National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

Process Validation (PV)

World Health Organization
WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

PIC/S
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

QUALITY SYSTEM
SIRIM
Certified to ISO 9001:2000
Cert. No: AR 2293

STANDARDS MALAYSIA
ACCREDITED LABORATORY
MS ISO/IEC 17025:2005
[illegible]

Process Validation Scheme
- For Aseptically Processed Products
- For Terminally Sterilised Products

Centre for Product Registration
National Pharmaceutical Control Bureau
Lot 36, Jalan Universiti, 46200 Petaling Jaya,
Selangor

DL: +6.03.78835400 (EXT:5527) | F: +6.03.79571200
WS : www.bpfk.gov.my

Definition

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

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

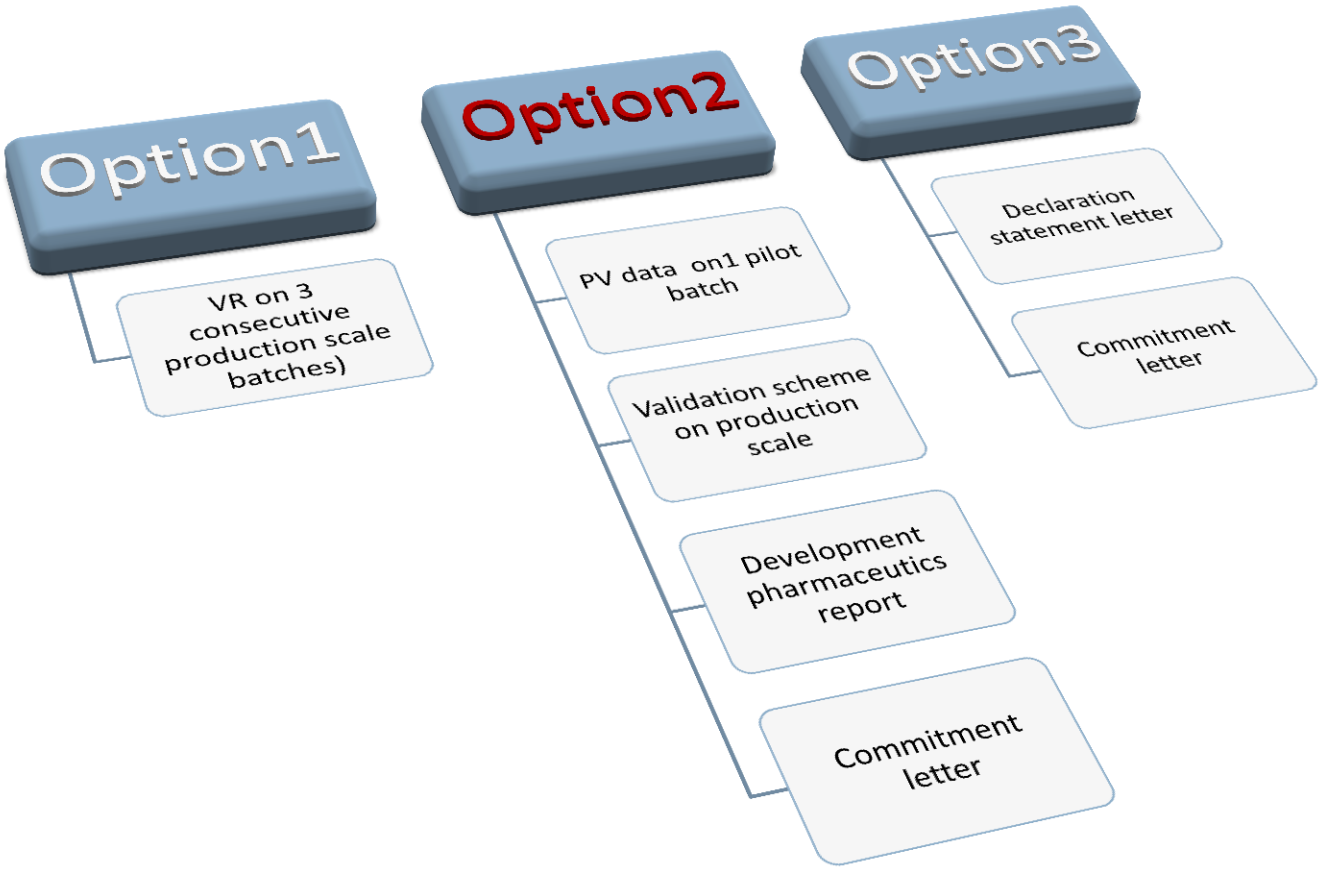
Outline

➢Process Validation Data of Aseptically Processed Products

1. Data Submission Requirements for PV of Aseptic Processes
2. Understand Annex A2 of ASEAN PV Guideline

1. Data Submission Requirements for Aseptically Processed Products

ASEAN Guideline Annex A2
1.Data Submission Requirements for Aseptically Processed Products



Is Option 2 applicable to aseptically processed products?

According to 'Note for option2' in main guide (section3), Option 2 is **NOT** recommended for product manufactured using **non-standard method of sterilization** such as aseptically processed products

ASEAN Guideline Annex A2
1.Data Submission Requirements for Aseptically Processed Products

Note for retrospective & concurrent validation:

1. Retrospective Validation is **NOT** applicable for sterile chemical drug product .

2. Concurrent Validation is only allowable for orphan drug, short lives, medical need product with prior approval according to main guide (section 7.1). Evidence of prior approval such as correspondences and/or pre-submission meeting minute should be provided for screening purpose.

2. Understand Annex A2 of ASEAN PV Guideline

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

ANNEX A2 GUIDANCE ON PROCESS VALIDATION SCHEME FOR ASEPTICALLY PROCEESED PRODUCTS

1. PURPOSE
2. SCOPE
3. GENERAL INFORMATION
4. INFORMATION NEEDED FOR ASEPTIC PROCESSES VALIDATION
   - 4.1. PREMISES
   - 4.2. STERILIZATION AND DEPYROGENATION OF CONTAINERS, CLOSURES, EQUIPMENT AND COMPONENTS
   - 4.3. FILTRATION AND HOLDING TIME
   - 4.4. MEDIA FILLS
   - 4.5. CONTAINER CLOSURE SYSTEM INTEGRITY

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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)

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

- 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.

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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.

- 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 STERILIZATION VALIDATION

4.1. Premises

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

4.3. Filtration and Holding Time

4.4. Media Fills

4.5. Container Closure System Integrity

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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.

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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

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.

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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

4.2.2. Process Validation

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

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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.

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

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 sterilization 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.

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

- 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.

4.3. Filtration and Holding Time

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.

4.4. Media Fills

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

ASEAN Guideline Annex A2
2.Understand Annex A2 of ASEAN PV Guideline

g. Simulations [1]

h. Process parameters[2]

i. Tabulated results and conclusion of microbiological environmental monitoring.

4.4. Media Fills

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.

