ASEAN GUIDELINE ON SUBMISSION OF MANUFACTURING PROCESS VALIDATION DATA FOR DRUG REGISTRATION

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GUIDELINE ON SUBMISSION OF MANUFACTURING PROCESS VALIDATION DATA FOR DRUG REGISTRATION

1. INTRODUCTION

Process Validation is a means of ensuring that manufacturing processes are capable of consistently producing a finished product of the required quality. It involves providing documentary evidence that key steps in the manufacturing process are consistent and reproducible. A validated manufacturing process is one that has been proven to do what it purports or is presented to do.

The term `validation' is intended to apply to final verification at the production scale. Typically a minimum of three consecutive production batches should be successfully validated prior to the marketing of the product.

2. SCOPE

This guideline is intended to outline the regulatory requirements with respect to the manufacturing process validation studies which fall under the remit of drug registration and to guide the applicant in preparing the dossiers for the product license and post-approval variation applications. These requirements are not intended for regulating the manufacture of active substance and other starting materials, but intended to apply to data generated to evaluate or validate the manufacturing process of the finished product. For biotechnological and biological products, more extensive data may be required.

3. DATA SUBMISSION REQUIREMENTS

Option 1 - The data submission should include a validation report (see Content of Validation Report) on three consecutive successfully validated production batches.

Option 2 - In circumstances where submission of data on 3 consecutive production batches is not feasible at the time of application, the following can be submitted to DRA to obtain marketing approval.

Documents required:
a) Development pharmaceutics report; and
b) Validation data on 1 pilot batch with validation scheme on production scale batches.

In addition, the applicant is required to fulfill the following standard commitments:
- To undertake that 3 consecutive full production batches are successfully validated before the product is marketed, subject to concurrence by the DRA;
- To submit the report to the Drug Regulatory Authority (DRA) within a specified time frame, or to make the information from these studies available for verification post authorisation by DRA according to national procedure.

Note: Option 2 is not recommended for biological/biotechnological product, product manufactured using non standard method of manufacture, such as non-standard methods of sterilization and aseptic processing, and other specialized products such as modified release dosage form.

Option 3 - For products that have been approved by a reference agency, the applicant is required to provide a declaration statement to the effect that the same pre-approval dossiers pertaining to

process validation that have been submitted to the reference regulatory agency are submitted to DRA for evaluation. Under certain circumstances where validation documents may not form part of the pre-approval dossiers, the DRA may request for Validation Report or Validation Scheme. In addition, the applicant is required to undertake that 3 consecutive full production batches are successfully validated before the product is marketed and to submit the report to DRA upon request.

4. CONTENT OF DEVELOPMENT PHARMACEUTICS

The report on pharmaceutical development or development pharmaceutics should address the following:

a) Rationale for selecting the dosage form

b) Choice of product components (Active substance and excipients)
- Compatibility considerations
- Physico-chemical characteristics

c) Formulation of product
- Use of overages
- Effect of pH and other parameters
- Effect of antioxidants, solvents, chelating agents, type/concentration of anti-microbial agents, etc
- Stability, homogeneity and batch reproducibility considerations

d) Choice of manufacturing processes, including sterilization procedures

e) Choice of containers and packaging materials
- Container-closure integrity
- Sorption and leaching issues

f) Microbial attributes of dosage form

g) Compatibility of drug product with diluents or dosage device (e.g precipitation of drug substance in solution, sorption on injection vessels etc) throughout shelf life of drug product

The development pharmaceutics report should establish that the type of dosage form selected and the formulation proposed are appropriate for the intended (medicinal) purpose specified in the application for drug registration. It should also identify the formulation and processing aspects that are critical for batch homogeneity and reproducibility, and that hence have to be monitored routinely. The development pharmaceutics report (and the pilot batch report) should provide a link to the validation scheme proposed for the manufacture of production scale batches.

5. CONTENT OF VALIDATION SCHEME

Process validation scheme outlines the formal process validation studies to be conducted on the production scale batches. It should contain, but not limited to, the following information:

a) A description of the manufacturing process with a schematic drawing or flow chart
b) A summary of the critical processes, control variables and justification for their selection
c) Finished product specification (release)

d) Details of analytical methods (reference to the dossier)
e) In process controls proposed with acceptance criteria
f) Additional testing intended to be carried out (e.g. With proposed acceptance criteria and analytical validation appropriate)
g) Sampling plan – where, when and how samples are taken
h) Details of methods for recording and evaluation of results
i) Proposed time frames for carrying out the studies
j) Critical equipment/facilities to be used (for example, measuring/recording equipment together with its qualification and calibration status)

6. CONTENT OF VALIDATION REPORT

The content of report should include, but not limited to the following information:
a) Summary
b) Introduction
c) Batches (for example, date of manufacture, batch size) used for validation
d) Manufacturing equipment
e) Critical process steps and parameters
f) Acceptance criteria
g) Sampling plan
h) Tabulation of the test results
i) Batch Analysis
j) Evaluation of data, including statistical process control analysis
k) Evaluation of data including comparison against acceptance criteria
l) Discussion on deviations and out of specification results
m) Conclusion and recommendations

Where appropriate a description of the manufacturing process with a schematic drawing or flow chart may be required by the DRA.

