ACTR

ASEAN COMMON TECHNICAL REQUIREMENTS

ACTR

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ASEAN COMMON TECHNICAL REQUIREMENTS (ACTR)

The ASEAN Secretariat
Jakarta

The Association of Southeast Asian Nations (ASEAN) was established on 8 August 1967. The Member States are Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand and Viet Nam.
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ASEAN: A Community of Opportunities

TABLE OF CONTENTS

ASEAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

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ASEAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

1. INTRODUCTION

Throughout the life of a pharmaceutical product, the marketing authorization holder is responsible for the product that is placed in the market and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the pharmaceutical products to be manufactured and checked by means of generally accepted scientific methods. Such amendments have to be approved by the Drug Regulatory Authority.

This guidance document is intended to provide supportive information on the requirements for submission of a variation application to implement a change to a pharmaceutical product. Variation applications are categorized into major variation, minor variation (prior approval) and minor variation (notification). Updating of this guideline will be done on a periodic basis as required.

2. SCOPE OF THIS GUIDELINE

This ASEAN Variation Guideline concerns the variation applications submitted by the marketing authorization holder for pharmaceutical products for human use only and not including biologics.

3. DEFINITION

3.1 Major variation (MaV)

Variation to a registered pharmaceutical finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

3.2 Minor Variation (MiV-N & MiV-PA)

Variation to a registered pharmaceutical finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

4. PROCEDURE AND TIMELINE

Variation application is submitted along with a declaration letter undersigned by the Head of Regulatory Officer that declares there is no other change except for the proposed variation

4.1 Minor Variation – Notification

Type of variation	Minor variation (Notification) MiV-N
Procedure	Notification "Do & Tell" If the notification fulfils the requirements (conditions and supporting documents) as per described under MiV-N, the Drug Regulatory Authority shall acknowledge receipt of a valid notification.
Timeline for the Drug Regulatory Authority to acknowledge the variation notification	Within a duration subject to country specific proposal, following receipt of a valid notification.

4.2 Minor Variation –Prior Approval and Major Variation

Type of variation	Minor variation (Prior approval) MiV-PA	Major variation MaV
Procedure	Prior approval If the application fulfils the requirements (conditions and supporting documents) as per described under MiV-PA, the Drug Regulatory Authority shall issue an approval for the proposed change.	Prior approval If the application fulfils the requirements (conditions and supporting documents) as per described under MaV, the Drug Regulatory Authority shall issue an approval for the proposed change.
Timeline for the Drug Regulatory Authority to evaluate the variation application	Within a duration subject to country specific proposal following receipt of a valid application.	Within a duration subject to country specific proposal following receipt of a valid application.
Implementation of the variation	Within a duration subject to country specific proposal after the marketing authorization holder has been informed of the approved variations.	

Note:

1. The 'timeline' and 'implementation of the variation' is subject to country specific proposals and be made publicly available.
2. The Drug Regulatory Authority reserves the right to re-categorize the application type, where deemed appropriate. Subject to country specific procedure, re- categorization may require the marketing authorization holder to withdraw the original application and resubmit a new application according to the correct category.

5. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

Changes requiring a new product registration may vary from country to country. Certain variations described in this guideline may require a new product registration in certain countries. Applicants are advised to check with individual country on the applicability of this variation guideline

6. OTHERS

6.1 Lead compendium refers to British Pharmacopeia (BP), United States Pharmacopeia (USP) and European Pharmacopeia (EP).

6.2 Any variations not yet listed in this guideline should be justified and decided by the Drug Regulatory Authority. Appropriate reference can be made to:

i. EMA Classification Guidance On Minor Variations of Type IA, Minor Variations of Type IB And Major Variations of Type II.

ii. 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.

iii. 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.

iv. WHO Guidance On Variations To A Prequalified Product Dossier.

6.3 Drug Regulatory Authority reserves the right to request for additional information, when deemed necessary.

6.4 Abbreviations:

C	=	Conditions to be fulfilled
D	=	Documents to be submitted
MaV	=	Major Variation
MiV-N	=	Minor Variation (Notification)
MiV-PA	=	Minor Variation (Prior Approval)

7. MAJOR VARIATION

Major Variation (MaV)	
MaV- 1	**Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product**
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed. 4. Clinical expert reports and/or clinical trial reports (where applicable). 5. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 6. Approval letters from reference countries or country of origin which have approved the new indication or dosing regimen (where applicable). 7. Clinical documents as per ASEAN Common Technical Dossier (ACTD) part IV (where applicable).
MaV-2	**Change of content of product labeling**
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a minor variation and not within the scope of MaV-1. 3. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).

D	1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed and supporting clinical documents when applicable. 4. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable).
MaV-3	**Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. Specifications of drug substances remain unchanged. 2. For Change and/or addition of alternative manufacturer/site of drug substance where European Pharmacopoeial Certificate of Suitability (CEP) is available, please refer to MiV-PA4.
D	1. Complete ACTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by the Drug Regulatory Authority. 2. Comparative tabulated format of the currently registered and revised drug substance manufacture information (where applicable). 3. Batch analysis data (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed manufacturing sites. 4. A letter of commitment from marketing authorization holder to conduct real time and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

MaV-4	Addition or replacement of the manufacturing site of the drug product
C	1. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. 2. For addition or replacement of the company or party responsible for batch release, please refer to MiV-PA3. 3. If there are changes to the manufacturing process, MaV-9 is also applicable.
D	1. Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. 2. Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action). 3. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 6. Comparative dissolution profile data manufactured in the currently approved and proposed manufacturing site for oral solid dosage forms as per compendium and validated dissolution test method. 7. Product formula. 8. Release and shelf-life specifications of drug product. 9. Batch numbering system (where applicable). 10. Specification of drug substance.

	11. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 12. In case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable).
MaV-5	**Addition or replacement of alternative site for primary packaging (direct contact with drug product)**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product).
D	1. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned such as a valid GMP Certificate and/or a CPP which covers GMP certification. 2. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 3. For sterile product, validation scheme and/or report on primary packaging processes as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 6. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable).

MaV-6	**Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]** **a) Specification limits are widened** **b) Deletion of test parameter and limits**
C	1. Test procedures remain the same, or changes in the test procedure are minor. 2. Not applicable to compendial drug substances/drug products. 3. Refer to MiV-PA12 if this change resulted in revision of CEP. 4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	**(a) Specification limits are widened** 1. Justification for change substantiated with scientific data to be provided. 2. Comparative tabulated format of the currently approved and revised specification of drug substance/drug product with changes highlighted. 3. Revised specification of drug substance / drug product. 4. Batch analysis data of the drug substance/drug product for all tests in the new specification for two pilot or production scale batches. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). **(b) Deletion of test parameter and limits** In addition to the above documents except D5, 6. Certificate of analysis of the drug substance/drug product for all tests with the new specification.

MaV-7	Change of batch size of sterile drug product
C	1. The change does not affect consistency of production. 2. Release and shelf-life specifications of drug product remain unchanged. 3. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. The product formulation remains unchanged.
D	1. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size should be provided upon submission. 2. Comparative tabulated format of proposed and currently approved batch manufacturing formula. 3. Batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to currently approved and proposed batch sizes. 4. Release and shelf-life specifications of the drug product. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-8	Change of batch size of non-sterile drug product
C	1. This is applicable to change of batch size more than 10-fold compared to the currently registered batch size. For change of batch size up to 10-fold compared to the currently registered batch size, please refer MiV-PA13. 2. The change does not affect consistency of production. 3. Release and shelf-life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration.
D	1. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration the proposed batch size should be provided upon submission. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. Batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to currently approved and proposed batch sizes and letter of undertaking to submit batch data on the next one full production batch. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 5. Release and shelf-life specifications of the drug product. 6. For oral solid dosage forms, comparative dissolution profile for at least one production batch (where applicable).

MaV-9	Major change in the manufacturing process for drug product
C	1. The same currently approved manufacturing site. If there is a change in manufacturing site, MaV-4 is also applicable. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA20.
D	1. Description of the new manufacturing process and technical justification for the change. 2. Validation scheme and/or report of the proposed manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 3. Copy of currently approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the new process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 4. Comparative batch analysis data of drug product for a minimum of one production batch manufactured according to currently registered and proposed processes. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 6. Comparative dissolution profile data between the products manufactured with the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validated dissolution test method. 7. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-10	**Qualitative or quantitative change of excipient** **a) For immediate release oral dosage forms** **(as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)** **b) For modified release oral dosage forms** **c) For other critical dosage forms such as sterile preparations.**
C	1. Change will need to comply with the finished product specifications for example release and shelf-life specifications of the drug product remain the same, excluding product description. 2. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed new product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Replacement of an excipient with a comparable excipient of the same functional characteristics. 5. For other qualitative or quantitative changes of excipient for immediate release oral dosage forms and other non-critical dosage forms, please refer to MiV-PA15.

D	1. Justification for the change must be given by appropriate development of pharmaceutics. 2. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 3. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation (where applicable). 4. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 5. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 6. Drug product release and shelf-life specifications. 7. Batch analysis data (in a comparative tabulated format) of drug product on at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 11. Revised batch manufacturing formula. 12. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission. 13. Revised ACTD Section P3.1 to P3.4 (where applicable).

MaV-11	**Quantitative change in coating weight of tablets or weight and/ or size of capsule shell for modified release oral dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The product release and shelf-life specifications have only been updated in respect of product description (where applicable). 3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA16.
D	1. Comparative dissolution profile data of at least one pilot/ production batch of the drug product between the currently approved and proposed composition. 2. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 3. Revised release and shelf-life specifications of the drug product. 4. A declaration that the change does not interfere with the drug product release and shelf-life specifications test method. 5. Current and proposed product and batch manufacturing formula. 6. Revised draft of product label incorporating the proposed change (where applicable). 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-12	**Change in primary packaging material for sterile product a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA28.

D	1. Validation scheme and/or report of the manufacturing and sterilization process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in primary packaging material should be provided upon submission. 2. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Comparative tabulated format of specifications of the proposed and current primary packaging material. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 6. Revised ACTD Sections P3 and/or P7 (where applicable). 7. Appropriate scientific data on new packaging (comparative data on permeability, e.g. moisture, O2, CO2).
MaV-13	**Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product**
C	1. Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. The packaging material remains the same. 4. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile drug product, please refer to MiV-PA30.

D	1. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 3. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MaV-14	**Inclusion or replacement of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2. For deletion of the solvent/diluent, please refer to MiV-PA18. 3. For change of shelf-life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please also refer to MaV-15/MiV- PA34 and/or MaV-16/MiV-PA35 (where applicable)
D	1. In addition to section P for the solvent/diluent and reconstitution stability data, section S is required (where applicable). 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. Batch numbering system (where applicable). 4. A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/ diluent (where applicable). 5. Revised artworks for the drug product labels incorporating the changes. 6. A declaration from the marketing authorization holder that the release and shelf-life specifications of drug product are not affected.

MaV-15	**Extension of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c)–The studies must show conformance to the currently approved shelf- life specification for the reconstituted product. 3. For reduction of shelf-life, please refer to MiV-PA34.
D	1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
	3. Justification letter for the change of shelf-life of the drug product (where applicable). 4. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).

MaV-16	**Change of storage conditions of the drug product (Lowering from the current approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf- life specification for the reconstituted product. 3. For change of storage condition (Increasing from the current approved storage condition), please refer to MiV-PA35.
D	1. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Technical justification for the change.

8. MINOR VARIATIONPRIOR APPROVAL

Minor Variation (MiV-PA)	
Prior Approval	
MiV- PA1	**Change of drug product name**
C	1. There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the product name change. 2. No confusion with another drug product either when spoken or written. 3. The new name does not (i) suggest greater safety or efficacy than supported by clinical data (ii) imply a therapeutic use (iii) imply superiority over another similar product and (iv) imply the presence of substance(s) not present in the product.
D	1. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 2. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change. 3. Revised draft package insert and labeling incorporating the proposed variation. 4. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 5. Trademark certificate (where applicable).

