERIFICATION



# EXAMPLE OF A VERIFICATION PROTOCOL

## (TABLE FORMAT)

- Scope
  - Systems included
- Defining critical components
  - Boundaries
- References
  - Regulations
  - Internal Documentation (PM system, Change Control, etc)
- Responsibilities
  - Protocol Owner
  - Training requirements

Specific Activity	Classification of Activity	Verifying Employee	Frequency	Outcome	Corrective Actions



# Verification of Utilities



# VERIFICATION OF UTILITIES

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- All key utility supplies, for example:
  - water
  - heating ventilation air conditioning (HVAC)
  - compressed gases (e.g. air, N<sub>2</sub>, CO<sub>2</sub>)

should have established operating procedures to ensure their continuous and efficient operation.

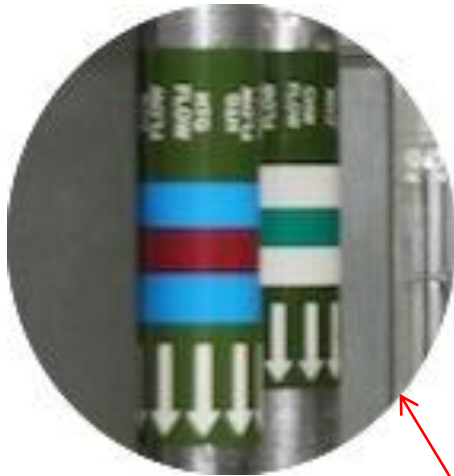




# VERIFICATION OF UTILITIES

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- All pipework for the transport of utilities should be clearly marked or labelled with appropriate colour coding.
- The direction of flow should also be indicated.



Example of colour coding and flow marking





# WATER SYSTEM

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- Verify that only treated water is used in the production and for any processing of the product.
  - Quality of treated water refer to NRA (National Regulatory Authority) requirements or alternatively to the 'WHO GMP: Water for Pharmaceutical Use' as a general guide
- In some cases higher standards, such as de-ionised, ultra-violet, RO treated water, may be required for certain operations.

**PURIFIED  
WATER**

**PROCESS  
WATER**

Example of how pipework for water used for different purposes can be separated and clearly labelled.



# WATER SYSTEM

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- The quality of the treated water should be verified at regular intervals.
- Checks should cover
  - physical parameters (e.g. flow rates, colour and odour),
  - chemical (e.g. conductivity, pH and TOC), and
  - microbiological tests (e.g. total microbial count and absence of Coliforms and *P. aeruginosa*).
- Documentation should be maintained and retained to show that all water used in production met the requirements.



# WATER SYSTEM

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- Verify that all fixed pipework for the water system is clearly labelled to indicate the content and direction.
- Pipework should be inspected at intervals for damage or leaks. Any faults found should be reported and rectified.
- If the water system is interrupted for rectification of faults, water samples should be taken to verify that the water quality is maintained prior to use.
- Pipes, hoses, pumps, and valves used for treated water shall be cleaned and sanitized according to written procedure that detail the action limit for microbiological contamination and the measures to be taken.



# HEATING, VENTILATION AND AIR CONDITIONING (HVAC)

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- For HVAC requirements refer to NRA regulation
- It should be verified that all components of HVAC are installed and operating within their manufacturers specifications and not using excess energy.
- Filters should be monitored and replaced as per manufacture's requirement and records should be retained.
- Records of all HVAC repair and maintenance should be retained in an accessible form.



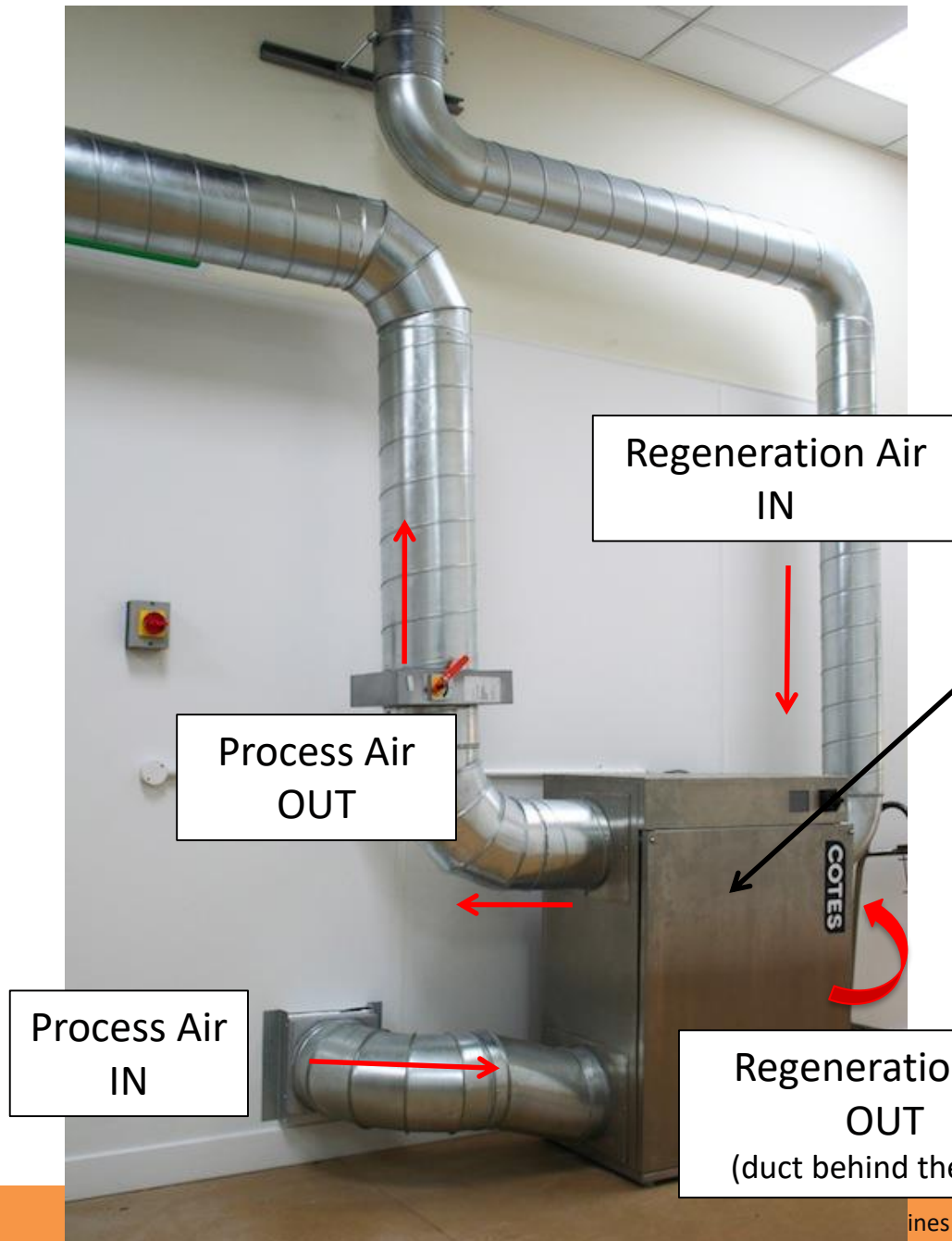
# HEATING, VENTILATION AND AIR CONDITIONING (HVAC)

