ANNEX A1 **GUIDANCE ON PROCESS VALIDATION SCHEME FOR SOLID ORAL DOSAGE PRODUCTS**

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1. PURPOSE

This document is intended to provide guidance for the process validation scheme of the manufacturing process of solid oral dosage formulations.

This guidance document should be read in conjunction with the guidance listed below:

- ASEAN Guidelines for Validation of Analytical Procedures
- Current United States Pharmacopoeia, European Pharmacopoeia and Japanese Pharmacopoeia
- Guidance for Industry, Process Validation: General Principles and Practices (FDA, January 2011)
- CPG Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval
- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (FDA, 1995)
- SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum (FDA, 1999)
- SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (FDA, 1997)
- Dissolution Testing of Immediate Release Solid Oral Dosage Forms (FDA, 1997)

2. SCOPE

This guidance document applies to the solid oral dosage formulations − capsules, tablets and powder / granules for solution / suspension.

3. GENERAL INFORMATION

The presentations of solid oral dosage formulations are generally capsules, tablets and powder / granules for solution / suspension. Solid oral dosage products could be packaged as unit dosage form such as blisters and sachets or as multi units in the form bottles.

Capsules are solid dosage forms in which the drug is enclosed in a hard or soft soluble shell, commonly made of gelatine or starch or other suitable substance. Capsules may be formulated for immediate or modified release of drugs that may be in the form of powder, liquids or semisolids. Capsules can also be filled with uncoated or coated pellets, mini-tablets, powder or granules to permit transit through the stomach to the small intestine before the medication is released to alleviate potential problems of drug inactivation or gastric mucous irritation, as in the case of modified release dosage forms.

Tablets are solid dosage forms that contain medicinal substances with suitable excipients manufactured by direct compression of powders or granules with the application of high pressures, using steel punches and dies. Tablets can be of any size, weight, colour and shapes, and may have surface markings. Tablets can also be film-coated and/or have imprints.

Powder / granules for solution / suspension may be presented in single dose units or multi-dose units and is required to be reconstituted in water before being administered orally. Presentations in multi-dose units may be used where strengths of each dose may not be critical.

Process validation of a solid oral dosage form has to be specific to its batch formula and the operating principles of equipment used for its manufacture. The process parameters that need to be controlled and / or monitored and testing that need to be conducted during process validation of a bulk solid oral dosage formulations depend on its method of manufacture and its presentation (compressed tablet, coated tablet, capsule, powder / granule). The acceptance criteria should take into consideration the nature of the solid oral dosage, for example its drug release characteristics (immediate release (IR) or modified release (MR)). The following validation scheme can be used as a guide for process validation of solid oral dosage form and should be evaluated on a case-by-case basis.

4. VALIDATION SCHEME OF SOLID ORAL DOSAGE MANUFACTURING PROCESSES

The following items should be taken into account for the execution of process validation of the solid oral dosage manufacturing process:

4.1. Batch Formula

For the execution of the manufacturing process validation, the batch formula of the solid oral dosage has to be well defined. All components of the dosage form to be used in the manufacturing process have to be listed, with their amounts on a per batch basis (including overages, if any).

4.2. Major Equipment and Equipment Class

The major equipment, used for the manufacturing process, are to be identified and the class of each equipment be indicated. The equipment are broadly categorized by the unit operation (for example, blending and mixing, drying, particle size reduction, granulation, unit dosage, coating, encapsulation, printing, packaging). For each operation, the equipment is further categorized by class (operating principle).

The following lists some examples of equipment class for equipment of each major unit operation, which are non-exhaustive.

Equipment	Equipment Class
Mixing Tank	Convective mixers
Blender	Diffusion blender (Tumble) Convective blender Pneumatic blender
Mill	Fluid energy mill Impact mill Cutting mill Compression mill Screening mill Tumbling mill