MiV- PA2	**Change of product labeling (in accordance to country specific labeling requirement)** Includes: a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication. c) Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labelling. d) Tightening of product's target population. e) Deletion of indication. f) Change of distributor's details.
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a MaV and does not contain promotional information. For major change in product labelling, please refer to MaV-2.
D	1. Current approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change. 4. Relevant document/reference to support the changes (where applicable).
MiV- PA3	**Addition or replacement of the company or party responsible for batch release**
C	1. Only applicable for batch release. 2. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed. 3. The manufacturer of the drug product remains the same.

D	1. Official letter from product owner authorizing the company/ manufacturer to be responsible for batch release (where applicable). 2. Proof that the proposed site is appropriately authorized (accredited by the authority) to be responsible for batch release such as a valid GMP certificate or CPP which covers the GMP certification. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- PA4	**Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]**
C	1. Specifications of drug substances remain unchanged. 2. For change and/or addition of alternative manufacturer/site of drug substance where CEP is not available, please refer to MaV-3.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by the European Directorate for the Quality of medicines (EDQM). 2. Batch analysis data (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed manufacturing sites. 3. If the re-test period is not stated in the CEP, real time and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided. 4. A letter of commitment from marketing authorization holder to conduct real time and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

MiV- PA5	**Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. The change does not affect the reproducibility of the process. 2. Specifications of drug substance remain unchanged. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Comparative batch analysis data with specification and results (in a comparative tabulated format) on a minimum of one production or pilot batch manufactured to both the currently approved and proposed batch sizes. Batch data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 2. A letter of declaration from marketing authorized holder that the specifications of drug substance have not changed and the reproducibility of the process has not been affected. 3. Amended relevant ACTD Section S (where applicable).
MiV- PA 6	**Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in- process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. In-process limits are tightened or addition of new tests. 2. Refer to MiV-PA12 if this change resulted in revision of CEP. 3. The change is not a consequence of any commitment from previous assessments to review specification limits. 4. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

D	1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable). 2. Comparative tabulated format of the proposed and current in-process controls and the relevant changes. 3. Comparative batch analysis data of two production batches of the drug substance for all tests in the proposed specification (where applicable).
MiV- PA7	**Change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. Specifications and stability performance of drug substance remain unchanged. 3. The synthetic route remains the same (for example, intermediates remain the same). 4. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 5. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 6. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Drug Master File (DMF), or relevant updated drug substance (DS) section or equivalent/audit document. 2. Comparative tabulated format of the currently approved and new processes with changes highlighted (where available). 3. Certificate of analysis for two batches of the drug substance. 4. Batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the currently approved and proposed processes.

	5. A letter of declaration from marketing authorization holder stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies. 6. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed or if there is any change to the specification (for example, tightening), the texts of the currently approved and proposed specifications should be provided (in a comparative tabulated format where possible). 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. For sterile drug substance, process validation report (where applicable).
MiV- PA8	**Change of the specification of drug substance** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. This is only applicable for drug substances which are non-compendial and generic drug substances without European Pharmacopoeial Certificate of Suitability (CEP) 2. For (b) - applicable to non-compendial method only. 3. Refer to MiV-PA12 if this change resulted in revision of CEP. 4. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-6. 5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 6. Test procedures remain the same, or changes in the test procedure are minor.

D	**(a) Specification limits are tightened** 1. Comparative tabulated format of the currently approved and revised specification of drug substance with changes highlighted. 2. Comparative batch analysis data of the drug substance for all tests in the new specification for two pilot or production scale batches. 3. Technical justification for the change. **(b) Addition of new test parameter and limits** In addition to the above documents, 4. Description of any new analytical method and summary of the validation data.
MiV- PA9	**Change of the test procedure of non-compendial drug substance**
C	1. Results of method validation show new test procedure to be at least equivalent to the former procedure. 2. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Description of the analytical methodology, a summary of validation data, and comparative analytical results between the currently approved and proposed test (where applicable). 2. Specification of the drug substance.
MiV- PA 10	**Change of shelf-life or re-test period for drug substance**
C	1. The stability studies must show compliance with specification. 2. No change in storage condition. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested shelf-life or retest period. 2. Specifications of the drug substance.

MiV- PA 11	Change of storage condition for drug substance
C	1. The stability studies must show compliance with specification. 2. No change in shelf-life/retest period. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	1. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested storage condition. 2. Specifications of the drug substance.
MiV- PA 12	**Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance**
C	None
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. Specifications of drug substance (where applicable). 3. Results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP (where applicable). 4. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc), if applicable. 5. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). *If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.

MiV- PA13	Change of batch size of non-sterile drug product
C	1. This is applicable to change of batch size up to 10-fold compared to the currently registered batch size. 2. The change does not affect consistency of production. 3. Release and end-of-shelf-life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches at the proposed new batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 5. For change of batch size for sterile products, please refer to MaV-7 and for change of batch size more than 10-fold compared to the currently registered batch size, please refer MaV-8.
D	1. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed batch size should be provided upon submission. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. Batch analysis data (in a comparative table) of drug production a minimum of one production batch according to currently approved and proposed batch sizes and a letter of undertaking to submit batch data on the next full production batch. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 5. Release and shelf-life specifications of the drug product. 6. Revised ACTD Section P3.1-3.4 (where applicable).

MiV- PA14	Reduction or removal of overage
C	1. Changes of previously approved manufacturing overages of drug substance only. 2. Release and end-of-shelf-life specifications of drug product remain unchanged.
D	1. Justification for the change. 2. Comparative tabulated format of currently approved and proposed batch manufacturing formula. 3. Certificate of analysis for two batches of the finished product. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MiV– PA15	**Qualitative and/or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)** **b) For other non-critical dosage forms eg. oral liquid, external preparation.**
C	1. Release and shelf-life specifications of the drug product remain unchanged 2. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Replacement of an excipient with a comparable excipient of the same functional characteristics (where applicable). 5. For qualitative or quantitative change of excipient for immediate release and modified release oral dosage forms and other critical dosage forms, please refer to MaV-10.

D	1. Justification for the change must be given by appropriate development of pharmaceutics. 2. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 3. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation. 4. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies. 5. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 6. Release and shelf-life specifications. 7. Batch analysis data (in a comparative tabulated format) of drug product of at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 11. Revised batch manufacturing formula. 12. A declaration that the new excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 13. Revised ACTD Section P3.1-3.4 (where applicable). 14. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission (where applicable).

MiV– PA16	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage form
C	1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The product release and end-of-shelf-life specifications of the drug product remain unchanged except for the weight and/or size. 3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral solid dosage forms please refer to MaV-11.
D	1. Comparative dissolution profile data of at least one pilot/ production batch of the drug product between the currently approved and proposed composition. 2. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 3. Revised release and shelf-life specifications of the drug product. 4. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 5. Comparative tabulated format of current and proposed product and batch manufacturing formula. 6. Revised draft of product label incorporating the proposed change (where applicable). 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). Except for the change in weight and/or size of capsule shell, a letter of declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline on Stability Study of Drug Product have been started will suffice.

MiV- PA17	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring/flavouring agents must not have been rejected for pharmaceutical use. 3. The release and shelf-life specifications of the drug product remain unchanged except for the change in colour/flavour.
D	1. Qualitative and quantitative information of the current and proposed colouring/flavouring agent in a comparative table. 2. Revised product formulation and batch manufacturing formula. 3. Revised release and shelf-life specifications of the drug product. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 6. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant veterinary authority of the issuing country (where applicable). 7. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 8. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).

MiV- PA18	Deletion of the solvent/diluent for the drug product
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	1. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/ diluent. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Amended relevant ACTD Section P (where applicable).
MiV- PA19	**Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in- process test)**
C	1. Release and shelf-life specifications of drug product remain unchanged. 2. The change is not a consequence of any commitment from previous assessments to review specification limits. 3. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	1. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 2. Revised in-process specifications together with justification and relevant process validation data. 3. Comparative batch analysis data of drug product of at least two production/pilot batches. 4. Comparative tabulated format change of the in-process controls.

MiV- PA20	Minor change of the manufacturing process for non-sterile product
C	1. The same currently approved manufacturing site. 2. The overall manufacturing principle remains the same. 3. The change does not cause negative impact on the quality, safety and efficacy of the drug product. 4. Release and end-of-shelf-life specifications of drug product remain unchanged. 5. The dissolution profile of the proposed product is comparable to that of the current approved product. 6. For major change in the manufacturing process for drug product, please refer to MaV-9.
D	1. Description of the new manufacturing process and technical justification for the change. 2. For semi solid and suspension products, validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 3. For solid oral dosage forms, comparative dissolution profile data of at least one representative production batch of the drug product between the currently approved and proposed solid oral dosage forms formulation. 4. Copy of currently approved release and shelf-life specifications. Or, alternately, copy of revised release and shelf-life specifications that supports that the new process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 5. Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance (where applicable). 6. Batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the currently approved and the proposed process; batch data on the next two full production batches should be made available upon request.

	7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action)." 8. Comparative tabulated format of present and proposed process with changes highlighted.
MiV- PA21	**Change of specifications of an excipient** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Applicable to non compendial excipients. For compendial excipients, please refer to MiV-N9. 2. Release and end-of-shelf-life specifications of drug product remain unchanged. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	1. Comparative tabulated format of the current and revised specification of the excipient with changes highlighted. 2. Batch analysis data of the excipient for all tests in the new specification. 3. Description of new method and summary of analytical validation (applicable for addition of new parameter).
MiV- PA22	**Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure**
C	1. Appropriate method validation studies have been performed in accordance with the ASEAN Guidelines For Validation of Analytical Procedures. 2. Results of method validation show new test procedure to be at least equivalent to the former procedure. 3. There have been no changes of the total impurity limits.

	4. Only applicable to the currently approved test parameters. 5. No new unqualified impurities are detected. 6. This applies for non-compendial excipient.
D	1. Description of the analytical methodology with a comparative tabulation of the changes. 2. For quantitative test change, comparative analytical validation results showing that the current and proposed tests are equivalent.
MiV- PA23	**Change in the source of empty hard capsule**
C	1. From TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 2. No change in the formulation and manufacturing process of drug product. 3. Not applicable to change from hard capsule to soft gel. 4. Excipient and finished product release and end of shelf-life specifications remain unchanged.
D	1. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product using hard capsule between the two sources (where applicable). 2. Certificate of Analysis of the empty hard capsule of the proposed new source. 3. Technical specifications and composition of the empty hard capsule of the new source. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 5. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued by a competent authority of the issuing country. 6. A letter of declaration from the manufacturer or the marketing authorization holder of the material that it is purely of vegetable, animal or synthetic origin.

MiV- PA24	**Change of release and shelf-life specifications of the drug product** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Applicable to non-compendial method. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. The test methods remain the same or changes in the test methods are minor. 4. If there are changes to the test procedure, MiV-PA27 is also applicable. 5. For widening of specification limits and deletion of test parameter and limits of drug product, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Comparative tabulated format of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 2. Comparative batch analysis of the drug product for all tests in the new specification of at least two batches. 3. Technical justification for the change. **(b) Addition of new test parameter and limits** In addition to the above documents: 4. Description of any new method and summary of analytical validation data for non-compendial method. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). (where applicable).

MiV- PA25	Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking
C	**(a) Except score/break-line** 1. New markings do not cause confusion with other registered products. 2. Any ink proposed must comply to relevant pharmaceutical legislation or of food grade and not a listed banned substance. 3. Release and shelf-life specifications of the drug product remain unchanged except for appearance. **(b) On score/break-line** In addition to the above conditions, 4. Score/break-line is not meant for cosmetic purpose. 5. Applicable to addition or removal of score/break-line.
D	**(a) Except score/break-line** 1. Details and specifications of the proposed new inks (where applicable). 2. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 3. Detailed drawing or written description of the current and proposed imprint/bossing/markings. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Release and shelf-life specifications of the drug product with the new product description. 6. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). **(b) On score/break-line** In addition to the above documents, 7. Justification for the change (i.e. change in dosing regimen). 8. Certificate of analysis of two production/pilot scale batches. 9. Data on test of content uniformity of the subdivided parts of the tablets at release should be submitted.