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- Verify that all production areas, microbiology laboratory and warehouses are ventilated with the appropriate air control facilities such as:
  - temperature
  - humidity
  - air filtration



## Example of HVAC containing a dehumidifying filtration system



The process air enters the system unit and passes through a filter. The unit contains a slowly turning rotor coated with silica gel, which absorbs the water molecules present in the process air passing through it. In a designated 'regeneration zone' within the unit, the saturated rotor is then dried with a separate flow of heated air (the regeneration air). The warm, humid regeneration air is then led away, and the rotor is once again ready to absorb water.



# HEATING, VENTILATION AND AIR CONDITIONING (HVAC)

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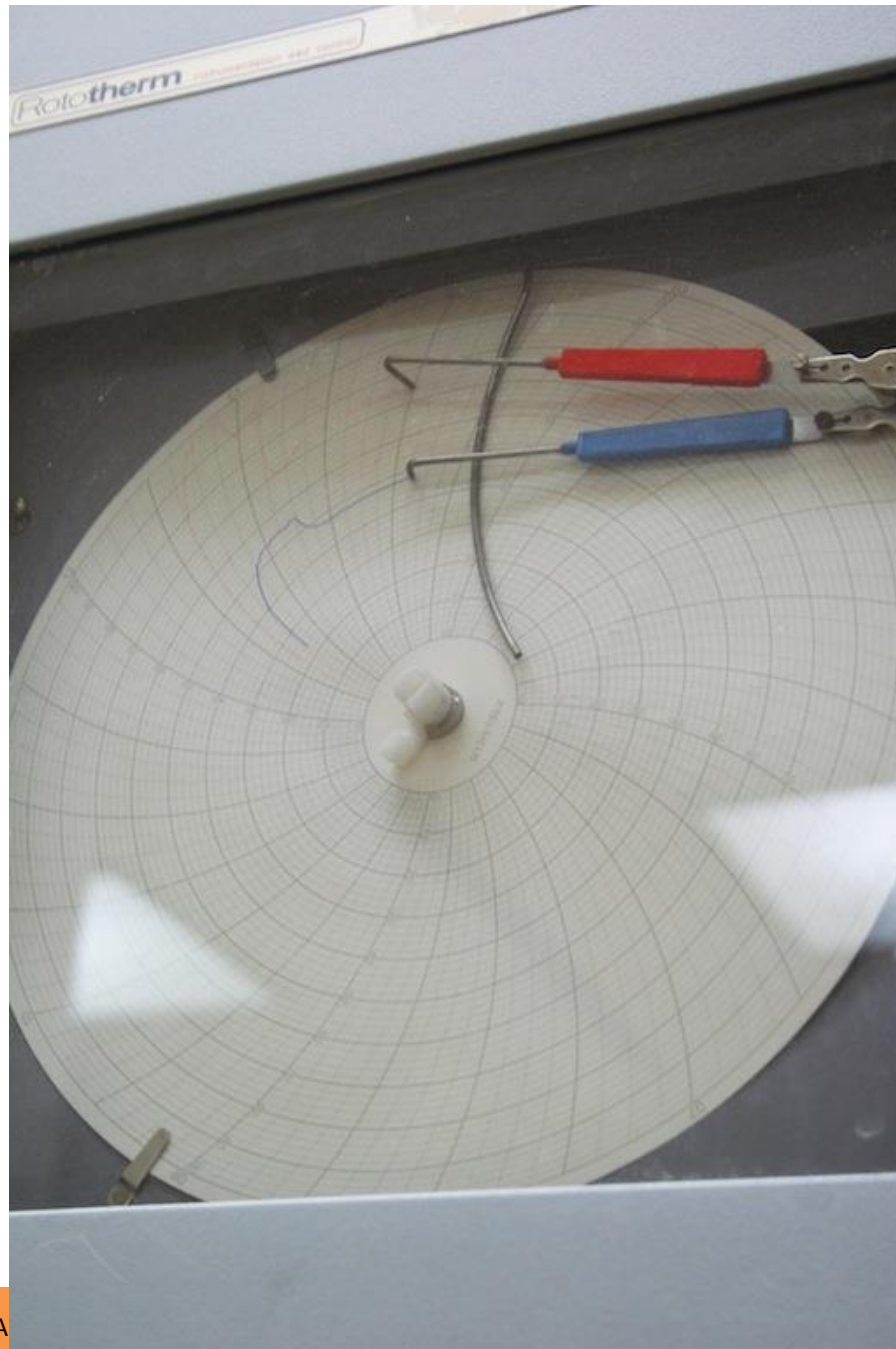
- Verify that :
  - the intake of noxious vapours, gases, dust or other solids into production facility, has been prevented by means of suitable filters.
  - the extraction system is avoiding nuisance to the local environment in the form of odour, dust or noise, and further contamination to the production facility.