Please refer to annexes listed below:
a) Annex A1 for guidance on process validation scheme for solid oral dosage products,
b) Annex A2 for guidance on process validation scheme for aseptically processed products and;
c) Annex A3 for guidance on process validation scheme for terminally sterilized products.

7. NOTES ON RETROSPECTIVE VALIDATION & CONCURRENT VALIDATION

7.1 Retrospective Validation

For existing products already on the market for some time, retrospective validation may be performed. Retrospective validation involves the trend analysis (using control chart, etc) of historical manufacturing and QC data (eg. Results of assays, dissolution test, pH, SG, etc) of the product. Data from 10-20 batches of the product produced using the same stable manufacturing process should be analysed, to demonstrate that the manufacturing process is under control and `capable'. A Cpk (Process Capability) and/or Ppk (Process Performance) of 1.0, 1.33 and 2.0 represents a 3, 4, 6 sigma respectively. The measurement of Cp, Cpk, Pp or Ppk will be accepted as one of the statistical methods for analysing the process control.

7.2 Concurrent Validation

In the case of orphan drugs, when the number of production batches per year is expected to be low, concurrent validation is acceptable. Other categories of drugs for which have short

lives (e.g. radiopharmaceuticals) and that are medically necessary (e.g. drug used to prevent or treat serious or life-threatening disease or medical condition, for which there is no other available source with sufficient supply of that drug or alternative drug available) may be considered on case by case basis. The applicant should seek prior consent from DRA before submitting the application to register any drug product that uses concurrent validation approach.

8. CHANGE CONTROL

Procedures are required to manage, plan and document the changes proposed in the manufacturing processes. Adequate supporting data should be generated to show evidence that the revised process would still ensure that the product meets the desired quality and approved specification.

Minor changes in SOP's, environment, equipment etc are unlikely to require regulatory approval if they can be shown not to affect the quality of the finished product.

Other types of changes that would have significant impact on the quality of the finished product would require re-validation and prior regulatory approval. Such significant changes include changes to process (e.g. mixing times, drying temperatures, sterilization process), change of equipment that involves different design and operating parameters/principles. The applicant should submit appropriate supporting data for these changes.

9. TABLE OF CONTENTS OF PROCESS VALIDATION DOCUMENTATION

Annex B is a form that needs to be completed by the applicant for checking purpose.

10. QUALITY BY DESIGN AS AN ALTERNATIVE APPROACH TO PROCESS VALIDATION

Traditional approach in process validation focuses on three validation lots at commercial scale. Process validation is considered complete when the results of these lots are within acceptance criteria as defined in the validation protocol.

An alternative approach to traditional process validation is the continuous process verification, which adopts the concept of Quality by Design (QbD). It emphasizes on a life cycle approach where the process is continued to be verified even after the validation lots. Please refer to the Annex C for more details.

11. GLOSSARY

Annex D gives definitions of the terms used in the guideline.

12. DOCUMENT VERSION HISTORY

Version 1.0: Effective date on January 2005
Version 2.0: Draft version for 18th ACCSQ-PPWG meeting (Jun 2011)
Version 3.0: Draft version for 19th ACCSQ-PPWG meeting (Jul 2012)

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.

ANNEX A2 **GUIDANCE ON PROCES VALIDATION SCHEME FOR ASEPTICALLY PROCESSED PRODUCTS**

TABLE OF CONTENTS

1. PURPOSE

This document is intended to provide guidance for the submission of information and data in support of the efficacy of sterilization processes in product license application which is required in the dossiers.

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

- Note for Guidance on Process Validation (EMA, 2001)
- Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (FDA, 1994)
- Annex 4 WHO Good Manufacturing Practices for Sterile Pharmaceutical Products (Technical Report Series No. 957, 2010)
- Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (FDA, September 2004)
- Recommendation on the Validation of Aseptic Process (PIC/S, January 2011)
- Guide To Good Manufacturing Practice For Medicinal Products Annexes (PIC/S, September 2009)
- EC Guide to Good Manufacturing Practice (Annex 1) March 2009

2. SCOPE

This guidance document applies to the sterile drug product processed using aseptic processing.

3. GENERAL INFORMATION

Sterilization can be achieved by the use of moist or dry heat, irradiation with ionizing radiation, ethylene oxide or by filtration with subsequent aseptic filling of sterile final containers.

Where possible and practicable, heat sterilization is the method of choice.

The decision to choose aseptic processing should be justified, for example, due to the instability of a formulation or incompatibility of a pack type.

4. INFORMATION NEEDED FOR ASEPTIC PROCESSES VALIDATION

The following information should be submitted for process validation of drug product manufactured by aseptic processing.