MiV- PA26	**Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass** **a) Immediate release oral solid dosage form, suppositories and pessaries** **b) Other than immediate release oral solid dosage forms, suppositories and pessaries.**
C	1. If appropriate, the dissolution profile of the proposed product is comparable to that of the current approved product. 2. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape.
D	**(a) Immediate release oral solid dosage form, suppositories and pessaries** 1. Detailed drawing or written description of the current and proposed appearance. 2. Release and shelf-life specifications of the drug product. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Comparative dissolution data on at least one pilot/production batch of the currently approved and proposed dimensions. 5. Data on test of content uniformity of the subdivided parts of tablets at release as conformed to compendial requirement should be submitted (only applicable for drug product with score/break-line). **(b) Other than immediate release oral solid dosage forms, suppositories and pessaries** In addition to the above condition, 6. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV- PA27	**Change in the test procedure of the drug product (including replacement or addition of a test procedure)**
C	1. Drug product specifications are not adversely affected unless the specifications are tightened. 2. Results of method verification/validation show new test procedure to be at least equivalent to the former procedure. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	1. Description of the analytical methodology. 2. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test. 3. Certificate of analysis of the finished product of two production batches when made available. 4. Justification for the proposed change. 5. Comparative tabulated format of the currently approved and proposed release and shelf-life specifications of the drug product.
MiV- PA28	**Change in primary packaging material for non-sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. Release and end-of-shelf-life specifications of drug product remain unchanged. 2. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 3. The change only concerns the same packaging type (for example from blister to blister). 4. For change in the primary packaging material for sterile drug product, please refer to MaV-12.

D	1. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 2. For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). 3. Comparative tabulated format of the currently approved and proposed specifications of the primary packaging material (where applicable). 4. Revised drafts of the package insert incorporating the proposed variation (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MiV- PA 29	**Addition or replacement of a manufacturer for secondary packaging**
C	None
D	1. Proof that the proposed site is appropriately authorized (accredited by the authority) for the packaging activity concerned such as a valid GMP certificate and/or CPP which covers the GMP certification. 2. Official letter from product owner authorizing the new manufacture or packager to perform secondary packaging (where applicable). 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- PA30	**Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. The new size is consistent with the dosage regimen and duration of use as approved in the package insert.

	3. Change in the dimension of the primary packaging material (where applicable). 4. For change of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product, please refer to MaV-13. 5. The change only concerns the same packaging type and material.
D	1. Justification for the proposed pack size. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).
MiV- PA31	**Change of outer carton pack sizes for a drug product**
C	1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a drug product. 3. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the marketing authorization holder stating that no other changes except for the change of outer carton pack sizes for a drug product.

MiV- PA 32	**Change in any part of the (primary) packaging material not in contact with the finished product formulation such as colour of flip- off caps, colour code rings on ampoules, change of needle shield (different plastic used)**
C	1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
D	1. Amendment of the relevant section(s) of the dossier (presented in the ACTD format), including revised product labeling as appropriate.
MiV- PA33	**Addition or replacement of measuring device for oral liquid dosage forms and other dosage form**
C	1. The size and where applicable, the accuracy of the proposed measuring device must be compatible with the approved posology. 2. The new device is compatible with the drug product.
D	1. Description of the device (including a drawing; where applicable). 2. The composition of the device material. Where applicable the materials should comply with the pharmacopoeia. 3. Justification that size and accuracy of the device are adequate for the posology as is approved in the product labeling. 4. Revised draft of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- PA34	**Reduction of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification.

	2. For (c) – The studies must show conformance to the currently approved shelf- life specification for the reconstituted product. 3. For extension of shelf-life, please refer to MaV-15.
D	1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf-life of the drug product (where applicable). 4. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).
MiV- PA35	**Change of storage conditions of the drug product (Increasing from the current approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf- life specification for the reconstituted product. 3. For change of storage condition (lowering from the current approved storage condition), please refer to MaV-16..

D	1. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Technical justification for the change of storage condition.

9. MINOR VARIATION NOTIFICATION

Minor Variation (MiV-N)	
Notification	
MiV-N1	**Change in name and/or address (for example: postal code, street name) of the marketing authorization holder** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The name change refers to the renaming of a company or organization. 2. The change does not include transfer of marketing authorization to another company. 3. For change on the part of marketing authorization holder in product labelling only. Please refer to MaV-2 and MiV-PA3 if other parts are involved.
D	1. Letter by the product owner authorizing the new name of marketing authorization holder to hold the product license. 2. Official document from the relevant authority confirming the change with the new name and/or address. 3. Revised draft package insert and labeling incorporating the proposed variation (where applicable).
MiV- N2	**Change of product owner**
C	1. The marketing authorization holder remains the same. 2. The manufacturing site remains the same.
D	1. Declaration on the transfer of ownership between old product owner and new owner. 2. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license.

	3. If the new product owner is not the manufacturer of the drug product, an official letter by the new product owner authorizing the manufacturer to manufacture the drug product on its behalf. 4. If the new product owner is not the manufacturer of the drug product, letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- N3	**Change in ownership of manufacturer** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturing site remains unchanged. 2. No other changes except for the change in ownership of manufacturer.
D	1. Letter of justification on the transfer of ownership such as a valid GMP certificate. 2. Official letter stating the transfer of ownership from old manufacturer to new manufacturer (where applicable). 3. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the new manufacturer to manufacture the drug products on its behalf. 4. In case of a contract manufacturer, letter of acceptance from the new manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- N4	**Change of the name or address (for example: postal code, street name) of the manufacturer of drug product** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]

C	1. The manufacturing site remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3. 3. No other changes except for the change of the name and/or address of a manufacturer of the drug product.
D	1. Official letter from product owner authorizing the manufacturer with new name/address to manufacture the drug product. 2. A valid GMP certificate, CPP which covers the GMP certification or official document from relevant authority confirming the new name and/or address. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- N5	**Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturer of the drug product remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3. 3. The batch release site remains the same.
D	1. Official letter from product owner authorizing company/ manufacturer with new name/address responsible for batch release. 2. A valid GMP certificate CPP which covers the GMP certification or official document from relevant authority confirming the new name or address (where applicable). 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. A declaration from the marketing authorization holder that the change does not involve ~~a~~ change of batch release site.

MiV- N6	**Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance**
C	1. The manufacturing site of the drug substance remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug substance.
D	1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence when required.
MiV-N7	**Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)**
C	1. An alternative manufacturer is registered.
D	1. Reason for withdrawal/deletion.
MiV-N8	**Renewal of European Pharmacopoeial Certificate of Suitability (CEP)**
C	1. Only applicable if the renewal of CEP does not involve any variation.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM.
MiV-N9	**Change of release and shelf-life specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium**
C	1. Applicable to compendial specifications only. 2. Change is made exclusively to comply with an update of the relevant monograph of the compendium.

D	1. Tabulation of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 2. Batch analysis of the drug product for all tests in the new specification of at least two batches. 3. Revised release and shelf-life specifications.
MiV-N10	**Deletion of pack size for a product**
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling. 2. For addition of pack size for sterile and non-sterile products, please refer to MaV-13 and MiV-PA30 respectively. For change in the outer carton pack size, please refer to MiV-PA31.
D	1. Reason for deletion. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

10. GLOSSARY

Refer to ACTD/ACTR Glossary

REFERENCES

1. European Medicine Agency Variation Guideline, 2008
2. Communication from the Commission — Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products - Official Journal of the European Union (C 17/1 of 22.01.2010)
3. Commission Regulation (EC) No 1234/2008 Official Journal of the European Union (L334 of 12 December 2008)
4. WHO Guidance on Variations To A Prequalified Product Dossier, 2007
5. SUPAC Guideline 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, November 1995
6. SUPAC-MR: Modified Release Solid, Oral Dosage Forms, Scale-Up and Post - approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997
7. WHO Technical Report Series, No. 953, 2009
8. WHO Quality Assurance of Pharmaceuticals – A Compendium of Guidelines and Related Materials – Volume 1
9. ASEAN Guideline on Stability Study of Drug Product, 22 February 2005
10. ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration
11. ASEAN Guideline for Validation of Analytical Procedures
12. ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Studies, 21 July 2004

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

TABLE OF CONTENTS

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: Version adopted in 19th ACCSQ-PPWG meeting (Jul 2012)

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

TABLE OF CONTENTS

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

Equipment	Equipment Class
Mill	Fluid energy mill Impact mill Cutting mill Compression mill Screening mill Tumbling mill
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

Equipment	Equipment Class
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
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

Process Step	Tablet	Capsule	PGS	Process Parameters
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
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

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 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 CONTENTS 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			
○ Pilot batch	☐	_____	_____
○ 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 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.

ASEAN GUIDELINE FOR THE CONDUCT OF BIOEQUIVALENCE STUDIES

Adopted from the :

"GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE" (European Medicines Agency,London,20 January 2010,CPMP/EWP/QWP/1401/98 Rev 1)

with some adaptation for ASEAN application.

Document Control

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Revision 1, Draft 3	May 2013, Bali, Indonesia
Revision 1, Draft 4	June 2014, Kuala Lumpur, Malaysia
Revision 1, Draft 4 **FINAL**	March 2015 , Vientiane ,Lao PDR

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This guideline specifies the requirements for the design, conduct, and evaluation of bioequivalence studies for immediate release dosage forms with systemic action.

1. INTRODUCTION

1.1 Background

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy.

In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption. Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products. AUC, the area under the concentration time curve, reflects the extent of exposure. C_{max}, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, t_{max}, are parameters that are influenced by absorption rate.

It is the objective of this guideline to specify the requirements for the design, conduct, and evaluation of bioequivalence studies. The possibility of using *in vitro* instead of *in vivo* studies is also addressed.

1.2 Generic medicinal products

In applications for generic medicinal products , the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a comparator medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator

medicinal product. A generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same dosage form as the medicinal product, and whose bioequivalence with the comparator medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

1.3 Other types of application

Other types of applications may also require demonstration of bioequivalence, including variations, fixed combinations and extensions applications.

The recommendations on design and conduct given for bioequivalence studies in this guideline may also be applied to comparative bioavailability studies evaluating different formulations used during the development of a new medicinal product containing a new chemical entity and to comparative bioavailability studies included in extension that are not based exclusively on bioequivalence data.

2. SCOPE

This guideline focuses on recommendations for bioequivalence studies for immediate release formulations with systemic action. It also sets the relevant criteria under which bioavailability studies need not be required (either waiver for additional strength, see section 3.1.6, a specific type of formulation, see Appendix II or BCS based Biowaiver, see Appendix III).

Specific recommendations regarding bioequivalence studies for other products, eg. Modified release products, transdermal products and orally inhaled products etc, refer to relevant guidelines as stated below.

The scope is limited to chemical entities. Recommendation for the comparison of biologicals to comparator medicinal products can be found in guidelines on similar biological medicinal products.

In case bioequivalence cannot be demonstrated using drug concentrations, in exceptional circumstances pharmacodynamic or clinical endpoints may be needed. This situation is outside the scope of this guideline and the reader is referred to therapeutic area specific guidelines.

Although the concept of bioequivalence possibly could be considered applicable for herbal medicinal products, the general principles outlined in this guideline are not applicable to herbal medicinal products, for which active constituents are less well defined than for chemical entities.

This guideline should be read in conjunction with other pertinent elements outlined in current and relevant guidelines and regulations including those on :

- General Considerations for Clinical Trials (ICH topic E8, CPMP/ICH/291/95)
- Guideline for Good Clinical Practice (ICH E6 (R1), CPMP/ICH/135/95)
- Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- Structure and Content of Clinical Study Reports (ICH E3, CPMP/ICH/137/95)
- Pharmacokinetic studies in man (Eudralex, Volume 3, 3CC3a)
- Modified Release Oral and Transdermal Dosage Forms: Sections I and II (CPMP/QWP/ 604/96, CPMP/EWP/280/96)
- Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev 1) Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) (CPMP/EWP/4151/00 Rev 1)
- Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents (CPMP/EWP/239/95)
- ASEAN Common Technical Dossier
- ASEAN Analytical Validation Guidelines

- Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to establish Interchangeability (WHO)
- Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009

The guideline should also be read in conjunction with relevant guidelines on pharmaceutical quality. The test products used in the bioequivalence study must be prepared in accordance with GMP regulations.