# HEATING, VENTILATION AND AIR CONDITIONING (HVAC)

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- Verify that:
  - the instruments for the monitoring and/or recording of the temperature and humidity have been placed in appropriate positions in the warehouse, production and packing areas.
  - the instruments for monitoring the pressure difference (for example, in the processing and primary packaging sections and in the microbiology laboratory) have been installed in appropriate areas.
  - the instruments for monitoring and/or recording have been periodically calibrated.
- The records should be inspected and retained, and it should be verified that any unusual fluctuations have been investigated and rectified.



Example of temperature and humidity recording pens and chart



# COMPRESSED GASES

- Verify that, where compressed air and/or gases are required in the manufacturing or packaging areas, the storage and use of the gases comply with all the safety requirements.





# COMPRESSED GASES

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- Compressed air and/or gases must only be handled, used and inspected by personnel who have received the appropriate safety training.
- Records of the training and refresher training should be retained.



# COMPRESSED GASES

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- Where the air or gas is supplied in cylinders, each cylinder should be marked with the identity of the contained gas and appropriate hazard warnings.
  - This is particularly important for inflammable gases.
- Storage of the cylinders should be in a well ventilated area.
- Cylinders should not be subjected to extremes of temperature.



# COMPRESSED GASES

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- Pipelines carrying compressed gas from cylinder to point of use should be marked with the type of gas and direction of flow.
- Gas cylinders and pipework must be checked regularly for damage or leakage. Records of these inspections should be retained.
- Verify that the cylinders for the compressed gas are identified and that the quality of the compressed gas, the flow rate and pressure are within the specified limits.





# Verification of Machinery and Equipment



# VERIFICATION OF MACHINERY AND EQUIPMENT

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- Machinery and Equipment that have a direct impact on quality should be verified, for both
  - processing and
  - packaging equipment.
- Verification of Machinery and Equipment consists of :
  - Installation
  - Operation
  - Performance



# VERIFICATION OF MACHINERY AND EQUIPMENT

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- Machinery and Equipment to be used should be verified before the verification of the production and control process.
- Machinery and Equipment used in the manufacture of product must be periodically verified, especially when there is a significant change. e.g:
  - replacement of spare parts which affect to machine/equipment performance
  - After repairto ensure they are operating within the acceptance criteria.



# VERIFICATION OF MACHINERY AND EQUIPMENT

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- Verify that
  - there is a manufacturer's operating manual for each processing and packaging machine and ancillary equipment, and that the company's operating procedures are consistent with the requirements of the manufacturer's manual.
  - all calibrated equipment/measuring devices settings and tolerances are in accordance with the operating range.



# VERIFICATION OF MACHINERY AND EQUIPMENT

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- All personnel taking part in the verification work must be appropriately trained in the operation of the equipment and machinery before commencement of the verification exercise.
- All measuring devices installed on the equipment and machinery, or used for the verification process, should be in the calibrated state before the commencement of verification.
- Where appropriate, it is important to use calibrated reference material for calibration of the measuring device.



# VERIFICATION OF MACHINERY AND EQUIPMENT

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- It should be verified that machinery and equipment which may come into contact with ingredients or product are not reactive, additive or absorptive.



# VERIFICATION OF MACHINERY AND EQUIPMENT

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## Installation Verification

- Installation Verification should be performed on equipment, facilities, utilities, or systems.
- Installation Verification should include, but is not limited to the following:
  - i. Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;
  - ii. Verification of the correct installation against pre-defined criteria;
  - iii. Collection and collation of supplier operating and working instructions and maintenance requirements;
  - iv. Calibration of instrumentation;
  - v. Verification of the materials of construction.



Example of a tablet press and its ancillary equipment placed in an isolated area





Example of a granulator placed with sufficient space around it to reduce cross-contamination



# VERIFICATION OF MACHINERY AND EQUIPMENT

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## Operational Verification

- Operational Verification normally follows Installation Verification but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Verification
- Operational Verification should include but is not limited to the following:
  - i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;
  - ii. Tests to confirm upper and lower operating limits, and/or “worst case” conditions.
- The completion of a successful Operational Verification should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements.



# VERIFICATION OF MACHINERY AND EQUIPMENT

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## Performance Verification

- Performance Verification should normally follow the successful completion of Installation Verification and Operational Verification. However, it may in some cases be appropriate to perform it in conjunction with Operational Verification or Process Verification.
- Performance Verification should include, but is not limited to the following:
  - i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;
  - ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.