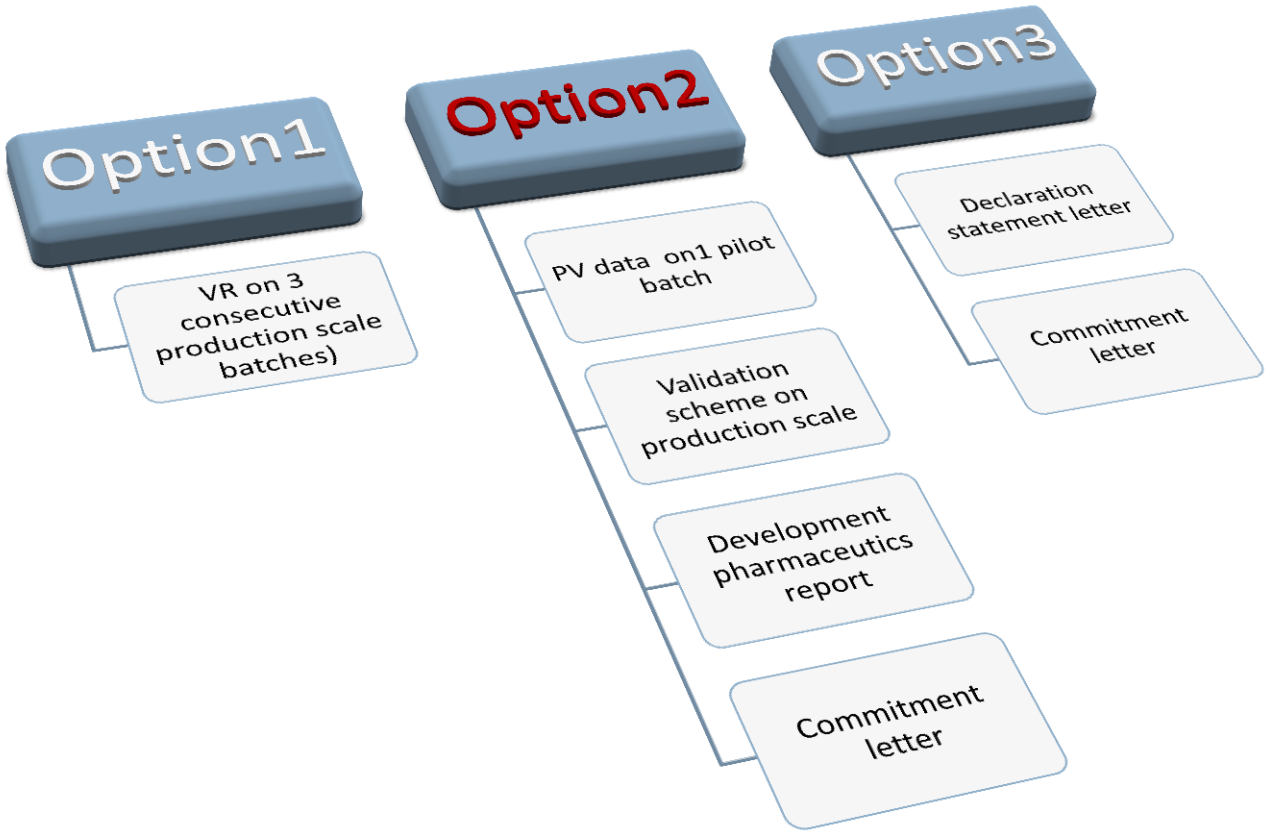
Outline

➢Process Validation Data of Terminally Sterilised Products

1. Data Submission Requirements for PV of Terminal Sterilization
2. Understand Annex A3 of ASEAN PV Guideline

1. Data Submission Requirements for PV of Terminal Sterilization

ASEAN Guideline Annex A3
1.Data Submission Requirements for PV of Terminal Sterilization



Is Option 2 applicable to terminal sterilized products?

According to 'Note for option2' in main guide (section3), Option 2 is **NOT** recommended for product manufactured using **non-standard method of sterilization.**

ASEAN Guideline Annex A3
1.Data Submission Requirements for PV of Terminal Sterilization

Note for retrospective & concurrent validation:

1. Retrospective Validation is **NOT** applicable for sterile chemical drug product

2. Concurrent Validation is only allowable for orphan drug, short lives, medical need product with prior approval according to main guide (section 7.1). Evidence of prior approval such as correspondences and/or pre-submission meeting minute should be provided for screening purpose.

2. Understand Annex A3 of ASEAN PV Guideline

ANNEX A3 GUIDANCE ON PROCESS VALIDATION SCHEME FOR TERMINALLY STERILISED PRODUCTS

1. PURPOSE
2. SCOPE
3. GENERAL INFORMATION
4. INFORMATION NEEDED FOR TERMINAL STERILIZATION PROCESSES
   - 4.1. TERMINAL STERILIZATION PROCESS BY MOIST HEAT
   - 4.2. OTHER TERMINAL STERILIZATION PROCESS
   - 4.3. CONTAINER-CLOSURE SYSTEM (CCS) INTEGRITY

ASEAN Guideline Annex A3

2.Understand Annex A3 of ASEAN PV Guideline

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

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 include:

- Identity of the autoclave (e.g. equipment number, manufacturer and model)
- Cycle type used (e.g. saturated stream, water immersion and water spray)
- Cycle parameters and performance specifications including temperature, pressure, time and minimum and maximum Fo
- 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

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 challenges 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.