3. MAIN GUIDELINE TEXT

3.1 Design, conduct and evaluation of bioequivalence studies

The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths (see sections 3.1.4, 3.1.5 and 3.1.6).

3.1.1 Study design

The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Standard design

If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this.

Alternative designs

Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half-life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics (see section 3.1.10).

Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.

In the rare situation where problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration and where the concentrations at steady state are sufficiently high to be reliably measured, a multiple dose study may be acceptable as an alternative to the single dose study. However, given that a multiple dose study is less sensitive in detecting differences in C_{max}, this will only be acceptable if the applicant can adequately justify that the sensitivity of the analytical method cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a supra-therapeutic dose in the bioequivalence study (see also section 3.1.6). Due to the recent development in the bioanalytical methodology, it is unusual that parent drug cannot be measured accurately and precisely. Hence, use of a multiple dose study instead of a single dose study, due to limited sensitivity of the analytical method, will only be accepted in exceptional cases.

In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life).

3.1.2 Comparator and test product

Comparator Product

Test products in an application for a generic product or an extension of a generic product are normally compared with the corresponding dosage form of a comparator product . The selection of comparator product should be based on the selection criteria of ASEAN comparator product as follows:

i. Innovator product and multiple manufacturing sites of the same innovator registered in the country is acceptable.

ii. If the innovator product used as comparator is not registered in the country, justification is required from the generic company to prove its interchangeability with the registered innovator (in vitro or in vivo).

iii. If the innovator product cannot be identified, the choice of comparator must be made carefully and be comprehensively justified by the applicant. The selection criteria of a comparator in order of preference are:
   - Approval in ICH and associated countries
   - Pre-qualified by WHO

   A well selected comparator must conform to compendia quality standards, if applicable.

It is recommended to clarify with the regulatory authority regarding the choice of comparator product before the bioequivalence study is conducted.

The selection of the batch of comparator product used in a bioequivalence study should be based on assay content and dissolution data and is the responsibility of the applicant . Unless otherwise justified, the assayed content of the batch used as test product should not differ more than 5% from that of the batch used as comparator product determined with the test procedure proposed for routine quality testing of the test product. Certificate of analysis

(CoA) of the comparator product can be submitted to support that the assayed content of the batch used as test product does not differ more than 5% from the comparator batch. The Applicant should document how a representative batch of the comparator product with regards to dissolution and assay content has been selected. It is advisable to investigate more than one single batch of the comparator product when selecting comparator product batch for the bioequivalence study.

Test product

The test product used in the study should be representative of the product to be marketed and this should be discussed and justified by the applicant.

For example, for oral solid forms for systemic action:

a) The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.

b) The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale.

   In case of a production batch smaller than 100,000 units, a full production batch will be required.

c) The characterisation and specification of critical quality attributes of the drug product, such as dissolution, should be established from the test batch, i.e. the clinical batch for which bioequivalence has been demonstrated.

d) Samples of the product from additional pilot and / or full scale production batches, submitted to support the application, shall be compared with those of the bioequivalence study test batch, and shall show similar in vitro dissolution profiles when employing suitable dissolution test conditions (see Appendix I).

Comparative dissolution profile testing shall be undertaken on the first three production batches. The results shall be provided at a Regulatory Authority"s request or if the dissolution profiles are not similar together with proposed action to be taken.

For other immediate release dosage forms for systemic action, justification of the representative nature of the test batch should be similarly established.

Packaging of study products

The comparator and test products should be packed in an individual way for each subject and period, either before their shipment to the trial site, or at the trial site itself. Packaging (including labeling) should be performed in accordance with good manufacturing practice.

It should be possible to identify unequivocally the identity of the product administered to each subject at each trial period. Packaging, labeling and administration of the products to the subjects should therefore be documented in detail. This documentation should include all precautions taken to avoid and identify potential dosing mistakes. The use of labels with a tear-off portion is recommended.

3.1.3 Subjects

Number of subjects

The number of subjects to be included in the study should be based on an appropriate sample size calculation.

For a standard two way crossover study,the number of subjects required is determined by :

a) the intra-subject coefficient of variation of the drug to be studied either estimated from a pilot study, results of previous clinical studies or from published literature.
b) the significance level desired (α=0.05)

c) the expected deviation from the comparator product ratio of T/R (delta between 5% to 10%)

d) the acceptance limit (should be in accordance with the respective sections in the guidance ie. 3.1.8, 3.1.9 & 3.1.10)

e) the required statistical power of study should be at least 80%

The clinical and analytical standards imposed may also influence the statistically determined number of subjects. However, generally the minimum number of subjects should not be smaller than 12.

Selection of subjects

The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical. This model, *in vivo* healthy volunteers, is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the comparator medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.).

The inclusion/exclusion criteria should be clearly stated in the protocol. Subjects should be 18-55 years of age and preferably have a Body Mass Index between 18 and 30 kg/m^2.

The subjects should be screened for suitability by means of clinical laboratory tests, a medical history, and a physical examination. Depending on the drug"s therapeutic class and safety profile, special medical investigations and precautions may have to be carried out before, during and after the completion of the study. Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. Phenotyping

and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.

In parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status). This is an essential pre-requisite to give validity to the results from such studies.

If the investigated active substance is known to have adverse effects, and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to include patients instead, under suitable precautions and supervision.

3.1.4 Study conduct

Standardisation

The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested. Therefore, it is recommended to standardise diet, fluid intake and exercise.

The time of day for ingestion should be specified. Subjects should fast for at least 8 hours prior to administration of the products, unless otherwise justified. As fluid intake may influence gastric passage for oral administration forms, the test and comparator products should be administered with a standardised volume of fluid (at least 150 ml). It is recommended that water is allowed as desired except for one hour before and one hour after drug administration and food is allowed no less than 4 hours after drug administration . Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time (e.g. 12 hours).

In case the study is to be performed during fed conditions, the timing of administration of the drug product in relation to food intake is

recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, it is recommended that subjects should start the meal 30 minutes prior to administration of the drug product and eat this meal within 30 minutes.

As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic drinks or certain fruit juices such as grapefruit juice) during a suitable period before and during the study. Subjects should not take any other concomitant medication (including herbal remedies) for an appropriate interval before as well as during the study. Contraceptives are, however, allowed. In case concomitant medication is unavoidable and a subject is administered other drugs, for instance to treat adverse events like headache, the use must be reported (dose and time of administration) and possible effects on the study outcome must be addressed. In rare cases, the use of a concomitant medication is needed for all subjects for safety or tolerability reasons (e.g. opioid antagonists, anti-emetics). In that scenario, the risk for a potential interaction or bioanalytical interference affecting the results must be addressed.

Medicinal products that according to the originator SmPC are to be used explicitly in combination with another product (e.g. certain protease inhibitors in combination with ritonavir) may be studied either as the approved combination or without the product recommended to be administered concomitantly.

In bioequivalence studies of endogenous substances, factors that may influence the endogenous baseline levels should be controlled if possible (e.g. strict control of dietary intake).

Sampling times

A sufficient number of samples to adequately describe the plasma concentration- time profile should be collected. The sampling schedule should include frequent sampling around predicted t_{max} to provide a reliable estimate of peak exposure. In particular, the sampling schedule should be planned to avoid C_{max} being the first point of a concentration time curve. The sampling schedule should also cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-\infty)}$. At least three to four samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant (which is needed for a reliable estimate of $AUC_{(0-\infty)}$). AUC truncated at 72 h ($AUC_{(0-72h)}$) may be used as an alternative to $AUC_{(0-t)}$ for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations. A sampling period longer than 72 h is therefore not considered necessary for any immediate release formulation irrespective of the half life of the drug.

In multiple-dose studies, the pre-dose sample should be taken immediately before (within 5 minutes) dosing and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of $AUC_{(0-\tau)}$.

If urine is used as the biological sampling fluid, urine should normally be collected over no less than three times the terminal elimination half-life. However, in line with the recommendations on plasma sampling, urine does not need to be collected for more than 72 h. If rate of excretion is to be determined, the collection intervals need to be as short as feasible during the absorption phase (see also section 3.1.5).

For endogenous substances, the sampling schedule should allow characterisation of the endogenous baseline profile for each subject in each period. Often, a baseline is determined from 2-3

samples taken before the drug products are administered. In other cases, sampling at regular intervals throughout 1-2 day(s) prior to administration may be necessary in order to account for fluctuations in the endogenous baseline due to circadian rhythms (see section 3.1.5).

Fasting or fed conditions

In general, a bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the SmPC recommends intake of the comparator medicinal product on an empty stomach or irrespective of food intake, the bioequivalence study should hence be conducted under fasting conditions. For products where the SmPC recommends intake of the comparator medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.

However, for products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state.

In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four- way cross-over study.

In studies performed under fed conditions, the composition of the meal is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high- calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with

regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

3.1.5 Characteristics to be investigated

Pharmacokinetic parameters

Actual time of sampling should be used in the estimation of the pharmacokinetic parameters. In studies to determine bioequivalence after a single dose, $AUC_{(0-t),}$ $AUC_{(0-\infty)}$, C_{max} and t_{max} should be determined. In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, $AUC_{(0-\infty)}$ and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, $AUC_{(0-72h)}$. Additional parameters that may be reported include the terminal rate constant, λ_z, and $t_{1/2}$.

In studies to determine bioequivalence for immediate release formulations at steady state, $AUC_{(0-\tau),}$ $C_{max,ss}$, and $t_{max,ss}$ should be determined.

When using urinary data, $Ae_{(0-t)}$ and $R_{max} = \left(\frac{dAe}{dt}\right)_{max}$ should be determined.

Non-compartmental methods should be used for determination of pharmacokinetic parameters in bioequivalence studies. The use of compartmental methods for the estimation of parameters is not acceptable.

Parent compound or metabolites

General recommendations

In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite.

Inactive pro-drugs

Also for inactive prodrugs, demonstration of bioequivalence for parent compound is recommended. The active metabolite does not need to be measured. However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound. In the context of this guideline, a parent compound can be considered to be an inactive pro- drug if it has no or very low contribution to clinical efficacy.

Use of metabolite data as surrogate for active parent compound

The use of a metabolite as a surrogate for an active parent compound is not encouraged. This can only be considered if the applicant can adequately justify that the sensitivity of the analytical method for measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a higher single dose in the bioequivalence study (see also section 3.1.6). Due to recent developments in bioanalytical methodology it is unusual that parent drug cannot be measured accurately and precisely. Hence, the use of a metabolite as a surrogate for active parent compound is expected to be accepted only in exceptional cases. When using metabolite data as a substitute for active parent drug concentrations, the applicant should present any available data supporting the view that the metabolite exposure will reflect parent drug and that the metabolite formation is not saturated at therapeutic doses.

Enantiomers

The use of achiral bioanalytical methods is generally acceptable. However, the individual enantiomers should be measured when all the following conditions are met:

(1) the enantiomers exhibit different pharmacokinetics

(2) the enantiomers exhibit pronounced difference in pharmacodynamics
(3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

The individual enantiomers should also be measured if the above conditions are fulfilled or are unknown. If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer.

The use of urinary data

The use of urinary excretion data as a surrogate for a plasma concentration may be acceptable in determining the extent of exposure where it is not possible to reliably measure the plasma concentration-time profile of parent compound. However, the use of urinary data has to be carefully justified when used to estimate peak exposure. If a reliable plasma C_{max} can be determined, this should be combined with urinary data on the extent of exposure for assessing bioequivalence. When using urinary data, the applicant should present any available data supporting that urinary excretion will reflect plasma exposure.