# Verification of Process



# VERIFICATION OF PROCESS

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## Outline

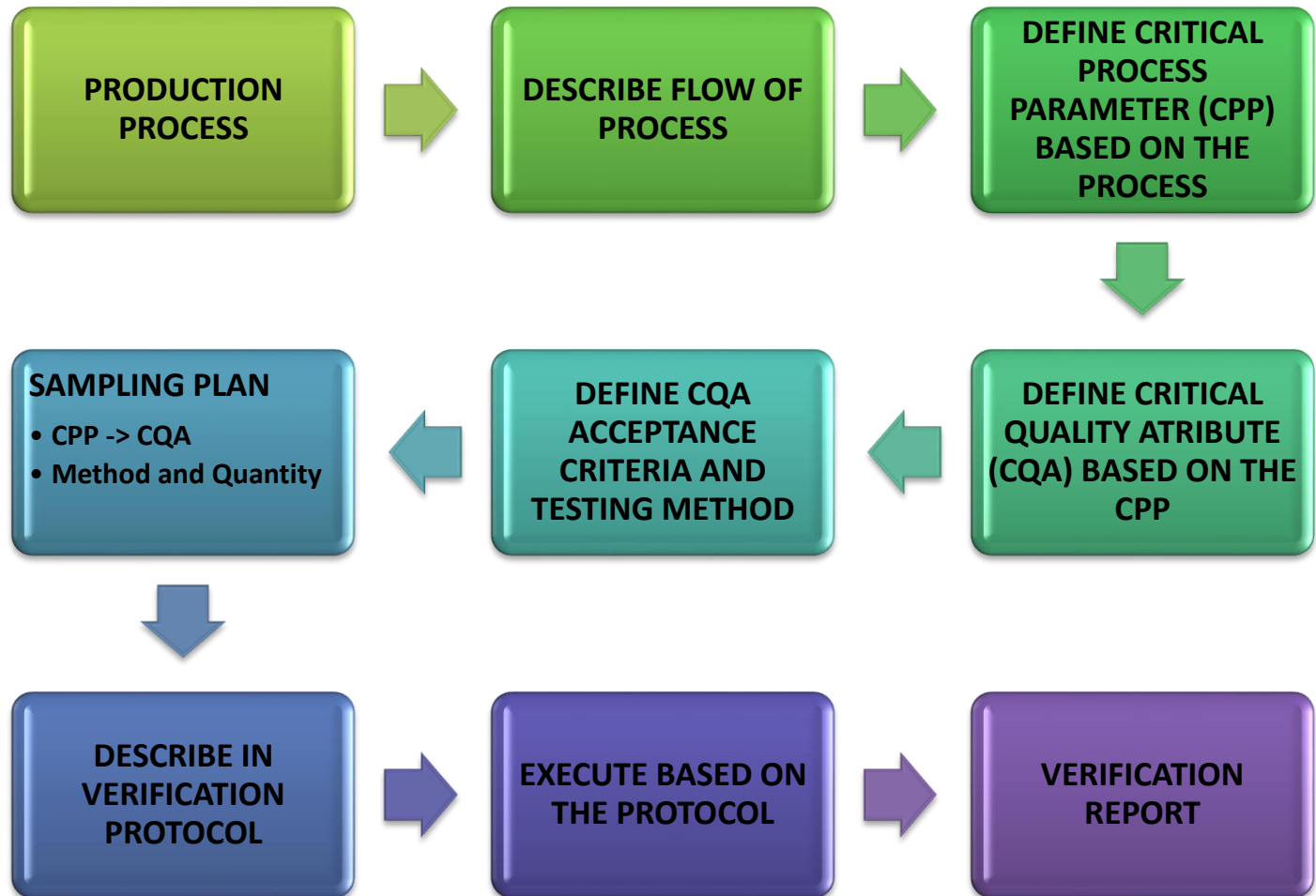
- Verification of Process
  - Production Processes (e.g. powder mixing for tablets)
  - Process Conditions , Equipment Setting and In-Process Controls
  - Packaging
  - Equipment Cleaning and Sanitising
- Verification of Testing and Analysis

*\* For Verification of Ingredients, Weighing and Dispensing, please refer to Chapter 6 – Production for details.*



# VERIFICATION OF PRODUCTION PROCESS

## FLOW OF PROCESS VERIFICATION





# VERIFICATION OF PRODUCTION PROCESS

## **CRITICAL PROCESS PARAMETER (CPP)**

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

## **CRITICAL QUALITY ATTRIBUTE (CQA)**

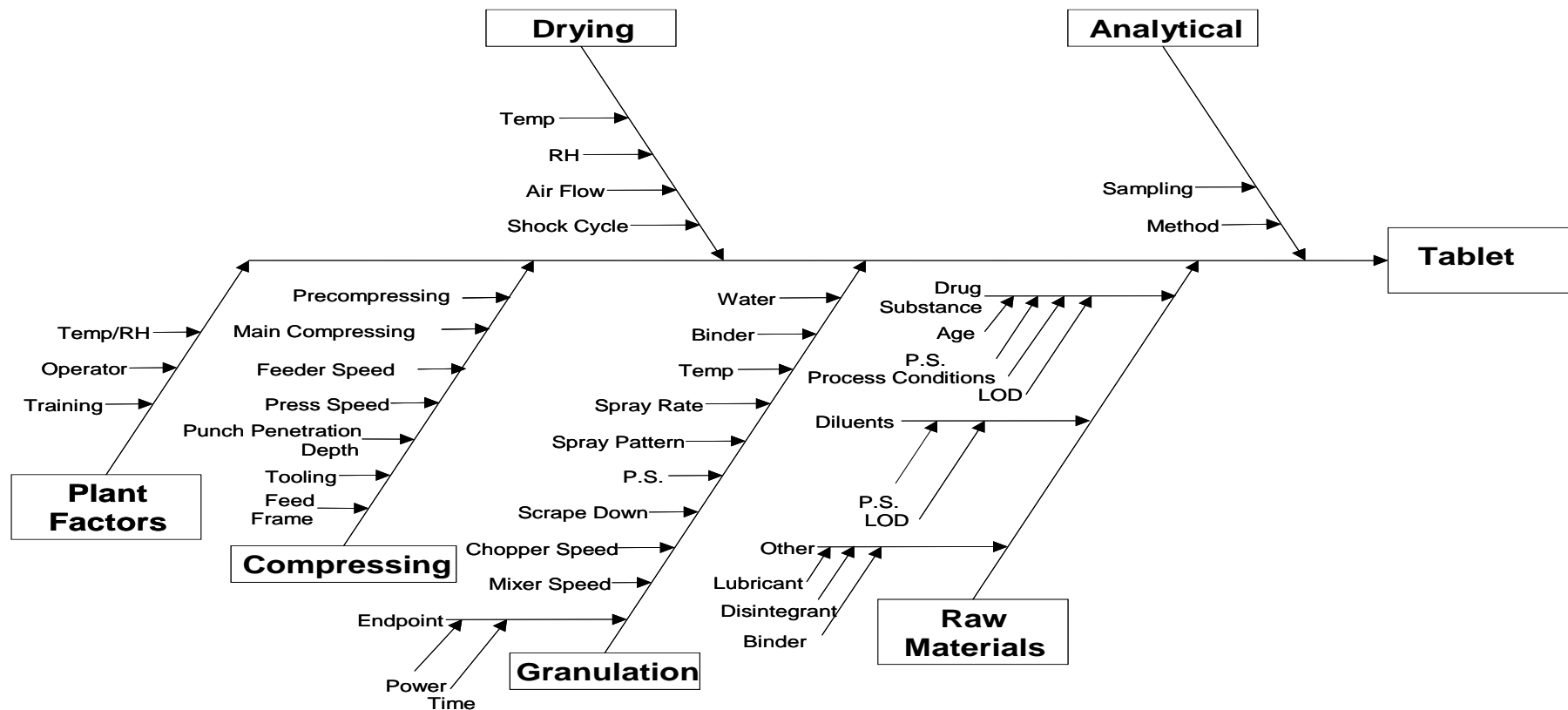
A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality.