4.1. Premises

It is recommended that a floor plan of the production areas is provided which includes the following information:

- Critical production areas such as preparation and holding areas, filtering and filling areas, changing rooms and their air cleanliness grade
- Isolators or barrier systems, where applicable
- Location of critical equipment, including, but not limited to, laminar flow hoods, autoclaves, lyophilizers and filling heads
- Material flow and personnel flow

Refer to Annex 4 WHO Good Manufacturing Practices for Sterile Pharmaceutical Products (Technical Report Series No. 957 2010) for the detailed requirement of the grades of clean areas in operation for the manufacture of sterile medicinal products.

4.2. Sterilization and Depyrogenation of Containers, Closures, Equipment and Components

4.2.1. Process Description

A summary of sterilization and depyrogenation processes for containers, closures, equipment and components should be provided.

4.2.2. Process Validation

a. For heat sterilization or depyrogenation, validation report should be submitted which includes the following information:

- Heat distribution and penetration study summary reports, including, but not limited to, load pattern diagram with identified cold spot
- Biological challenge study report

If the bulk drug solution is aseptically formulated from components that are sterilized separately, validation report of each of the separate sterilization processes should be provided.

For depyrogenation, information on the method of endotoxin challenge used and results showing reduction of endotoxin titer by three or more logs should be presented.

b. For sterilization by irradiation, validation report should be submitted which includes the following information:

- Radiation facility
- Radiation source, method of exposure (i.e. movement through the irradiator)
- Type and location of dosimeters used to monitor routine production loads
- Packaging configuration data
- Multiple-dose mapping studies
- Microbiological methods and controls used to establish, validate and audit the efficacy of the cycle

c. Validation information for sterilization processes other than heat or irradiation should also be provided. Refer to Annex A3 (Section 4.2) for more details.

4.3. Filtration and Holding Time

a. A description of bulk solution filtration process should be provided which includes:

- Filtration processes and specification
- Tandem filter units, pre-filters and bacterial retentive filters

Pore sizes of 0.2 µm or less are acceptable without further justification. A proposal to use a larger pore size in combination with an additional sterilisation step has to be validated and justified.

Pre-filters and bacterial retentive filters integrity testing information should be provided. Justification should be provided if pre-filtration is not applied.

Information on compatibility and microbial retention capacity of the filters should be provided. Effects of the filter on the product formulation should be described, if any.

b. Specifications for holding time between the compounding of the bulk drug product and its filling into final containers should be provided which includes:

- Holding container
- Duration
- Temperature
- Other conditions of storage, if any

4.4. Media Fills

Approach and specification used for media fills as well as the summary of recent media fill results (at least three consecutive separate successful runs), including failures, should be provided.

These data should be obtained using the same filling line(s) that are to be used for the routine production of the finished product.

The number of containers filled during the media fills should be in the range of 5000 to 10000 units. For operations with production sizes under 5000 units, the number of media filled units should at least equal to the maximum batch size made on the processing line.

In general, the following information is recommended to be provided for each media fill run:

a. Date of each media fill
b. Filling room and list of equipment
c. Container-closure type and size
d. Volume and type of medium used in each container
e. Number of units filled, rejected, incubated and positive results observed
f. Incubation information, e.g. duration, temperature and orientation of container
g. Simulations [1]
h. Process parameters[2]
i. Tabulated results and conclusion of microbiological environmental monitoring

Note 1: The procedures used to simulate any steps of a normal production fill should be described. This might include, for example, slower line speed, personnel shift changes, equipment failure and repair, mock lyophilization and substitution of vial headspace gas.

Note 2: The parameters used for production filling and for media fills (e.g., line speed, fill volume, number of containers filled or duration of filling) should be compared.

4.5. Container Closure System Integrity

The data, including a short description of method and summary of test results, demonstrating the integrity of microbiological barrier of the container-closure system should be provided.

5. GLOSSARY

Aseptic Processing:
Processing of product in grade A or an environment and typically it includes sterile filtration and filling steps.

Bioburden:
The total number of all viable aerobic bacteria, yeasts and moulds expressed as colony forming units (CFU) per unit or gram of product.

Depyrogenation:
A process used to destroy or remove pyrogens (e.g. endotoxin).

Media fills:
Method of evaluating an aseptic process using a microbial growth medium. Media fills are understood to be synonymous to simulated product fills, broth trials and broth fills etc.

ANNEX A3 **GUIDANCE ON PROCES VALIDATION SCHEME FOR TERMINALLY STERILISED PRODUCTS**

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1. PURPOSE

This document is intended to provide guidance for the submission of information and data in support of the efficacy of terminal sterilization processes in product license application which is required in the dossiers.

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

- Note for Guidance on Process Validation (EMA, 2001)
- Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (FDA, 1994)
- Annex 4 WHO Good Manufacturing Practices for Sterile Pharmaceutical Products (Technical Report Series No. 957, 2010)
- EC Guide to Good Manufacturing Practice (Annex 1) March 2009
- Guide To Good Manufacturing Practice For Medicinal Products Annexes (PIC/S, September 2009)

2. SCOPE

This guidance document applies to the sterile drug product processed using terminal sterilization.