Endogenous substances

If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment. Administration of supra-therapeutic doses can be considered in bioequivalence studies of endogenous drugs, provided that the dose is well tolerated, so that the additional concentrations over baseline provided by the treatment may be reliably determined. If a separation in exposure following administration of different doses of a particular endogenous substance has not been previously

established this should be demonstrated, either in a pilot study or as part of the pivotal bioequivalence study using different doses of the comparator formulation, in order to ensure that the dose used for the bioequivalence comparison is sensitive to detect potential differences between formulations.

The exact method for baseline correction should be pre-specified and justified in the study protocol. In general, the standard subtractive baseline correction method, meaning either subtraction of the mean of individual endogenous pre- dose concentrations or subtraction of the individual endogenous predose AUC, is preferred. In rare cases where substantial increases over baseline endogenous levels are seen, baseline correction may not be needed.

In bioequivalence studies with endogenous substances, it cannot be directly assessed whether carryover has occurred, so extra care should be taken to ensure that the washout period is of an adequate duration.

3.1.6 Strength to be investigated

If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues described below. The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.

In case of non-linear pharmacokinetics (i.e. not proportional increase in AUC with increased dose) there may be a difference between different strengths in the sensitivity to detect potential differences between formulations. In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered. In order to

assess linearity, the applicant should consider all data available in the public domain with regard to the dose proportionality and review the data critically.

If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, *in vivo* bioequivalence studies for the other strength(s) can be waived.

General biowaiver criteria

The following general requirements must be met where a waiver for additional strength(s) is claimed:

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

   If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) **or** i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

   i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content

   ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed

   iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing (see section 3.2).

Linear pharmacokinetics

For products where all the above conditions a) to d) are fulfilled, it is sufficient to establish bioequivalence with only one strength.

The bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble (see Appendix III), selection of a lower strength than the highest is also acceptable. Selection of a lower strength may also be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Further, if problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration of the highest strength, a higher dose may be selected (preferably using multiple tablets of the highest strength). The selected dose may be higher than the highest therapeutic dose provided that this single dose is well tolerated in healthy volunteers and that there are no absorption or solubility limitations at this dose.

Non-linear pharmacokinetics

For drugs with non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above.

For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or a strength in the linear range), i.e. in this situation two bioequivalence studies are needed. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that conditions a) to d) above are fulfilled and the test and comparator products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength (or a strength in the linear range). Selection of other strengths may be justified if there are analytical sensitivity problems preventing a study at the lowest strength or if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons.

Bracketing approach

Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies.

Where bioequivalence assessment is needed both in fasting and in fed state and at two strengths due to nonlinear absorption or deviation from proportional composition, it may be sufficient to assess bioequivalence in both fasting and fed state at only one of the strengths. Waiver of either the fasting or the fed study at the other strength(s) may be justified based on previous knowledge and/or pharmacokinetic data from the study conducted at the strength tested in both fasted and fed state. The condition selected (fasting

or fed) to test the other strength(s) should be the one which is most sensitive to detect a difference between products.

Fixed combinations

The conditions regarding proportional composition should be fulfilled for all active substances of fixed combinations. When considering the amount of each active substance in a fixed combination the other active substance(s) can be considered as excipients. In the case of bilayer tablets, each layer may be considered independently.

3.1.7 Bioanalytical methodology

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP). (EMA/OECD GLP/WHO GLP STANDARD/ISO/IEC 17025/2005). If national GLP requirements are in accordance with Organisation for Economic Co-operation and Development (OECD),drug regulatory authority may conduct site inspection based on the OECD principle.

The bioanalytical methods used must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. Within study validation should be performed using Quality control samples in each analytical run.

The main characteristics of a bioanalytical method that is essential to ensure the acceptability of the performance and the reliability of analytical results are: selectivity, lower limit of quantitation, the response function (calibration curve performance), accuracy, precision and stability.

The lower limit of quantitation should be 1/20 of C_{max} or lower, as pre-dose concentrations should be detectable at 5% of C_{max} or lower (see section 3.1.8. *Carry-over effects*).

Reanalysis of study samples should be predefined in the study protocol (and/or SOP) before the actual start of the analysis of

the samples. Normally reanalysis of subject samples because of a pharmacokinetic reason is not acceptable. This is especially important for bioequivalence studies, as this may bias the outcome of such a study.

Analysis of samples should be conducted without information on treatment.

3.1.8 Evaluation

In bioequivalence studies, the pharmacokinetic parameters should in general not be adjusted for differences in assayed content of the test and comparator batch. However, in exceptional cases where a comparator batch with an assay content differing less than 5% from test product cannot be found (see section 3.1.2) content correction could be accepted. If content correction is to be used, this should be pre-specified in the protocol and justified by inclusion of the results from the assay of the test and reference products in the protocol.

Subject accountability

Ideally, all treated subjects should be included in the statistical analysis. However, subjects in a crossover trial who do not provide evaluable data for both of the test and comparator products (or who fail to provide evaluable data for the single period in a parallel group trial) should not be included.

The data from all treated subjects should be treated equally. It is not acceptable to have a protocol which specifies that „spare" subjects will be included in the analysis only if needed as replacements for other subjects who have been excluded. It should be planned that all treated subjects should be included in the analysis, even if there are no drop-outs.

In studies with more than two treatment arms (e.g. a three period study including two comparator ,one from EU and another from USA, or a four period study including test and reference in fed and fasted

states), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question.

Reasons for exclusion

Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules. These rules should be independent from treatment or outcome. In consequence, the decision to exclude a subject from the statistical analysis must be made before bioanalysis.

In principle any reason for exclusion is valid provided it is specified in the protocol and the decision to exclude is made before bioanalysis. However the exclusion of data should be avoided, as the power of the study will be reduced and a minimum of 12 evaluable subjects is required.

Examples of reasons to exclude the results from a subject in a particular period are events such as vomiting and diarrhoea which could render the plasma concentration-time profile unreliable. In exceptional cases, the use of concomitant medication could be a reason for excluding a subject.

The permitted reasons for exclusion must be pre-specified in the protocol. If one of these events occurs it should be noted in the CRF as the study is being conducted. Exclusion of subjects based on these pre-specified criteria should be clearly described and listed in the study report.

Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics.

The exceptions to this are:

1) A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data due to this reason will only be accepted in exceptional cases and may question the validity of the trial.

2) Subjects with non-zero pre-dose concentrations > 5% of C_{max}. Such data should be excluded from bioequivalence calculation (see carry-over effects below).

The above can, for immediate release formulations, be the result of subject non- compliance and an insufficient wash-out period, respectively, and should as far as possible be avoided by mouth check of subjects after intake of study medication to ensure the subjects have swallowed the study medication and by designing the study with a sufficient wash-out period. The samples from subjects excluded from the statistical analysis should still be assayed and the results listed (see *Presentation of data* below).

As stated in section 3.1.4, $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-\infty).}$ Subjects should not be excluded from the statistical analysis if $AUC_{(0-t)}$ covers less than 80% of $AUC_{(0-\infty),}$ but if the percentage is less than 80% in more than 20% of the observations then the validity of the study may need to be discussed. This does not apply if the sampling period is 72 h or more and $AUC_{(0-72h)}$ is used instead of $AUC_{(0-t).}$

Parameters to be analysed and acceptance limits

In studies to determine bioequivalence after a single dose, the parameters to be analysed are $AUC_{(0-t),}$ or, when relevant, $AUC_{(0-72h)}$, and C_{max}. For these parameters, the 90% confidence interval for the

ratio of the test and reference products should be contained within the acceptance interval of 80.00- 125.00%.

For studies to determine bioequivalence of immediate release formulations at steady state, $AUC_{(0-\tau)}$ and $C_{max,ss}$ should be analysed using the same acceptance interval as stated above.

In the rare case where urinary data has been used, $Ae_{(0-t)}$ should be analysed using the same acceptance interval as stated above for $AUC_{(0-t).}$ Rmax should be analysed using the same acceptance interval as for C_{max}.

A statistical evaluation of tmax is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median t_{max} and its variability between test and reference product.

In specific cases of products with a narrow therapeutic range, the acceptance interval for AUC may need to be tightened (see section 3.1.9). Moreover, for highly variable drug products the acceptance interval for C_{max} may in certain cases be widened (see section 3.1.10).

Statistical analysis

The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/ reference) for the parameters under consideration. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level.

The pharmacokinetic parameters under consideration should be analysed using ANOVA. The data should be transformed prior to analysis using a logarithmic transformation. A confidence interval for the difference between formulations on the log-transformed scale is obtained from the ANOVA model. This confidence interval is then back-transformed to obtain the desired confidence interval

for the ratio on the original scale. A non-parametric analysis is not acceptable.

The precise model to be used for the analysis should be pre-specified in the protocol. The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable. The terms to be used in the ANOVA model are usually sequence, subject within sequence, period and formulation. Fixed effects, rather than random effects, should be used for all terms.

Carry-over effects

A test for carry-over is not considered relevant and no decisions regarding the analysis (e.g. analysis of the first period only) should be made on the basis of such a test. The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable).

If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis should be performed with the data from that subject for that period excluded. In a 2-period trial this will result in the subject being removed from the analysis. The trial will no longer be considered acceptable if these exclusions result in fewer than 12 subjects being evaluable. This approach does not apply to endogenous drugs.

Two-stage design

It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated, an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted, appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be

clearly defined prior to the study. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company"s discretion. The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

When analysing the combined data from the two stages, a term for stage should be included in the ANOVA model.

Presentation of data

Refer to APPENDIX IV (ASEAN Bioequivalence Study Reporting Format)

3.1.9 Narrow therapeutic index drugs

In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where C_{max} is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.

3.1.10 Highly variable drugs or drug products

Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate

and/or extent of absorption, a replicate cross-over design study can be carried out.

Those HVDP for which a wider difference in C_{max} is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case, the acceptance criteria for C_{max} can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened, the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for C_{max} of the reference compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

The extent of the widening of C_{max} criteria follows the table as below:

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

* CV (%) = $100 \sqrt{e^{s2WR} - 1}$

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

3.2 *In vitro* dissolution tests

General aspects of *in vitro* dissolution experiments are briefly outlined in Appendix I including basic requirements how to use the similarity factor (f_2-test).

3.2.1 *In vitro* dissolution tests complementary to bioequivalence studies

The results of *in vitro* dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media,if applicable and available), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics.

Unless otherwise justified, the specifications for the *in vitro* dissolution to be used for quality control of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the comparator product (see Appendix I).

In the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails.

However, possible reasons for the discrepancy should be addressed and justified.

3.2.2 *In vitro* dissolution tests in support of biowaiver of strengths

Appropriate *in vitro* dissolution should confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous section (normally pH 1.2, 4.5 and 6.8) unless

otherwise justified. Similarity of *in vitro* dissolution (see App. I) should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) (i.e. batch(es)) used for bioequivalence testing.

At pH values where sink conditions may not be achievable for all strengths *in vitro* dissolution may differ between different strengths. However, the comparison with the respective strength of the reference medicinal product should then confirm that this finding is drug substance rather than formulation related. In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 5 mg versus one tablet of 10 mg could be compared).

3.3 Study report

3.3.1 Bioequivalence study report

The report of the bioequivalence study should give the complete documentation of its protocol, conduct and evaluation. It should be written in accordance with APPENDIX IV (ASEAN Bioequivalence Study Reporting Format) and be signed by the investigator. The responsible investigator(s), if any, should sign for their respective sections of the report.

Names and affiliations of the responsible investigator(s), the site of the study and the period of its execution should be stated. Audits certificate(s), if available, should be included in the report.

The study report should include the reference product name, strength, dosage form, batch number, manufacturer, expiry date and country of purchase.

The name and composition of the test product(s) used in the study should be provided. The batch size, batch number, manufacturing date and, if possible, the expiry date of the test product should be stated.

Certificates of analysis of reference and test batches used in the study should be included in an appendix to the study report.

Concentrations and pharmacokinetic data and statistical analyses should be presented in detail .

3.3.2 Other data to be included in an application

The applicant should submit a signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorisation. A confirmation whether the test product is already scaled-up for production should be submitted. Comparative dissolution profiles (see section 3.2) should be provided.