*Source: ICH Q8 Pharmaceutical Development*



# VERIFICATION OF PRODUCTION PROCESS

- An example of CPP



Source : ICH Q8 Pharmaceutical Development





# VERIFICATION OF PRODUCTION PROCESS

**EXAMPLE**

## FLOW OF PROCESS -Tabletting





# Verification of Production Process

**EXAMPLE**

FLOW OF PROCESS	CRITICAL PROCESS PARAMETER (CPP)	CRITICAL QUALITY ATTRIBUTE (CQA)	ACCEPTANCE CRITERIA
Mixing and Granulation	Time Speed	Flow property	Based on defined angle of repose
		Blend Uniformity	Visually uniform granules and Active content 90-110%
Tabletting	Pressing speed Compression force Moisture of material Granules flow property	Weight of tablet Thickness Hardness Friability Disintegration Content uniformity	Define in Product Specification



# VERIFICATION OF MIXING PROCESS

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- To ensure that the ingredients are present in each dose in the required amount, the mix must be homogenous; that is, all ingredients should be in the same ratio in any given weight of the product (homogeneity).
- Mixing process will be affected by the powder characteristics such as:
  - Range of ingredient powder densities and particle sizes;
  - Range of ingredient powder surface and shapes.
- Trials should be carried out on every new product powder mixture, to ensure homogeneity can be achieved.



# VERIFICATION OF MIXING PROCESS

- An analogous example of a range of powder characteristics.





# VERIFICATION OF MIXING PROCESS

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- Verify that homogeneity can be achieved by using the mixer and assigned mixing conditions.
- Where appropriate, verify that trials have been carried out on production batch sizes to check for de-mixing during in-process handling and packing.

## EXAMPLES OF TWO OF THE MANY TYPES OF MIXERS THAT MAY BE USED FOR MIXING POWDERS.



A double-cone powder mixer  
(tumble blender)

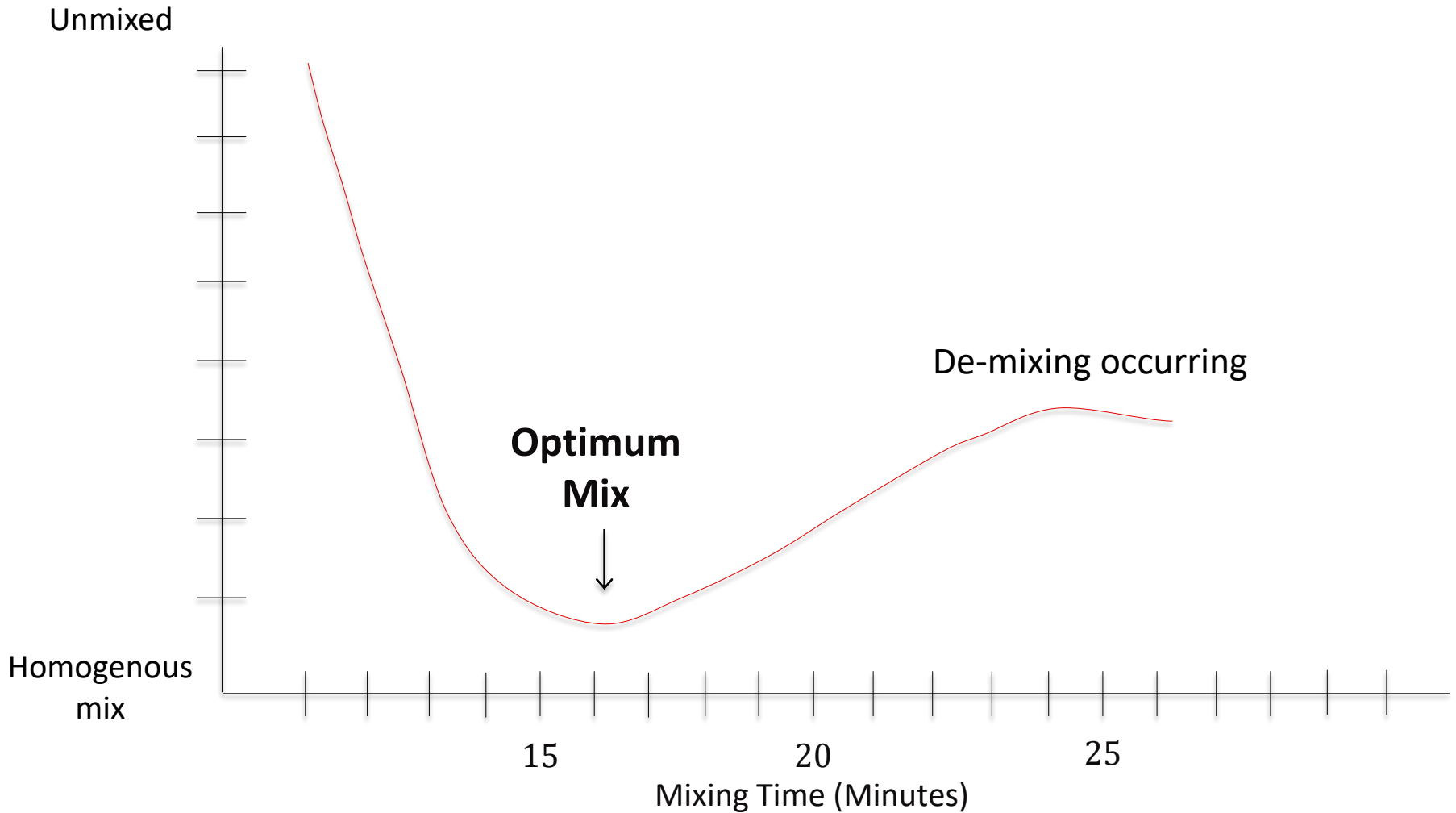
Tumble blending offers the lowest shear method of mixing friable or delicate solids. The simple double-cone or V-designs provide complete discharge and, because there is no agitator, there are no seals and they are easily inspected and cleaned.