3. GENERAL INFORMATION

Sterilization can be achieved by the use of moist or dry heat, by radiation with ionizing radiation, by gases or by filtration with subsequent aseptic filling of sterile final containers.

Where possible and practicable, heat sterilization is the method of choice.

4. INFORMATION FOR TERMINAL STERILIZATION PROCESSES

In general, description of sterilization process and process validation data for the following items should be provided.

- Drug product in its final container-closure system
- Containers, closures, equipment and components
- Product intermediate

Where reprocessing (e.g. additional thermal processing) of product are allowed, supporting data should be provided.

4.1. Terminal Sterilization Process by Moist Heat

4.1.1. Process Description of Moist Heat Sterilization

A description of the autoclave process should be provided which includes:

- Identity of the autoclave (e.g. equipment number, manufacturer and model)

- Cycle type used (e.g. saturated steam, water immersion and water spray)

- Cycle parameters and performance specifications including temperature, pressure, time and minimum and maximum F_0

- Methods and controls used to monitor routine production cycles (e.g. temperature probes, chemical and biological indicators, leak test results) including the number and location of each as well as acceptance and rejection specifications [optional]

4.1.2. Process Validation and/or Evaluation of Moist Heat Sterilization

a. Heat distribution and penetration study

Approach and specification used for heat distribution and penetration study as well as the summary of recent study results:

- Approach and specification

- Diagrams showing the number of thermocouples, chemical indicators and/or biological indicators, which applicable, used, and their locations in the autoclave chamber

- Diagrams showing minimum and maximum load with identified cold spot

- Results obtained from a minimum of three consecutive, successful cycles

b. Microbiological challenge study

A sterility assurance level (SAL) of 10^{-6} or better should be achieved for all parts of the finished product claimed to be sterile.

A summary report for microbiological challenge study, which may be combined with heat penetration study report, should be provided with the following data:

- Bioburden data, especially when overkill approach is not used

- Certificate of Analysis of biological indicators used, which should include information on identification, resistance and stability

- The resistance of biological indicators
  Resistance in or on the product (i.e. in the product solution, or on the surface of container or closure parts or interfaces) or product-substitute should be determined. If spore carriers, e.g. spore strips, are used, the resistance of spores on the carrier relative to that of directly inoculated product should be determined, if necessary.

- Results and conclusion of microbiological validation studies demonstrating the effectiveness of the minimum cycle to provide a SAL of 10^{-6} or better to the product under the most difficult sterilization conditions.

4.2. Other Terminal Sterilization Process

The types of information outlined in moist heat sterilization process are, in general, also applicable to sterilization by dry heat, gases, e.g. ethylene oxide, and sterilization by radiation, e.g. gamma and electron beam.

As a minimum, the following information should be provided:

- Descriptions of load (pattern)
- Validation data in support of the efficacy of the minimum cycle
- Container-closure integrity
- Re-process, if applicable
- Sterilization process impact on the chemical and physical attributes of the drug substance or drug product, where applicable

Specific requirements are provided below for process validation of the sterilization by ethylene oxide and by radiation.

4.2.1. Ethylene Oxide (EO)

a. Decision to choose EO sterilization should be justified.

b. The sterilizer(s) and controlled site(s) for pre-humidification and aeration of the product load.

c. The parameters and limits for all phases of the cycle, e.g. pre-humidification, gas concentration, vacuum and gas pressure cycles, exposure time and temperature, humidity, degassing, aeration and determination of residuals.

d. The microbiological methods (growth medium, incubation temperature and time interval) for cultivating spores from inoculated samples during validation experiments.

4.2.2. Radiation

a. Radiation facility

b. The radiation source and method of exposure (i.e. movement through the irradiator)

c. Type and location of dosimeters used to monitor routine production loads

d. Packaging configuration data

e. Multiple-dose mapping studies

f. The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle

4.3. Container-Closure System (CCS) Integrity

In general, the following types of information and data in support of the microbial integrity of the drug packaging components should be provided:

a. Simulation of the stresses from processing

Experimental designs should simulate the stresses of sterilization process, handling and storage of the drug and their effects on the container-closure system. Physical, chemical and microbiological challenge studies may be necessary.

b. Demonstrate Integrity Following the Maximum Exposure

CCS integrity should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s). If a product is exposed to more than one process, then exposure to the maximum cycle of all processes should be incorporated into the study design.

c. The Sensitivity of the Test [optional]

The sensitivity of the experimental method used for container closure integrity testing should be specified and provided.

5. GLOSSARY

Biological Indicator (BI):
A population of microorganism inoculated onto a suitable medium and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process

Component
Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.