Data sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual times of blood sampling, drug concentrations, the values of the pharmacokinetic parameters for each subject in each period and the randomisation scheme, should be available in a suitable electronic format (e.g. as comma separated and space delimited text files or Excel format) to be provided upon request.

3.4 Variation applications

If a product has been reformulated from the formulation initially approved or the manufacturing method has been modified in ways that may impact on the bioavailability, an *in vivo* bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per APPENDIX III, or on whether an acceptable *in vitro / in vivo* correlation has been established .

In cases where the bioavailability of the product undergoing change has been investigated and an acceptable correlation between in vivo performance and *in vitro* dissolution has been established, the requirements for in vivo demonstration of bioequivalence can be

waived if the dissolution profile *in vitro* of the new product is similar to that of the already approved medicinal product under the same test conditions as used to establish the correlation (see APPENDIX I).

When variations to a generic product are made, the comparative medicinal product for the bioequivalence study should normally be a current batch of the reference medicinal product. If a valid reference medicinal product is not available on the market, comparison to the previous formulation (of the generic product) could be accepted, if justified. For variations that do not require a bioequivalence study, the advice and requirements stated in other published regulatory guidance should be followed.

DEFINITIONS

Pharmaceutical equivalence

Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.

Pharmaceutical alternatives

Pharmaceutical alternatives are medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength.

Pharmacokinetic parameters

$Ae_{(0-t)}$	Cumulative urinary excretion of unchanged drug from administration until time t;
$AUC_{(0-t):}$	Area under the plasma concentration curve from administration to last observed concentration at time t;
$AUC_{(0-\infty)}$	Area under the plasma concentration curve extrapolated to infinite time;
$AUC_{(0-\tau):}$	AUC during a dosage interval at steady state; $AUC_{(0-72h)}$ Area under the plasma concentration curve from administration to 72h;
C_{max}	Maximum plasma concentration;
$C_{max,ss}$	Maximum plasma concentration at steady state;
residual area	Extrapolated area (AUC(0-∞) - AUC(0-t))/ AUC(0-∞);
$R_{max} = \left(\frac{dAe}{dt}\right)_{max}$	Maximal rate of urinary excretion;
t_{max}	Time until Cmax is reached;
$t_{max,ss}$	Time until Cmax,ss is reached;
$t_{1/2}$	Plasma concentration half-life;
λ_z	Terminal rate constant;
SmPC	Summary of Product Characteristics

APPENDIX I

Dissolution testing and Similarity of Dissolution Profiles

1. General aspects of dissolution testing as related to bioavailability

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a bioequivalence study. Therefore, dissolution studies can serve several purposes:

i – Testing on product quality

- To get information on the test batches used in bioequivalence studies and pivotal clinical studies to support specifications for quality control
- To be used as a tool in quality control to demonstrate consistency in manufacture
- To get information on the reference product used in bioavailability/ bioequivalence studies and pivotal clinical studies.

ii – Bioequivalence surrogate inference

- To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product (biowaivers e.g., variations, formulation changes during development and generic medicinal products; see section 3.2 and App. III)
- To investigate batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the *in vivo* study.

Test methods should be developed product related based on general and/or specific pharmacopoeial requirements. In case those requirements are shown to be unsatisfactory and/or do not reflect the *in vivo* dissolution (i.e. biorelevance) alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product *in vivo*. Current state-of-the-art information including the interplay of characteristics derived from the BCS classification and the dosage form must always be considered.

Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pHrange and the excipients are known not to affect bioavailability. In contrast, if an active substance is considered to have a limited or low solubility, the rate limiting step for absorption may be dosage form dissolution. This is also the case when excipients are controlling the release and subsequent dissolution of the active substance. In those cases a variety of test conditions is recommended and adequate sampling should be performed.

2. Similarity of dissolution profiles

Dissolution profile similarity testing and any conclusions drawn from the results (e.g. justification for a biowaiver) can be considered valid only if the dissolution profile has been satisfactorily characterised using a sufficient number of time points.

For immediate release formulations, further to the guidance given in section 1 above, comparison at 15 min is essential to know if complete dissolution is reached before gastric emptying.

Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%.

For modified release products, the advice given in the relevant guidance should be followed.

Dissolution similarity may be determined using the f_2 statistic as follows:

$$\mathbf{f}_2 = 50 \log \left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} (R_t - T_t)^2}{n}}} \right)$$

In this equation f_2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent test drug dissolved at time t after initiation of the study. For both the reference and test formulations, percent dissolution should be determined.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for any of the formulations.
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less thann10% from second to last time point.

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

When the f_2 statistic is not suitable, then the similarity may be compared using model-dependent or model-independent methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points.

Alternative methods to the f_2 statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified.

The similarity acceptance limits should be pre-defined and justified and not be greater than a 10% difference. In addition, the dissolution variability of the test and reference product data should also be similar, however, a lower variability of the test product may be acceptable.

Evidence that the statistical software has been validated should also be provided. A clear description and explanation of the steps taken in the application of the procedure should be provided, with appropriate summary tables.

APPENDIX II

Bioequivalence study requirements for different dosage forms

Although this guideline concerns immediate release formulations, Appendix II provides some general guidance on the bioequivalence data requirements for other types of formulations and for specific types of immediate release formulations.

When the test product contains a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference medicinal product, bioequivalence should be demonstrated in *in vivo* bioequivalence studies. However, when the active substance in both test and reference products is identical (or contain salts with similar properties as defined in Appendix III, section III), *in vivo* bioequivalence studies may in some situations not be required as described below and in Appendix III.

Oral immediate release dosage forms with systemic action

For dosage forms such as tablets, capsules and oral suspensions, bioequivalence studies are required unless a biowaiver is applicable (see APPENDIX III). For orodispersable tablets and oral solutions specific recommendations apply, as detailed below.

Orodispersible tablets

An orodispersable tablet (ODT) is formulated to quickly disperse in the mouth. Placement in the mouth and time of contact may be critical in cases where the active substance also is dissolved in the mouth and can be absorbed directly via the buccal mucosa. Depending on the formulation, swallowing of the e.g. coated substance and subsequent absorption from the gastrointestinal tract also will occur. If it can be demonstrated that the active substance is not absorbed in the oral cavity, but rather must be swallowed and absorbed through the gastrointestinal tract, then the product might be considered for a BCS based biowaiver (see Appendix III). If this cannot be demonstrated, bioequivalence must be evaluated in human studies.

If the ODT test product is an extension to another oral formulation, a 3-period study is recommended in order to evaluate administration of the orodispersible tablet both with and without concomitant fluid intake. However, if bioequivalence between ODT taken without water and reference formulation with water is demonstrated in a 2-period study, bioequivalence of ODT taken with water can be assumed.

If the ODT is a generic to an approved ODT reference medicinal product, the following recommendations regarding study design apply:

- if the reference medicinal product can be taken with or without water, bioequivalence should be demonstrated without water as this condition best resembles the intended use of the formulation. This is especially important if the substance may be dissolved and partly absorbed in the oral cavity. If bioequivalence is demonstrated when taken without water, bioequivalence when taken with water can be assumed.
- if the reference medicinal product is taken only in one way (e.g only with water), bioequivalence should be shown in this condition (in a conventional two-way crossover design).
- if the reference medicinal product is taken only in one way (e.g. only with water), and the test product is intended for additional ways of administration (e.g. without water), the conventional and the new method should be compared with the reference in the conventional way of administration (3 treatment, 3 period, 6 sequence design).

In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing 20 ml of water directly before applying the ODT on the tongue. It is recommended not to allow fluid intake earlier than 1 hour after administration.

Other oral formulations such as orodispersible films, buccal tablets or films, sublingual tablets and chewable tablets may be handled in a similar way as for ODTs. Bioequivalence studies should be conducted according to the recommended use of the product.

Oral solutions

If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), *in vivo* solubility (e.g. co-solvents) or *in vivo* stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers (see Appendix III, Section IV.2 Excipients).

In those cases where the test product is an oral solution which is intended to be bioequivalent to another immediate release oral dosage form, bioequivalence studies are required.

Fixed combination dosage forms

Bioequivalence requirements are covered in the "Guideline on Clinical Development of Fixed Combination Medicinal Products". The possibility for a biowaiver of Fixed Combination Medicinal Products is addressed in Appendix III section V.

Non-oral immediate release dosage forms with systemic action

This section applies to e.g. rectal formulations. In general, bioequivalence studies are required. A biowaiver can be considered in the case of a solution which contains an active substance in the same concentration as an approved solution and with the same qualitative and similar quantitative composition in excipients (conditions under oral solutions may apply in this case).

Parenteral solutions

Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any

excipients interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required. Moreover, a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity.

Liposomal, micellar and emulsion dosage forms for intravenous use

- **Liposomal formulations**: Pharmacokinetic issues related to liposomal formulations for iv administration require special considerations which are not covered by the present guideline.
- **Emulsions**: emulsions normally do not qualify for a biowaiver. However, emulsion formulations may be considered eligible for a biowaiver where:

  (a) the drug product is not designed to control release or disposition

  (b) the method and rate of administration is the same as the currently approved product

  In these cases, the composition should be qualitatively and quantitatively the same as the currently approved emulsion and satisfactory data should be provided to demonstrate very similar physicochemical characteristics, including size distribution of the dispersed lipid phase, and supported by other emulsion characteristics considered relevant e.g. surface properties, such as Zeta potential and rheological properties.

- **Lipids for intravenous parenteral nutrition** may be considered eligible for a biowaiver if satisfactory data are provided to demonstrate comparable physicochemical characteristics. Differences in composition may be justified taking into consideration the nature and the therapeutic purposes of such dosage forms.
- **Micelle forming formulations**: micelle solutions for intravenous administration may be regarded as „complex" solutions and therefore normally do not qualify for a biowaiver. However, micelle formulations may be considered eligible for a biowaiver where:

  (a) rapid disassembly of the micelle on dilution occurs and the drug product is not designed to control release or disposition

  (b) the method and rate of administration is the same as the currently approved product

  (c) the excipients do not affect the disposition of the drug substance.

  In these cases, the composition of the micelle infusion, immediately before administration, should be qualitatively and quantitatively the same as that currently approved and satisfactory data should be provided to demonstrate similar physicochemical characteristics. For example, the critical micelle concentration, the solubilisation capacity of the formulation (such as Maximum Additive Concentration), free and bound active substance and micelle size.

This also applies in case of minor changes to the composition quantitatively or qualitatively, provided this does not include any change of amount or type of surfactants.

Modified release dosage forms with systemic action

Modified release oral and transdermal dosage forms

Requirements for bioequivalence studies in accordance with the specific Guidelines on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96).

Modified release intramuscular or subcutaneous dosage forms

For suspensions or complexes or any kind of matrix intended to delay or prolong the release of the active substance for im or sc administration, demonstration of bioequivalence follows the rules for extra vascular modified release formulations, e.g. transdermal dosage forms as per corresponding guideline.

Locally acting locally applied products

For products for local use (after oral, nasal, pulmonary, ocular, dermal, rectal, vaginal etc. administration) intended to act at the site of application, recommendations can be found in other guidelines(eg. CPMP/EWP/4151/00 rev 1,CPMP/EWP/239/95).

A waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved. Minor differences in the excipient composition may be acceptable if the relevant pharmaceutical properties of the test product and reference product are identical or essentially similar. Any qualitative or quantitative differences in excipients must be satisfactorily justified in relation to their influence on therapeutic equivalence. The method and means of administration should also be the same as the medicinal product currently approved, unless otherwise justified.

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic

exposure should be measured. It should be demonstrated that the systemic exposure is not higher for the test product than for the reference product, i.e. the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit 125.00.

Gases

If the product is a gas for inhalation, bioequivalence studies are not required.

APPENDIX III

BCS-based Biowaiver

I. Introduction

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e*., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index (see section 3.1.9). The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same dosage form. However, it is not applicable for sublingual, buccal, and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

It is recommended to clarify with the regulatory authorities regarding the implementation of BCS-based biowaiver in the respective countries.