A heavy duty ribbon mixer

The moderate shear of the ribbon naturally breaks down lumps and agglomerates. The horizontal ribbon mixers are generally reliable, fast and economical. Discharge of finished product from the blender is typically done by gravity with assistance from the ribbon agitator. A small quantity of material always remains in the blender. Removal of the ribbon or paddle may be required for cleaning for highly sensitive applications.

# Powder Mixing





# VERIFICATION OF MIXING PROCESS

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- For some powders, homogeneity can only be achieved with clearly defined conditions such as batch size and weight of ingredients, mixing speed and mixing time.
- If these conditions are not observed and defined, partial mixing can occur.
- Exceeding the conditions can also result in a non-homogenous mix.





# VERIFICATION OF MIXING PROCESS

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- The handling of a mixed powder during and after discharge from a mixer can induce de-mixing.
- De-Mixing
  - De-mixing of a homogeneous powder can occur at various stages of handling.
  - Some of the most common are:
    - Gravity discharge from a mixer into a container.
    - Screw or air transported closed conveying systems.
    - Discharge into hoppers above tableting and encapsulating machines.
    - During gravity feed from hoppers into tableting / encapsulating machines.
  - Numerous literature resources are available to explain powder handling and mixing.



# VERIFICATION OF MIXING PROCESS

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- It should be verified that the integrity of the homogeneous mix is retained after mixing and until the powder is incorporated into the final product.
- Verification of integrity requires a sampling procedure specific to each mixer.

Feed to hopper

Vertical drop  
from hopper  
to tablet press

De-mixing may  
potentially occur  
within the feed to  
hopper and in the  
drop from the  
hopper to the  
tablet press

Air conveying  
equipment

Illustration of where de-mixing  
may potentially occur





# VERIFICATION OF PROCESS

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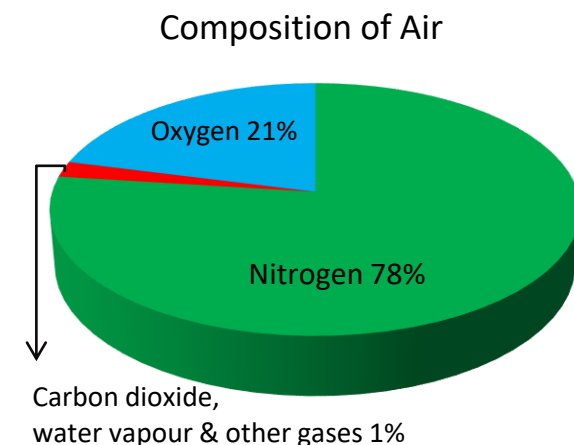
## **Process Conditions, Equipment Setting and In-Process Controls**



## PROCESS CONDITIONS AND EQUIPMENT SETTING AND IN-PROCESS CONTROLS

Verify that all ingredients and products are protected from the effects of moisture and oxygen during storage and the manufacturing processes, for example:

- A number of ingredients, such as spray-dried ingredients, can be hygroscopic and absorb and retain moisture from the atmosphere.
- Some products, such as effervescent tablets, are also hygroscopic and require de-humidified conditions during the production process.
- A number of ingredients commonly used in health supplements, such as some vitamins, are sensitive to atmospheric oxygen and must be protected and not exposed to air during storage and manufacturing.





## PROCESS CONDITIONS, EQUIPMENT SETTING AND IN-PROCESS CONTROLS

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- Verify that all ingredients and products are protected from the effects of light during storage and the manufacturing processes, for example:
  - Some ingredients, particularly vitamin B2, can be degraded by the ultra-violet component of light.
  - These ingredients, and products containing them, should not be unnecessarily exposed to natural light or certain forms of artificial light.





## PROCESS CONDITIONS, EQUIPMENT SETTING AND IN-PROCESS CONTROLS

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- It should be verified from trial and production data that all equipment settings such as:
  - time
  - speed
  - temperature
  - Residence/holding timeare optimum for product consistency and quality.
- Verify that the selected process conditions can consistently maintain product quality and safety within the required parameters.

## EXAMPLE OF A MECHANICAL CONTROL PANEL WITH BUTTONS (THIS ONE IS ON A GRANULATION MACHINE)





## EXAMPLE OF AN ELECTRONIC CONTROL SYSTEM ON A COMPUTER SCREEN

(This one is for a tableting machine)

Whether control is managed via manual buttons or an electronic control system on a computer screen will depend upon the specific types of equipment.

Both forms of control require correct procedures for operation, and the equipment settings must be verified.





## PROCESS CONDITIONS, EQUIPMENT SETTING AND IN-PROCESS CONTROLS

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- It should be verified that the in-process control procedures are appropriate and valid for the maintenance of product consistency.
- Verification and in-process control should be carried out using relevant statistical techniques.



## PROCESS CONDITIONS, EQUIPMENT SETTING AND IN-PROCESS CONTROLS

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- It should be verified that there is a procedure for the routine performance of a 'mass balance' to ensure the yield of material is within acceptable limits.
  - A 'mass balance' (sometimes called a 'material balance') accounts for the material entering and leaving a process. It measures the difference between the total weight or volume of all ingredients entering the process and the weight or volume of the product coming out.



# VERIFICATION OF PROCESS

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## Packaging



# PACKAGING PROCESS

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- Verify that the appropriate packaging process and materials have been selected for the specific product.
- Primary packaging: for example, bottling, blister packing, pouch packing.
  - Verify that there is evidence that the process and material chosen are appropriate for the safety, quality and stability of the product.
- Secondary packaging into distribution units / Stock Keeping Unit (SKU) : for example, manual or automatic cartooning machine.