F_0 Value:
Equivalent amount of time in minutes at 121°C, which has been delivered to a product by the sterilization process. For example, 15 minutes sterilization at a reduced temperature of 111 °C produces a lethal effect, which is equivalent to 1.5 minutes at 121.0 °C

Terminal Sterilization:
Final sterilization of the product using steam heat and/or dry heat or radiation sterilization of a given product

ANNEX B TABLE OF CONTENT OF PROCESS VALIDATION DOCUMENTATION

I. Document Submission (tick if submitted)**:**

	Document	Check Box	Enclosure	Page
a)	Development Pharmaceutics Report	☐	_____	_____
b)	Validation Scheme	☐	_____	_____
c)	Validation Report			
	o Pilot batch	☐	_____	_____
	o 3 full production batches	☐	_____	_____

II. Details of Validation:

a) Manufacturing site at which the validation is carried out:

No.	Name of manufacturer	Country

b) Type of Validation:

- ☐ Retrospective
- ☐ Prospective
- ☐ Concurrent
- ☐ Others; please specify: _____

c) Number of batches validated: _____

d) Details of batches:

Batch Number	Date of Production	Batch Size	Batch Type (production/pilot)

ANNEX C GUIDANCE ON PROCES VALIDATION ADOPTING QUALITY BY DESIGN APPROACH

TABLE OF CONTENTS

1. PURPOSE

This guidance document is intended to provide guidance for the submission of information and data for process validation which adopts quality by design (QbD) approach.

The guidance documents and references below should be read in conjunction with this guidance:

- Process Validation: General Principles and Practices (FDA, Jan 2011)
- Pharmaceutical Development Q8(R2) (ICH, August 2009)
- ICH Quality Risk Management Q9 (ICH, Nov 2005)
- ICH Pharmaceutical Quality System Q10 (ICH, June 2008)
- ICH Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11 (ICH, May 2012)
- ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) (ICH, Nov 2010)
- ICH Quality Implementation Working Group Points To Consider (R2) (ICH, Dec 2011)

2. SCOPE

This guidance applies to both chemical or biological drug products and active pharmaceutical ingredients.

3. GENERAL INFORMATION

FDA released “Guideline on General Principles of Process Validation” in 1987. This guideline emphasize that process validation is complete with the 3 validation lots at the commercial scale. An alternative approach to this traditional process validation is the continuous process verification, also known as life-cycle approach which is the essence of the concept of QbD.

In Aug 2009, ICH released a guideline Q8R(2) (Step 4) to guide the industry in the implementation of quality by design (QbD) in Section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH guideline M4). QbD (ICH Q8(R2)) is defined as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.” This is a more systematic approach to development which include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management (ICH Q9), and use of knowledge management (ICH Q10) throughout the lifecycle of the product.

Subsequently, the fourth set of Questions and Answers intended to facilitate the implementation of the Q8(R2), Q9 and Q10 Guidelines was released in Nov 2010 (Q8/Q9/Q10 Q&As (R4)). The ICH Quality IWG also released ‘Points to Consider’ covering topics relevant to the implementation of Q8(R2), Q9 and Q10, to supplement the existing Q&A in Dec 2011. Simultaneous with the development of QbD, evolution of process validation and its associated components occurs concurrently. Eventually, FDA released “Process Validation: General Principles and Practices” in Jan 2011. This guidance incorporated QbD, Process Analytical Technology (PAT), risk management and the concept of life cycle approach to process validation. This new concept emphasizes a more holistic approach to process validation.

In FDA new guidance, process validation is defined as “The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the process validation activities in three stages.

- Stage 1 – *Process Design (PD): The commercial process is defined during this stage based* on knowledge gained through development and scale-up activities.
- Stage 2 – *Process Qualification (PQ): During this stage, the process design is evaluated to* determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – *Continued Process Verification (CPV): Ongoing assurance is gained during routine* production that the process remains in a state of control.

4. RECOMMENDATION

In the following sections, specific activities for each stage in the product lifecycle are described.

4.1 Stage 1 - Process Design

The objective of this stage is to provide fundamental understanding of the product and process. Product development activities are critical to the process design stage. Information such as the intended dosage form, the quality attributes, and a general manufacturing pathway affects process design. In this early stage, the functionality and limitations of commercial manufacturing equipment should be considered, as well as predicted variability at commercial scale such as different component lots, production operators, environmental conditions and measurement systems. The use of statistical experimental design such as Design of Experiment (DoE) is very useful to determine relationships, including multivariate interactions, between the variable inputs and the resulting outputs. Risk analysis tools can be used to screen potential variables for DoE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, in-process material quality attributes, and also to establish design space.

4.1.1 Design and development

The following are some of the key points to consider in the design and development of a process.

- Quality Target Product Profile **(**QTPP) - These targets should be defined early in product and process development. Elements of QTPP include intended use in clinical setting, dosage form, route of administration, dosage strength, container closure system, pharmacokinetics and etc.
- Critical Quality Attribute (CQA) - CQA are those physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are derived from

QTPP and scientific rationale for CQAs should be explained. They are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product (ICH). CQAs depend on the type of delivery system which will define product specific requirement such as aerodynamic properties for inhaled products, adhesion properties for transdermal patches and etc. Some examples of product CQA for an immediate release (IR) tablet are appearance, physical attributes, dissolution, assay, content uniformity, impurity, microbial limits and etc.