II. Summary Requirements

BCS-based biowaiver are applicable for an immediate release drug product if

- the drug substance has been proven to exhibit high solubility and complete absorption (BCSclass I; for details see section III.1 and III.2) and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see section IV.1) and

- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see section IV.2).

Generally the risks of an inappropriate biowaiver decision should be critically reviewed. (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks)

III. Drug Substance

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the drug substance characteristics of importance for the biowaiver concept.

Biowaiver may be applicable when the active substance(s) in test and reference products are identical. Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption; see sections *III.1* and *III.2*). Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

The drug substance should not belong to the group of „narrow therapeutic index" drugs (see section 3.1.9 on narrow therapeutic index drugs).

III.1 Solubility

The pH-solubility profile of the drug substance should be determined and discussed. The drug substance is considered highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g.

shake-flask method or other justified method). Solution pH should be verified prior and after addition of the drug substance to a buffer.

III.2 Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from

- absolute bioavailability or
- mass-balance

studies could be used to support this claim.

When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption. Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged drug substance in the gastric or intestinal fluid. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

The more restrictive requirements will apply for compounds proposed to be BCS class I but where complete absorption could not convincingly be demonstrated.

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed *in vitro* permeability investigations including reference standards may also be considered supportive to *in vivo* data.

IV. Drug Product

IV.1 In vitro Dissolution

IV.1.1 General aspects

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar *in vitro* dissolution under physiologically relevant experimental pH conditions. However, this does not establish an *in vitro*/*in vivo* correlation. *In vitro* dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. The use of any surfactant is not acceptable.

Test and reference products should meet requirements as outlined in section 3.1.2 of the main guideline text. In line with these requirements it is advisable to investigate more than one single batch of the test and reference products.

Comparative *in vitro* dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation. Usual experimental conditions are e.g.:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less
- Temperature of the dissolution medium: 37±1 °C
- Agitation: paddle apparatus - usually 50 rpm
  basket apparatus - usually 100 rpm
- Sampling schedule: e.g. 10, 15, 20, 30 and 45 min
- Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; Ph.Eur. buffers recommended)

- Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.

Complete documentation of *in vitro* dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

IV.1.2 Evaluation of *in vitro* dissolution results

Drug products are considered „very rapidly" dissolving when more than 85 % of the labelled amount is dissolved within 15 min. In cases where this is ensured for the test and reference product the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation.

Absence of relevant differences (similarity) should be demonstrated in cases where it takes more than 15 min but not more than 30 min to achieve almost complete (at least 85 % of labelled amount) dissolution. F_2-testing (see App. I) or other suitable tests should be used to demonstrate profile similarity of test and reference. However, discussion of dissolution profile differences in terms of their clinical/therapeutical relevance is considered inappropriate since the investigations do not reflect any *in vitro/in vivo* correlation.

IV.2 Excipients

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS-class I) is considered rather unlikely, it cannot be completely excluded. Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product.

As a general rule, for BCS-class I drug substances, well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients

is required with a justification whether the amount of each excipient is within the normal range. Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on

- gastrointestinal motility
- susceptibility of interactions with the drug substance (e.g. complexation)
- drug permeability
- interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product.

V. Fixed Combinations (FCs)

BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I and the excipients fulfil the requirements outlined in section IV.2. Otherwise *in vivo* bioequivalence testing is required.

APPENDIX IV

ASEAN Bioequivalence Study Reporting Format

1. **Title Page**
   - 1.1 Study Title
   - 1.2 Name and address of Sponsor
   - 1.3 Name, person in charge and address of Institution
   - 1.4 Name and address of Principal Investigator
   - 1.5 Name of Medical/ Clinical Investigator
   - 1.6 Name, person in charge and address of clinical laboratory
   - 1.7 Name, person in charge and address of analytical laboratory
   - 1.8 Name, person in charge and address for Data Management, Pharmacokinetics and Statistical Analysis
   - 1.9 Name and address of Other Investigator(s) & study personnel
   - 1.10 Start and end date of clinical and analytical study
   - 1.11 Signature and date of investigator(s), (medical writer, QA Manager – if applicable)
2. **Study Synopsis**
3. **Table of Contents**
4. **Abbreviation and Definition of Terms**
5. **Introduction**
   - 5.1 Pharmacology
   - 5.2 Pharmacokinetics
   - 5.3 Adverse events
6. **Objective**
7. **Product Information**
   - 7.1 Test Product Information

- Trade Name
- Active Ingredient, Strength, and Dosage Form
- Batch Number, Manufacturing Date and Expiry Date
- Batch size compliance (can be directly provided by sponsor)
- Product Formulation (can be directly provided by sponsor)
- Finished Product Specifications (can be directly provided by sponsor)
- Name and Address of Manufacturer

7.2 Comparator Product Information
- Trade Name
- Active Ingredient, Strength, and Dosage Form
- Batch Number, Manufacturing Date and Expiry Date
- Name and Address of Manufacturer
- Name and Address of Importer or Authorization Holder

7.3 Pharmaceutical Equivalence Data
- Comparing content of Active Ingredient / Potency
- Uniformity of Dosage Units

7.4 Comparison of Dissolution Profiles (can be directly provided by sponsor)

7.5 Letter with a signed statement from the applicant/sponsor confirming that the test product is the same as the one that is submitted for marketing authorization

8. Investigational Plan

8.1 Clinical Study Design
- Study design (crossover, parallel)
- Fed, fasted
- Inclusion, exclusion, restriction
- Standardization of study condition
- Drug administration
- Removal of Subject from Assessment
- Health screening
- Subject detail, no of subjects, deviation
- Sampling protocol/time, sample preparation/handling, storage, deviation
- Volume of blood collected
- Subject monitoring

- Genetic phenotyping (if applicable)

8.2 Study Treatments
- Selection of Doses – single, multiple
- Identity of Investigational Products, dosing
- Randomization
- Blinding
- Washout period
- Water intake volume

8.3 Clinical and Safety Records
- Adverse Event
- Drug related Adverse Drug Reaction

8.4 Pharmacokinetic Parameters and Tests
- Definitions and calculation

8.5 Statistical Analyses
- Log transformed data analysis (AUC, Cmax)
- Sampling Time Adjustments
- t max,
- t ½
- Acceptance Criteria for Bioequivalence
- ANOVA presentation
- Power

8.6 Assay Methodology and Validation
- Assay method description
- Method of detection
- Validation procedure and summary results
  - Specificity;
  - Accuracy;
  - Precision;
  - Recovery;
  - Stability;
  - LOQ Linearity

8.7 Data Quality Assurance

9. Results and Discussion

9.1 Clinical Study Results
- Demographic characteristics of the subjects.

- Details of clinical activity.
- Deviation from protocol, if any.
- Results of drug/alcohol/smoking usage, medical history and medical examination, vital sign and diagnostic laboratory test of subjects.
- Adverse event/reaction reports for test product and comparator product.

9.2 Summary of analytical results

9.3 Pharmacokinetic Analyses
- Drug levels at each sampling time, descriptive statistics
- Table of individual subject pharmacokinetic parameters, descriptive statistics
- Figure of mean plasma or urine concentration-time profile
- Figure of individual subject plasma or urine concentration-time profile

9.4 Statistical Analyses
- Statistical considerations
- Time points selected for Kel, $t_{1/2}$
- Summary statistics of pharmacokinetic parameters: AUCt, % AUC extrapolated, AUC_{inf}, C_{max}, t_{max}, $t_{1/2}$
- Summary of statistical significance for AUC and C_{max} (based on log-transformed data calculated as point estimate and 90 % CI of test/comparator Geometric Means) and for t_{max} (based on non-transformed data calculated as p value).
- Similar calculation for urine data: Ae and dAe/dt (Ae corresponds to AUC, $(dAe/dt)_{max}$ corresponds to C_{max}).
- Intra-subject variability
- Power of study
- Assessment of sequence, period and treatment effects
- Table - Analysis of Variance, Geometric least-squares means for each pharmacokinetic parameters.
- Table - Calculation of 90% confidence interval for the ratio of pharmacokinetic parameters under consideration in logarithmic transformation.

10. Conclusions

11. Appendices

11.1 Protocol and Approval
- Letter of approval from DRA (if applicable)
- Study protocol and its amendments together with Institutional Review Board/Ethical Committee approvals
- Informed Consent Form
- Protocol deviation listing
- Adverse Event listing
- FP specification and CoA

11.2 Validation Report (including 20% of raw chromatograms)

11.3 Analytical Report (including 20% of raw chromatograms)

11.4 Certificate of Clinical Facility, Clinical Laboratory and Certificate of Analytical Laboratory (if any)

11.5 Dose proportionality comparative dissolution profiles between various strengths (when BE study investigating only one strength but application for registration consists of several strengths (from sponsor).

ASEAN GUIDELINE
ON STABILITY STUDY OF DRUG PRODUCT

Update revision : 15 May 2013

20th ACCSQ-PPWG Meeting, Bali, Indonesia, 13 - 17 May 2013

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Stability is an essential factor of quality, safety and efficacy of a drug product. Insufficient stability of a drug product can result in changes in physical (like hardness, dissolution rate, phase separation, etc.) as well as in chemical characteristics (formation of high risk decomposition substances). Microbiological instability of a sterile drug product could also be hazardous.

1.2. In principle, stability testing should be biased towards more stressful rather than less stressful conditions so as to provide a margin of error in favour of the patients and to increase the likelihood of identifying substances or formulations that pose particular stability problems.

1.3. The objective of a stability study is to determine the shelf-life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications.

1.4. The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the specifications of the drug product packed in its specified packaging material and stored at the established storage condition within the determined time period.

1.5. The general conditions for long term stability testing in the ASEAN region are the Zone IVb conditions (30°C/75% RH).

2. OBJECTIVES

This guideline is intended to provide recommendations on the core stability study package required for drug products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the products being evaluated. This guideline can also be used to propose shelf- life based on the stability data generated from the study package.

3. SCOPE

This guideline addresses the information to be submitted during application for marketing authorization/registration and variations of drug products in ASEAN Member States including examples of a protocol of stability study, a report format, reduced design and extrapolation of data, and examples of types, thickness and permeability coefficient which are covered in Annexes.

The drug products covered in this guideline include NCE, Generics and Variations (MaV and MiV) but exclude biologicals and drug products containing vitamin and mineral preparations.

4. DESIGN

4.1. General

The design of the stability studies for the product should be based on knowledge of the behavior and properties of the drug substance and dosage form.

4.2. Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

4.3. Selection of Batches

At the time of submission, stability data should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

- For NCE stability data should be provided on at least three primary batches of the drug products.
- For Generics and Variations the following will apply :
  - For conventional dosage forms (e.g., immediate release solid dosage forms, solutions) and when the drug

substances are known to be stable, stability data on at least two pilot scale batches are acceptable.

- For critical dosage forms (e.g., prolonged release forms) or when the drug substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be at least of a pilot scale; the third batch may be smaller, if justified.

- The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specification as that intended for marketing.
- Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.
- Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

4.4. Specification

i. Specification is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf-life specifications.

ii. Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during development

of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the drug product should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf- life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

4.5. Testing Parameters

i. Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). The analytical procedure should be fully validated and stability-indicating according to the ASEAN guideline on Analytical Validation. Whether and to what extent replication should be performed will depend on the results from validation studies.

ii. In general, appearance, assay and degradation products should be evaluated for all dosage forms. For generic products, degradation products should use current compendia as a minimum requirement. The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every listed test be included in the design of a stability protocol for a particular drug product (for example, a test for odour should be performed only when necessary and with consideration for analyst's safety).

- 1. Tablets

  Tablets should be evaluated for appearance, odour, colour, assay, degradation products, dissolution (or disintegration, if justified), water content, and hardness/ friability.

- 2. Capsules

  Hard gelatin capsules should be evaluated for appearance (including brittleness), colour, and odour of content, assay, degradation products, dissolution, water content and microbial limits.

  Testing of soft gelatin capsules should include appearance, colour, and odour of content, assay, degradation products, dissolution, microbial limits, pH, leakage, and pellicle formation. In addition, the fill medium should be examined for precipitation and cloudiness.