# PACKAGING PROCESS

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- Verify that appropriate in-process controls of primary and secondary packaging are in operation. For example:
  - Seal / leakage tests;
  - Torque tests;
  - Visual controls for package defects;
  - Confirmation of content quantity, e.g. weight or number.



# PACKAGING PROCESS

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- Verify that the packaging process is operating effectively at the optimum speed with the minimum level of rejected packages.
- Verify that records are kept for all packaging operations.



# PACKAGING PROCESS

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- Such records (packaging record) should include details of:
  - the product that was packed, including all reference and batch numbers and expiry date;
  - confirmation that the correct packaging and labels were used:
    - this should be signed by a responsible person;
  - batch numbers and expiry dates applied to each packaging run or period;





# PACKAGING PROCESS

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- It should be verified that procedures are in place to ensure that:
  - only authorised personnel have access to the packaging/label stores.
  - the labels issued for packaging are those for the particular product and that this has been checked by the authorised person;
  - there is a secured system for the issue of labels from the store and for the return of unused labels to the store;
  - appropriate records are maintained for the transfers to and from the store;



# PACKAGING PROCESS

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- that there is a reconciliation procedure accounting for:
  - the number of packs/labels issued to production;
  - the number of units packed;
  - the number of waste packs/labels; and
  - the number of packs/labels returned to the store.



# PACKAGING PROCESS

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- It should be verified that:
  - there is full identification accompanying each delivery/batch of packaging, such as to identify the packaging at all stages of storage, packaging and return to store;
  - that each label or label pack contains a code, or similar means of unique identification, which cross-references it to the product formulation;



# VERIFICATION OF PROCESS

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## Equipment Cleaning and Sanitising



# EQUIPMENT CLEANING AND SANITISING

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- Verify that appropriate procedures are in place for the cleaning and sanitising of all processing, packaging and ancillary equipment immediately after they have been used.
- Verify that the procedures are being carried out, inspected and signed off by the responsible person.
- Records of all cleaning and sanitising operations should be retained in an easy accessible form.



# EQUIPMENT CLEANING AND SANITISING

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- Cleaning procedures should be specific to each item of machinery and equipment and should take into account:
  - the removal of all product residue after each processing/packaging operation or at the end of a prescribed period;
  - any specific precautions where known allergens may have been present in the product or material that was previously processed or packed (as required by the NRA);
  - the sanitising to remove or prevent microbiological contamination, including details of the concentrations of sanitising agents and holding time.
  - the removal of all cleaning and sanitising residues.



# EQUIPMENT CLEANING AND SANITISING

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- Verify that there are written procedures containing details of the cleaning and sanitising agents to be used on specified equipment;
  - The procedures should include any hazard risks, health and safety requirements and personal protective equipment (e.g. mask, gloves) required.
- Verify that the written procedures contain detailed dilution requirements for the cleaning and sanitising agents.



# EQUIPMENT CLEANING AND SANITISING

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- Verify that tools and utensils used for the cleaning and sanitising are clearly specified, e.g. 'brush: soft/medium/hard', especially for manual cleaning.
- Also verify that there are relevant cleaning procedures for the tools and utensils.



Example of cleaning equipment storage area with clearly labelled equipment that is colour coded for the different areas of use.





# EQUIPMENT CLEANING AND SANITISING

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- It should be verified that all personnel involved in the cleaning and sanitising of the equipment are appropriately trained for their duties, including the handling of hazardous cleaning and sanitising agent.
- Records of the training should be available for inspection.



# VERIFICATION OF CLEANING AND SANITISING

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- Verification of cleaning and sanitising operations should include:
  - visual checking of difficult to clean areas, such as joints, for product/material and allergen residues (as required by the NRA);
  - testing of product/material contact surfaces for cleaning and sanitising agent residues, (using procedures appropriate for the relevant agent);
  - microbiological testing of product/material contact surfaces.



# VERIFICATION OF PROCESS

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## Testing & Analysis



# TESTING & ANALYSIS

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- Verify that written procedures based on the principles of Good Quality Control Laboratory Practice are available for all aspects of laboratory testing (chemical, physical and microbiological) and that there are records to show that these procedures are being followed.



# TESTING & ANALYSIS

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- Verify that Quality Control procedures are available for the releasing, rejecting or quarantining of starting materials, packaging materials and products.
- Also verify that the final decision is signed off by an authorised person.
- Details of all results of tests should be retained in an easily accessible form.



# TESTING & ANALYSIS

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- Verify that all Quality Control:

- written procedures;
- test methods;
- laboratory equipment;
- sampling methods; and
- sampling plans

are appropriate for the products being manufactured.