- Formulation and process development – Majority of process understanding work is carried out during formulation and process development. This includes study at lab scale, pilot scale and commercial scale equipment. The preferred ingredients and its concentration are determined. Each unit operation of the entire manufacturing process are identified and it must be consistent with the manufacturing capabilities at future commercial site. Risk assessment tools as described in ICH Q9 can be used to identify potential impact of certain material attributes or process parameters to CQAs. It can be used to rank these parameters in terms of risk level based on prior knowledge and any available initial experimental data.

Below are some of the main considerations:

a. Active Pharmaceutical Ingredient (API):
Properties of API that potentially relevant to the manufacturing process and drug product CQA should be discussed. For examples, particle size, shape, polymorphism, solubility, flowability, compressibility, compatibility with other excipients and etc. Potential risk of API attributes on drug product CQAs should be assessed based on prior knowledge or scientific rationale. The results of the risk assessment should be discussed for each of the API attribute. If the risk is high, then further investigation is required to study the impact. Once the impact is verified, appropriate strategy to control API attribute should be put in place to ensure CQAs can be achieved. Examples of how material attributes of API affect CQAs for both chemical and biological drug can be found in ICH Q11.

b. Formulation development:
The chosen excipients in terms of grade/level can influence CQAs or manufacturability. Functionality of excipients, compatibility of excipients with API and other excipients should also be established. In QbD approach, understanding on how the components of the formulation affect CQAs should be discussed in greater details. The effects need to be studied either mechanistic in nature or empirical. These understanding can help to justify the choice and quality attributes of excipients. For an example, certain excipient is known to cause degradation of API based on its chemical structure. If the use of this excipient cannot be avoided, then further study is required to mitigate the risk such as by reducing the amount or the chances of contact.

During initial formulation development, detailed manufacturing process has not yet been established. Manufacturer can propose a suitable process based on prior knowledge on similar product, similar formulation and/or pre-formulation. An initial risk assessment can be performed to rate the risk based on the flexibility of the unit operation if formulation changes slightly. Risk assessment is performed

based on assumptions and context. Manufacturer should provide justification on the results of initial risk assessment and which factors will be studied in the actual formulation development. After the completion of formulation development experimental studies, often performed in lab scale, formulation risk assessment can be revised accordingly. A proposed product formula is developed and this can now proceed to process development.

c. Process development:
Critical process parameter (CPP) affects CQA and these parameters or variables should be studied based on risk assessment and statistically designed experiment. Types of risk assessment tool are described in ICH Q9. Initial risk assessment can be performed to study the impact of unit operation to CQAs. Initial list of potential critical parameters can be quite extensive, but this can be refined through experimentation. Conventional approach to study effect of process parameter one-factor-at-a-time should not be considered in QbD approach. Instead, DoE should be performed to screen potential critical parameters with reduced number of experimentation. Once CPPs are identified, more detailed DoE study usually at pilot scale can be performed to gain higher level of process understanding and to establish control strategy.

A range of process scales building towards commercial scale can be proposed based on prior knowledge or empirical experiment data. Thereafter, the effect of scale up for each of the unit operation should also be studied or discussed. Scale-up factor can be used for some equipment if properly justified. Once adequate product and process understanding are established at lab and pilot scale, the next step is to transfer this knowledge to the actual manufacturing site. Manufacturing at commercial scale may be significantly different from small scale processing. In fact, some aspects of manufacturing process can only be studied at commercial scale. Effective technology transfer to commercial scale is a critical step to the future process validation and routine manufacturing. Manufacturer may conduct partial scale process to provide more assurance of capabilities at full scale. Thereafter, validation of conformance lots can then commence to confirm the success of QbD development and scale-up.

d. Design space:
In ICH Q8(R2), It is defined as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” Working within this space is not considered as a change and hence does not require regulatory approval. Design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is generally determined through statistically designed experiment such as Design of Experiment (DoE). This enables maximum information with minimum experimental trials. Design space is only for CPP or critical material attributes that has direct impact to product CQA. It can be established for each unit operation or spans a few unit operations or the entire process.

When DoE is performed to establish CPPs and/or design space, manufacturer should provide rationale for selection of DoE variables (including ranges), justification for the type of experimental design used including the power of the design, whether factors are scale-dependent, suitability of the analytical method used, results and statistical analysis of DoE data showing the statistical

significance of individual factor and their interactions and predictions with relevant to scale and equipment differences. Below is an example of design space (non-linear and linear expression) of two CPPs in granulation step in relation to dissolution (extracted from ICH Q8(R2)).