ASEAN Guideline Annex A3

2.Understand Annex A3 of ASEAN PV Guideline

- 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 type 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

ASEAN Guideline Annex A3

2.Understand Annex A3 of ASEAN PV Guideline

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

4.2.1. Ethylene Oxide (EO)

- Decision to choose EO sterilization should be justified
- The sterilizer(s) and controlled site(s) for pre-humidification and aeration of the product load.
- 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
- The microbiological methods (growth medium, incubation temperature and time interval) for cultivating spores from inoculated samples during validation experiments.

4.2.2. Radiation

- Radiation facility
- The radiation source and 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
- 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

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

References

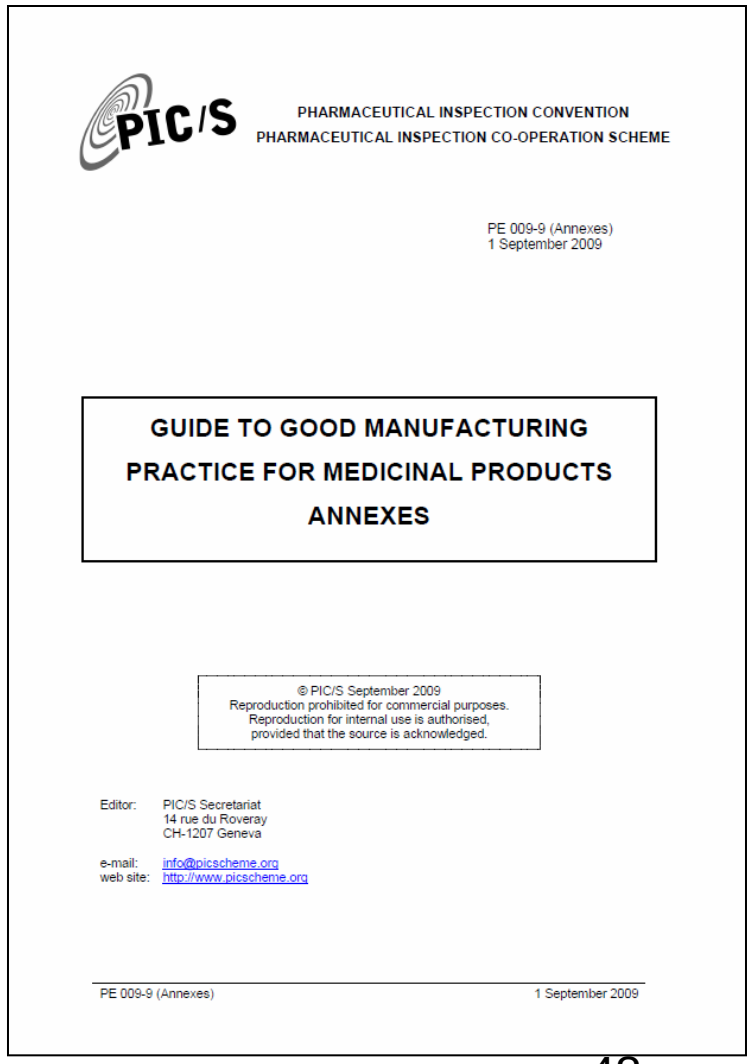
A) **ASEAN Guideline on Submission of manufacturing Process Validation Data for Drug Registration (http://www.bpfk.gov.my)**

- **Annex A2 - Guidance on Process Validation Scheme for Aseptically Processed Products**

- **Annex A3 -Guidance on Process Validation Scheme for Terminally Sterilised Products**

B) PIC/S:

http://www.picscheme.org



Thank You

Kok Chuan Fung

Centre for Product Registration

National Pharmaceutical Control Bureau

kok@bpfk.gov.my