Equipment	Equipment Class
Granulator	Dry granulator Wet high-shear granulator Wet low-shear granulator Low-shear tumble granulator Extrusion granulator Rotary granulator Fluid bed granulator Spray dry granulator
Dryers	Direct Heating, Static Solids Bed Direct Heating, Moving Solids Bed Direct Heating, Fluidized Solids Bed (Fluid Bed Dyer) Direct Heating, Dilute Solids Bed, Spray Dryer Direct Heating, Dilute Solids Bed, Flash Dryer Indirect Conduction, Moving Solids Bed Indirect Conduction, Static Solids Bed Indirect Conduction, Lyophilization Gas Stripping Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)
Separators	Vibratory/Shaker Centrifugal
Tablet Press	Gravity Power assisted Rotary (centrifugal) Compression coating
Coating machine	Pan coating Gas suspension Vacuum film coating Dip coating Electrostatic coating
Encapsulator (hard capsule)	Auger Vacuum Vibratory Dosing disk Dosator
Encapsulator (soft capsule)	Positive displacement pump Gravity or force fed Mixers and Mixing Vessels Deaggregators Deaerators Holding Vessels
Powder filler	Vacuum Auger
Blister packaging machine	Plate-type
Bottle packaging machine	None identified

The product owner / applicant will determine the level of equipment information to be registered. Where information on the equipment class is deemed critical but not made available in the submission, the Drug Regulatory Authority (DRA) reserves the right to request for such information.

4.3. Manufacturing Process Description and Process Parameters

The manufacturing process may be described or presented in a flow diagram.

The following process parameters are recommended to be controlled or monitored as part of the process validation, depending on the dosage form and the type of manufacturing process. The process parameters listed below are non-exhaustive. They serve only as examples and may differ depending on the class of equipment used.

Process Step	Tablet	Capsule	PGS	Process Parameters
Raw Materials Sieving, if required	✓	✓	✓	• Mesh / sieve size
Premix, if required	✓	✓	✓	• Mixing time, speed, load size
Fill liquid mixing, if required	NA	✓	NA	• Mixing time, speed, volume
Dry milling (particle sizing), if applicable	DB	DB	DB	• Screen size • Milling speed • Feed rate
Final Blending	✓	✓	✓	• Blending time, load size, speed • Sieve size, for dry blending, if required
Granulation binder preparation	WG	WG	WG	• Binder amount, concentration • Temperature
Granulation	WG	WG	WG	• Load size • Mixing time, speed • Temperature • Rate of liquid addition • Application spray pattern

Process Step	Tablet	Capsule	PGS	Process Parameters
Wet milling (if applicable)	WG	WG	WG	• Rounds per minute • Pressure • Temperature
Wet screening (if applicable)	WG	WG	WG	• Mesh / sieve size
Drying	WG	WG	WG	• Drying time • Temperature distribution
Cooling	WG	WG	WG	• Cooling Time • Cooling Set Temperature
Tabletting (including Metal detection and Dedusting)	✓	NA	NA	• Compressing machine settings • Tabletting speed (tbs/hr)
Coating solution / suspension preparation (if required)	✓	✓	NA	• Temperature • Mixing speed / time
Coating (if required)	✓	✓	NA	• Load size • Coating pan settings • Temperature • Spray rate • Rounds per minute • Air flow rate
Printing on product (when required)	✓	✓	NA	• Printing feed rate (units/hr) • Temperature
Capsule filling (including dedusting)	NA	✓	NA	• Capsule machine settings • Machine speed (caps/hr) • Feeding system
Primary packaging	✓	✓	✓	• Machine settings • Machine speed • Feeding speed

Process Step	Tablet	Capsule	PGS	Process Parameters
Environmental monitoring – throughout manufacturing process (Applicable for heat and / or moisture sensitive products only)	✓	✓	✓	• Temperature • Relative humidity

Where PGS denotes Powder / Granule for Solution / Suspension
DB denotes applicable for Dry Blending only
WG denotes applicable for Wet Granulation only
✓ denotes applicable (if required)
NA denotes Not Applicable

The product owner / applicant will determine the level of process information to be registered. Where process parameters are deemed critical but not well defined in the submission, the DRA reserves the right to request for such information.

4.4. Sampling Plan and Acceptance Criteria

It is the responsibility of the manufacturer to ensure that the sampling plan and acceptance criteria defined are adequate to ascertain that the manufacturing process is well-controlled and robust to produce drug product consistently meeting specifications. The following sampling plan and acceptance criteria provide a guide for the process validation of a typical solid oral dosage manufacturing process with medium risk indication.