Example 1: Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

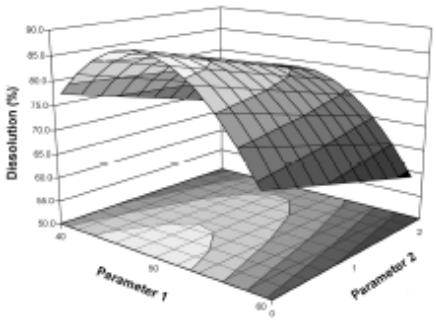

Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

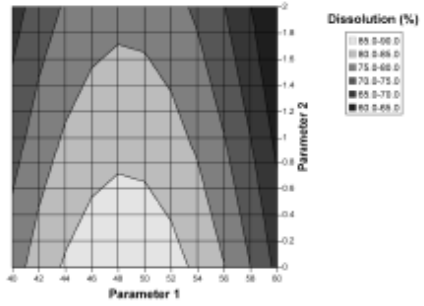

Figure 1b: Contour plot of dissolution from example 1a.

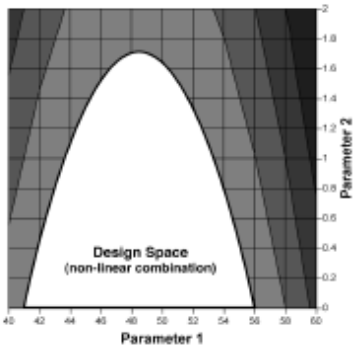

Figure 1c: Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

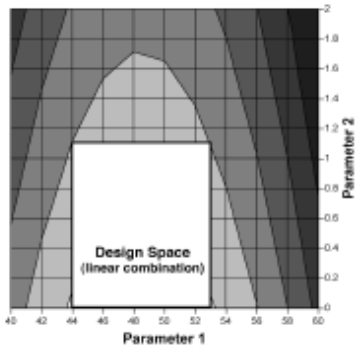

Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

It is important to justify the relevance of a design space developed at small or pilot scale to the proposed production scale manufacturing process and discuss the potential risks in the scale-up operation. Design space should be verified and operational at full scale, although thee is no requirement to develop a design space at the full manufacturing scale. Verification of design space should not be confused with process validaiton. However, it can include monitoring or testing of CQAs that are influenced by scale-dependent parameters. Factors that could trigger design space verification are change of equipment, change of manfuacturing site and etc.

There is no need to run the qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space

must be sufficiently explored earlier during development studies. It is encouraged to determine the edge of failure for process parameters or material attributes, but these are not essential parts of establishing a design space.

A combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space. Proven acceptable ranges from only univariate experimentation may lack an understanding of interactions between the process parameters and/or material attributes.

Mathematical modeling is not required to develop a Design Space, but if chosen the model needs to be verified, updated and maintained. One of the methods to validate the model is through internal cross-validation techniques using the same data set. Prediction accuracy and variability due to process operation and/or analytical method should be explained. The model has to show scale and equipment independent. Design space can be updated over the lifecycle as more knowledge is gained. Operating within design space is part of a control strategy and it is not considered a change, hence post approval filing is not necessary.

4.1.2 Establishing a Strategy for Process Control

The aim of process control is to control variability and it can be achieved by reducing input variation and/or adjust for input variation during manufacturing. Before that, identification of formulation and process variables are key element of life cycle approach to process validation. This includes variation at each unit operation and examples of process input variables are materials, equipments, processes, measurement system, personnel, environment and etc. Strategy to control these variables should be justified based on product and process understanding.

A robust process is able to produce product with acceptable quality despite reasonable variation in process inputs. Manufacturer should study these variables and verify control strategy during commercial production. It may be necessary to revisit the process design stage and strategy for control if the process is found to be not robust. The control strategy should be established in the master production and control records.

More advanced control strategy may include the use of process analytical technology (PAT) which can provide real time analysis and control of the output quality. PAT method is recommended but its process qualification will be different than the other process designs. PAT is often regarded as the enabler tool for QbD where it can enhance process understanding. The use of PAT provides manufacturer the opportunity for real time release without end product testing. However, implementation of real time release testing (RTRT) does not replace the review and quality control steps in releasing a batch under GMP. If RTRT is proposed in product specification, then it should be routinely used for the batch release decisions and not be substituted by end product testing when there is failure. The release of the implicated batch will only be made based on the results of the investigations. In addition, stability studies still need to be performed with the implementation of RTRT.

4.2 Stage 2 – Process Qualification

The objective is to determine whether the process design is capable of reproducible commercial manufacture. It consists of two elements: (1) design of the facility and qualification of the equipment and utilities and (2) Process Performance Qualification (PPQ).

Qualification of utilities and equipment is to ensure they are suitable for their intended use and perform properly. It should include challenging the equipment and system with comparable load, intervention, stoppage and start-up during routine production. This is the pre-requisite for the commencement of PPQ.

PPQ is to confirm process design at commercial scale and it must be successfully executed before the commercial distribution of drug product. It is not typically necessary to study the entire operating range at commercial scale if sufficient assurance can be provided by process design data. However, it is expected to have higher level of sampling, additional testing and greater scrutiny in this stage. It should be continued through the process verification stage as appropriate. Consideration for the duration of the heightened sampling and monitoring period should be based on scientific justification such as prior knowledge, volume of production, process complexity and etc. The use of PAT may warrant a different PPQ approach where it focuses more on the measurement system and control loop of the measured attributes. However, new sampling techniques or new tests should not be attempted in this stage where it should be studied during process design stage. There should be no new requirements or specifications that have not been evaluated.