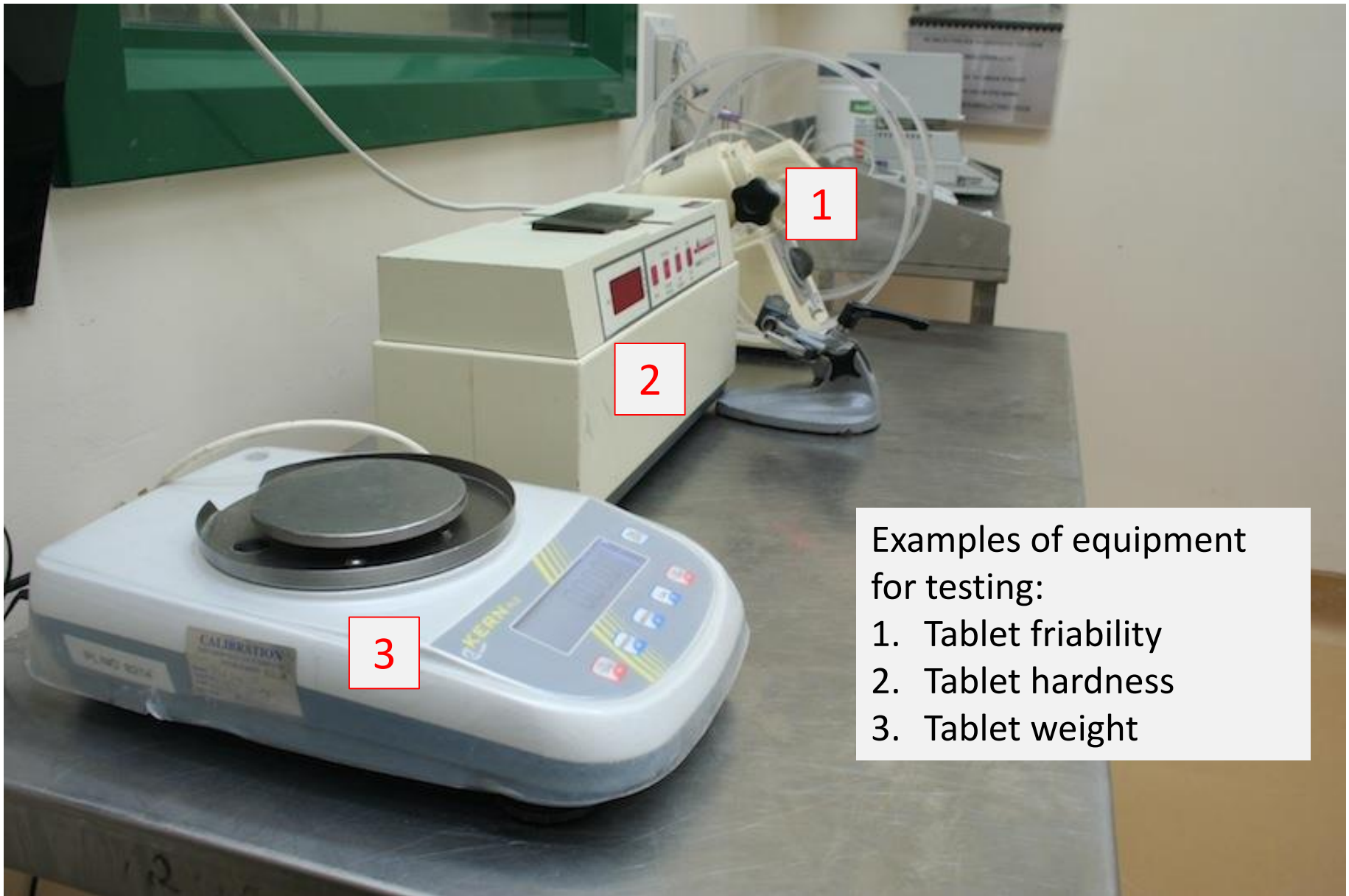


# TESTING & ANALYSIS

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- All laboratory equipment and instrumentation;
  - should be appropriate to the approved test procedure; and
  - should be regularly serviced and calibrated by assigned and trained persons or specialist organisations.
- All records of servicing and calibration should be retained in an accessible form.





Examples of equipment for testing:

1. Tablet friability
2. Tablet hardness
3. Tablet weight



# TESTING & ANALYSIS

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- It should be verified that all starting material and product samples are only taken by trained personnel, and also that records of:
  - the identification of the sample;
  - the batch number;
  - location in the consignment/batch; and
  - the date of samplingare retained in an accessible form.



# TESTING & ANALYSIS

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- Verify that all chemical, physical and microbiological analytical tests are carried out according to the standard procedures.
- The ICH Q2B 'Validation of Analytical Procedures: Methodology' can be used as a guide for this verification.

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)



# TESTING & ANALYSIS

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- Any internal modifications to, or deviations from the standard and/or compendia procedures should be verified and agreed by authorised personnel.
- All modifications must be recorded in detail.



# TESTING & ANALYSIS

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- Verify that procedures are in place to record the use of 'change parts' (such as chromatographic columns or viscosity spindles) and to ensure that the specified component is used in the test.



# TESTING & ANALYSIS

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- It should also be verified that there are procedures for recording:
  - the replacement of components of instruments;
  - the replacement or replenishment of chemical reagents; and
  - identification of the technician/operator undertaking the test.



# Change Control



# CHANGE CONTROL

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- A written Change Control procedure shall be in place to manage key changes, for example:
  - starting material,
  - product component,
  - process equipment,
  - process environment (or site),
  - method of production or testing,
  - or any other change that may affect product quality or reproducibility of the process.
- Change Control procedure shall ensure that sufficient supporting data are available to ensure that the revised process will result in a product of the desired quality, that is consistent with the approved specifications.





# CHANGE CONTROL

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- A system should be established for checking the essential criteria before a change is implemented.
- A risk analysis of the effects of the change should be carried out for any changes that have the potential of affecting:
  - Product consistency.
  - Product quality.
  - Product safety.
  - Product stability.
- Records should be retained of the checks carried out and the rationale behind any decision to accept or reject the proposed change.
- All changes that may affect product quality or reproducibility of the process shall be formally requested, documented and approved by the relevant department.



# CHANGE CONTROL

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- The need for the extent of a re-verification (partial or complete) should be based on the outcome of the risk assessment.
- Any limitations noted during the verification of the test procedures or any necessary modifications to the test procedures should be carried out with a proper change control process and recorded.

## Example of limitations:

- Where the product matrix contains an ingredient, or combination of ingredients, that can interfere with the accuracy of the analysis.
- Where limitations have been identified, the use of alternative validated test procedures should have been investigated.



# CHANGE CONTROL

- Re-verification is necessary where there are changes to:
  - Product formulae.
  - Raw materials/ingredients.
  - Production operations (e.g. new or replacement equipment).
  - Testing procedures.
  - Cleaning and sanitation procedures.
- Re-verification of any changes should use the original verification protocol as the starting point and should focus on:
  - Maintenance of product consistency.
  - Product quality.
  - Product safety.
  - Product stability.



# REFERENCES

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1. ASEAN Guidelines on Good Manufacturing Practice for Traditional Medicines/Health Supplements - Appendix 2.
2. ICH Q8 Pharmaceutical Development.
3. ICH Q9 Quality Risk Management.
4. ICH Q10 Pharmaceutical Quality System.
5. PIC/S Guide to Good Manufacturing Practice for Medicinal Products – Annex 15

# THANK YOU!



**ONE VISION, ONE IDENTITY, ONE COMMUNITY**