Stage	Sampling Plan	Test	Acceptance Criteria
Drying, if required	At least 3 samples from at least three different locations or time points throughout the oven chamber or drying process[(1)].	Loss on drying (LOD) – analyze one sample per location	Based on production specification for LOD
Final Blend / Mix	At least 3 samples from at least ten different locations evenly distributed throughout the mixer[(1)] *(Twenty locations for convective blender)*	Blend / Mix uniformity (Assay) – analyze one sample per location	Stage 1 Individual results: Mean ± 10% (absolute) All individual results: RSD ≤ 5.0%
		If required, • Flowability • Density • Appearance	In-house

Stage	Sampling Plan	Test	Acceptance Criteria
	Composite sample (may be performed as part of release testing)	• *Visual inspection • *Uniformity • *Assay (Potency) • *Impurities • *Microbial contamination • Other internal specifications * May be omitted if next step is tabletting and / or encapsulation.	Uniformity: As per compendia Microbial Limit Test (MLT): As per compendial MLT method Others: Compendia / In-house
Tabletting	Stratified sampling	• Uniformity • Any other internal specifications, if required	Uniformity: As per compendia Others: Compendia / In-house
	Composite sample (may be performed as part of release testing)	• Visual inspection • Uniformity • Assay (Potency) • Friability • **Hardness • **Disintegration • **Dimension • **Dissolution • **Impurities • **Microbial contamination • Other internal specifications ** May be performed after coating and / or encapsulated, if applicable.	Uniformity: As per compendia MLT: As per compendial MLT method Others: Compendia / In-house

Stage	Sampling Plan	Test	Acceptance Criteria
Capsule filling	Stratified sampling	• Uniformity • Visual inspection • Length of filled capsules	Uniformity: As per compendia Others: Compendia/ In-house
	Composite sample (may be performed as part of release testing)	• Visual inspection • Uniformity • Assay (Potency) • Dimension • Dissolution/ Disintegration • Impurities • Microbial contamination • Other internal specifications	Uniformity: As per compendia MLT: As per compendial MLT method Others: Compendia / In-house
Coating	1 sampling from each coating pan	• Assay (for coating of active only) • Moisture content / residual solvent	Assay: In-house Moisture / solvent: ICH guidelines
	At least ten locations distributed throughout all batch subdivisions(1)	Uniformity	As per compendia

Stage	Sampling Plan	Test	Acceptance Criteria
	Composite sample (may be performed as part of release testing)	• Visual inspection • Uniformity (for active coating only) • Assay (Potency) • ***Hardness • ***Disintegration • ***Dissolution • ***Impurities • ***Microbial contamination • Other internal specifications *** May be omitted if encapsulated	Uniformity: As per compendia Others: Compendia / In-house
Printing	Stratified sampling	Visual inspection	In-house
Filling of powder / granules into bottles	Stratified sampling	Weight uniformity	Label claim ± 5% (absolute)
Primary packaging (may be performed as part of equipment qualification)	Stratified sampling	• Visual inspection • CCS integrity test, if required	In-house
Environmental Monitoring (Applicable for heat and / or moisture sensitive products only)	Throughout the manufacturing process	• Temperature • Relative humidity	In-house

Where RSD denotes Relative Standard Deviation
ICH denotes International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MLT denotes Microbial Limit Test
CCS denotes Container Closure System

(1)Note: Other sampling plans may be acceptable if they are statistically sound and justified.

The extent of sampling, tests and acceptance must take into consideration, the level of risk, e.g. the equipment type and capacity, to patient health of the drug product and should be considered on a case-by-case basis.

The finished product specifications have to be adequately justified and the analytical methods have to be validated as per the ASEAN Guidelines for Validation of Analytical Procedures.

4.5. Holding Time for Drug Products

Where holding times are involved as part of the manufacturing process of the bulk drug product (including the premix and intermediate stages), these have to be well justified. It is recommended for any holding times to be supported by stability data (degradation studies and / or microbial limit tests). Holding time studies may be performed as part of the main process validation scheme or conducted as a separate exercise. Hold time may be established as a deliberate effort in that the samples or batches are withheld for the predetermined holding time before subjecting to analysis. Holding time may also be established as part of the routine manufacturing process, using incurred holding times, which had been supported by data.

In the case where hold time information is not included in the submission, such information or justification / data to support the omission must be made available upon request of the DRA.

5. GLOSSARY

Delayed Release:
Release of a drug (or drugs) at a time other than immediately following oral administration.

Extended Release:
Extended release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., as a solution or an immediate release dosage form).

Immediate Release:
Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Modified Release Dosage Forms:
Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

Stratified Sampling
The process of selecting units deliberately from various locations within a lot or batch or from various phases or periods of a process to obtain a sample.

Stratified sampling of the blend and dosage units specifically targets locations either in the blender or throughout the compression / filling operation which have a higher risk of producing failing content uniformity results.