Before executing the validation, a Validation Master Plan (VMP) that states site validation/qualification general philosophy and approach should be defined. In the VMP, validation plan for this specific PPQ to be executed should include technical considerations to demonstrate process understanding, approach and strategy, documentation requirement and references documents. A written PPQ protocol that specifies the manufacturing conditions, controls, sampling plan, testing, and expected results must be defined and approved by appropriate department before it is being executed. Scientific rationale for the number of batches and sampling plan in PPQ should be statistically justified.

PPQ lots or sometimes called conformance lots should be manufactured under normal routine condition by the expected personnel. PPQ report should summarize data collected and data analysis, discussion on any deviations, unexpected observations, corrective actions and changes, conclusion of whether process is in a state of control. If it does not meet the pre-defined acceptance criteria, manufacturer can re-visit the process design stage to gain more understanding and confidence before repeating the PPQ. The discussion on Stage 3 of Continued Process Verification should also be included in PPQ report.

4.3 Stage 3 – Continued Process Verification

The objective is to provide continual assurance that the process remains in a state of control during routine commercial production. Quality system to monitor process data, to detect any undesirable process variability and the necessary actions should be established. Data collected include process trend and quality of in-coming material, in-process material and finished product. The use of modern statistical software which enable literally instantaneous evaluation of data such as control charting and process capability indicators is recommended. These data should be statistically trended and reviewed periodically by statistician to confirm the validated state. It is recommended to use heightened sampling and testing of process parameters and quality attributes in this stage until sufficient data generated for estimation of variability. This will form the basis for establishing level and frequency of routine sampling and monitoring. Process variability should be reviewed periodically. Annual review of manufacturing data should be regarded as minimum requirement. The frequency and extent of review should be based on product/process risk considerations where more frequent review is expected for

critical process parameters and critical quality attributes. Periodic review can be adjusted accordingly when sufficient reliable product and process history is demonstrated.

(ICH-PtC) CQAs and CPPs can evolve throughout the product life cycle when more product and process understanding are gained. For an example, change of manufacturing process, raw material variability and etc. As such, control strategy to ensure CQAs are met will also evolve throughout the lifecycle. Company should file post approval variation if the change of control strategy is outside the approved design space.

5. REGULATORY SUBMISSION OF DOCUMENTS IN ASEAN COMMON TECHNICAL FORMAT (ACTD)

Information obtained from pharmaceutical development studies could be accommodated by the ACTD format in different ways. Below are some recommendations on how to arrange these information during regulatory submission. Applicant should clearly indicate where the different information is located for ease of reference.

For drug product, most of the product and process development information can be included in the relevant section of Part II P2. For instance, information on impact of API attributes to CQAs can be included in Part II P2.2.1. Formulation development and process development can be included in Part II P2.3 and P2.4 respectively. These include quality risk management, DoE study and basis for design space established through developmental study. However, the proposed design space at commercial scale can be included in Part II P3.2 and P3.3 as it is an element of proposed manufacturing process and control. Information on process qualification (stage 2) at commercial scale should be presented in Part II P3.4. Overall drug product control strategy including continued process verification can be included in Part II P5.6, but detailed information about input material control (i.e. Part II P4) and process control (i.e. Part II P3.3) should be included in the relevant ACTD sections.

Although the above discussion focus on pharmaceutical development Part II P2 of drug product, process validation adopting QbD approach can also be applied to API manufacturing. For API, development of synthesis process at smaller scale including selection of starting material, reagents, equipment, DoE study and basis for design space can be included in Part II S2.6. Verification of the process validation at the commercial scale can be included in Part II S2.5. Proposed design space at commercial scale should be described in Part II S2.2 and S2.4. Overall drug substance control strategy including continued process verification can be included in Part II S4.5 but detailed information about input material control (i.e. Part II S2.3) and process control (i.e. Part II S2.4) should be included in the relevant ACTD sections.

6. GLOSSARY

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 appropriate limit, range, or distribution to ensure the desired product quality.

Design Space:
The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).

Proven Acceptable Range (PAR):
A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

Quality by Design (QbD):
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Quality Target Product Profile (QTPP):
A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

Real Time Release Testing:
The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

ANNEX D GLOSSARY

Concurrent Validation

Validation carried out during routine production of products intended for sale.

Finished Product

A product that has undergone all stages of production and quality control, including packaging in its final container and labelling.

Pilot Batches

These may be used in the development or optimization stage. Pilot batch size should correspond to at least 10% of the future industrial-scale batch. For oral solid dosage forms this size should be at least 10% or 100,000 units whichever is greater unless otherwise justified.

Production Batch

A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Prospective Validation

Establishing documented evidence that a process, procedure, system, equipment or mechanism used in manufacture does what it purports to do based on a pre-planned validation protocol.

Retrospective Validation

Validation of a process for a product that has been marketed based upon accumulated manufacturing, testing and control batch data.