- 3. Emulsions

  Emulsions should be evaluated for appearance (including phase separation), colour, odour, assay, degradation products, pH, viscosity, microbial limits, preservative content, and mean size and distribution of dispersed globules.

- 4. Oral Solutions and Suspensions

  Oral Solutions and Suspensions should be evaluated for appearance (including formation of precipitate, clarity for solutions), colour, odour, assay, degradation products, pH, viscosity, preservative content and microbial limits.

  Additionally for suspensions, redispersibility, rheological properties and mean size and distribution of particles should be considered. After storage, sample of suspensions should be prepared for assay according to the recommended labeling (e.g. shake well before using).

- 5. Oral Powders for Reconstitution

  Oral powders should be evaluated for appearance, colour, odour, assay, degradation products, water content, and reconstitution time.

  Reconstituted products (solutions and suspensions) should be evaluated as described in Oral Solutions and Suspensions above, after preparation according to the recommended labeling, through the maximum intended use period.

- 6. Metered-dose Inhalations and Nasal Aerosols

  Metered-dose inhalation**s** and nasal aerosols should be evaluated for appearance (including content, container, valve, and its components), colour, taste, assay, degradation products, assay for co-solvent (if applicable), dose content uniformity, labeled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, microbial limits, valve delivery (shot weight) and extractables/leachables from plastic and elastomeric components. Samples should be stored in upright and inverted/on-the-side orientations.

  For suspension-type aerosols, the appearance of the valve components and container's contents should be evaluated microscopically for large particles and changes in morphology of the drug surface particles, extent of agglomerates, crystal growth, as well as foreign particulate matter.

  These particles lead to clogged valves or non-reproducible delivery of a dose. Corrosion of the inside of the container or deterioration of the gasket may adversely affect the performance of the drug product.

- 7. Nasal Sprays : Solutions and Suspensions

  Nasal solutions and suspensions equipped with a metering pump should be evaluated for appearance, colour, clarity for solution, assay, degradation products, preservative and antioxidant content, microbial limits, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractable/bleachable from plastic and elastomeric components of the container, closure and pump.

- 8. Topical, Ophthalmic and Otic Preparations

  Included in this broad category are ointments, creams, lotions, paste, gel, solutions and non-metered aerosols for application to the skin. Topical preparations should be evaluated for appearance, clarity, colour, homogeneity, odour, pH, resuspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), assay, degradation products, preservative and antioxidant content (if present), microbial limits/sterility and weight loss (when appropriate).

  Ophthalmic or otic products (e.g., creams, ointments, solutions, and suspensions) should be evaluated for the following additional attributes: sterility, particulate matter, and extractable volume.

  Non-metered topical aerosols should be evaluated for appearance, assay, degradation products, pressure, weight loss, net weight dispensed, delivery rate, microbial limits, spray pattern, water content, and particle size distribution (for suspensions).

- 9. Suppositories

  Suppositories should be evaluated for appearance, colour, assay, degradation products, particle size, softening range, disintegration and dissolution (at 37°C) and microbial limits.

- 10. Small Volume Parenterals (SVPs)

  SVPs include a wide range of injection products such as Injection, Powder for Injection, Suspension for Injection, and Emulsion for Injection. Samples should be stored in upright and inverted/on-the-side orientations.

  Injection products should be evaluated for appearance, clarity, colour, assay, preservative content (if present), degradation products, particulate matter, pH, sterility and pyrogen/endotoxin.

  Powder for Injection products should be evaluated for appearance, colour, reconstitution time and water content. The stability of Powder for Injection products should also be evaluated after reconstitution according to the recommended labeling. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended in labeling, should include appearance, clarity, odour, colour, pH, assay (potency), preservative (if present), degradation products/aggregates, sterility, pyrogen/endotoxin and particulate matter.

  Suspension for Injection products should also be evaluated for particle size distribution, redispersibility and rheological properties in addition to the parameters cited above for Injection and Powder for Injection products.

  Emulsion for Injection products should be evaluated for in addition to the parameters cited above for Injection, phase

separation, viscosity, and mean size and distribution of dispersed phase globules.

- 11. Large Volume Parenterals (LVPs)

  LVPs should be evaluated for appearance, colour, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, pyrogen/endotoxin, clarity and volume.

- 12. Drug Admixture

  For any drug product or diluent that is intended for use as an additive to another drug product, the potential for incompatibility exists. In such cases, the drug product labeled to be administered by addition to another drug product (e.g. parenterals, inhalation solutions), should be evaluated for stability and compatibility in admixture with the other drug products or with diluents both in upright and in inverted/on-the side orientations, if warranted.

  A stability protocol should provide for appropriate tests to be conducted at 0-, 6- to 8- and 24-hour time points, or as appropriate over the intended use period at the recommended storage/use temperature(s). Tests should include appearance, colour, clarity, assay, degradation products, pH, particulate matter, interaction with the container/closure/device and sterility. Appropriate supporting data may be provided in lieu of an evaluation of photo degradation.

- 13. Transdermal Patches

  Devices applied directly to the skin for the purpose of continuously infusing a drug substance into the dermis through the epidermis should be evaluated for appearance, assay, degradation products, in-vitro release

rates, leakage, microbial limits/sterility, peel and adhesive forces, and the drug release rate.

- 14. Freeze-dried Products

  Freeze-dried products should be evaluated for appearance of both the freeze-dried and its reconstituted product, assay, degradation products, pH, water content and rate of solution.

iii. The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status. It is not expected that every test listed be performed at each time point. This applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and at the end of the stability test period; if the long term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided.

iv. The storage orientation of the product, i.e., upright versus inverted, may need to be included in a protocol where there has been a change in the container/closure system.

4.6. Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all can be applied, if justified; see Annex 5.3.

Storage Condition	Products	Testing Frequency
Long term	NCE , Generics, and Variations (MaV and MiV)	0, 3, 6, 9, 12, 18, 24 months and annually through the proposed shelf-life
Accelerated	NCE , Generics, and Variations (MaV and MiV)	0, 3 and 6 months

NCE :New chemical entity; MaV : Major Variation; MiV : Minor Variation

4.7. Storage Conditions

4.7.1. General Case

i. In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use (e.g., after reconstitution or dilution as recommended in the labeling).

ii. Stability studies should generally be conducted under the following storage condition:

STUDY/TYPE OF CONTAINER	STORAGE CONDITION
Long term (for products in primary containers semi-permeable to water vapour)	30°C ± 2°C/75% RH ± 5% RH
Long term (for products in primary containers impermeable to water vapour)	30°C ± 2°C /RH not specified
Accelerated	40°C ± 2°C/75% RH ± 5% RH
Stress testing*	40°C ± 2°C/75% RH ± 5% RH or at more stressful conditions

* Stress testing is necessary for analytical method validation, pharmaceutical formulation, identifying and monitoring potential degradants during stability testing.

iii. The long term testing will be continued for a sufficient time to cover shelf-life at appropriate test periods.

iv. Data from the accelerated storage condition can be used to evaluate the effect of short- term excursions outside the label storage conditions (such as might occur during shipping).

v. If submitted data is based on conditions that are less stressful (e.g. 30°C/65% RH, 25°C/60% RH) than those required, the data should be accompanied by appropriate complementary

data which will permit conduct of a proper scientific evaluation. Factors to be taken into consideration will include:

1. Whether any instability is seen;
2. Whether data have also been provided under accelerated conditions;
3. Whether more protective packaging is provided/ required.

A suitable label recommendation such as “Store below 30°C and protect from moisture” may also be applied.

vi. Additional data accumulated during the assessment period of the registration application should be submitted to the regulatory authorities if requested.

vii. Other storage conditions are allowable if justified, e.g., under the following circumstances:

- Heat sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long term storage temperature.
    * Products containing less stable active ingredients and formulations not suitable for experimental studies on storage at elevated temperature (e.g., suppositories) will need more extensive long term stability studies.
- Special consideration may need to be given to products which change physically or even chemically at lower storage temperature conditions e.g., suspensions or emulsions which may sediment or cream, oils and semi-solid preparations which may show an increased viscosity.
    * Where a lower temperature condition is used, the 6 month accelerated testing should be carried out at a temperature at least 15°C above the expected actual storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term

under refrigerated conditions, accelerated testing should be conducted at 25ºC ± 2ºC/60% RH ± 5% RH. The designated long term testing conditions will be reflected in the labeling and shelf-life (expiration date).

4.7.2. Drug Products Packaged in Impermeable Containers

i. Generally considered moisture-impermeable containers include glass ampoules, aluminum/aluminum blisters, High Density Polyethylene (HDPE) or glass bottles fitted with metal or HDPE closures.

ii. Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for products stored in impermeable containers can be conducted under any controlled or ambient relative humidity condition.

4.7.3. Drug Products Packaged in Semi-Permeable Containers (Aqueous-Based Products)

i. Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately it should be demonstrated that aqueous-based drug products stored in semi-permeable containers could withstand environments with low relative humidity.

Study Storage	**Condition**	**Minimum time period covered by data at submission**
Long term	30°C ± 2 °C/35% RH ± 5% RH	12 months
Accelerated	40°C ± 2 °C/not more than (NMT) 25% RH	6 months

ii. Products meeting either of the long term storage conditions and the accelerated conditions, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers.

iii. A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40 °C/not more than (NMT) 25% RH. However, for small containers (1 ml or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

iv. An alternative approach to studies at the low relative humidity as recommended in the table above (for either long term or accelerated testing) is to perform the stability studies under higher relative humidity and deriving the water loss at the low relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed drug product.

- **Example of an approach for determining water loss**
  - For a product in a given container closure system, container size and fill, an appropriate approach for deriving the rate of water loss at the low relative humidity is to multiply the rate of water loss measured at an alternative relative humidity at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate

at the alternative relative humidity over the storage period should be demonstrated.

- For example, at a given temperature, e.g. 40 °C, the calculated rate of water loss during storage at NMT 25% RH is the rate of water loss measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-humidity testing conditions V	Alternative testing condition	Ratio of water loss rates	Calculation
[a]30 °C/35% RH	30 °C/75% RH	2.6	(100-35)/ (100-75)
40 °C/NMT 25% RH	40 °C/75% RH	3.0	(100-25)/ (100-75)

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

v. Other comparable approaches can be developed and reported for non-aqueous, solvent based products.

4.7.4. Drug Products Intended for Storage in a Refrigerator

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches
Long term	5°C ± 3°C	12 months	Min. 3
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months	Min. 3

If the drug product is packed in a semi-permeable container, appropriate information should be provided to assess the extent of water loss. Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

4.7.5. Drug Products Intended for Storage in a Freezer

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	-20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf-life should be based on the long term data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5°C±3°C or 25°C±2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

4.7.6. Drug Products Intended for Storage below -20°C

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

4.7.7. NCE Drug Products

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches
Long term	30°C ± 2°C/75% RH ± 5% RH	12 months	Min. 3
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months	Min. 3

4.7.8. Generic Products

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches
Long term	30°C ± 2°C/75% RH ± 5% RH	6 months	Min. 2 For conventional dosage form and stable drug substances
		12 months	Min.3. For critical dosage form or unstable drug substances
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months	Min. 2 For conventional dosage form and stable drug substances
			Min.3. For critical dosage form or unstable drug substances

4.7.9. Variations (MaV and MiV if appropriate)

Once the Drug Product has been registered, additional stability studies are required whenever variations that may affect the stability of the Drug Products are made, refer to ASEAN Variation Guideline

Major Variation (MaV)

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches
Long term	30°C ± 2°C/75% RH ± 5% RH	6 months	Min. 2 For conventional dosage form and stable drug substances
			Min.3. For critical dosage form or unstable drug substances
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months	Min. 2 For conventional dosage form and stable drug substances
			Min.3. For critical dosage form or unstable drug substances

Minor Variaton (MiV)

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches
Long term	30°C ± 2°C/75% RH ± 5% RH	3 months*	Min. 2 For conventional dosage form and stable drug substances
		6 months	Min.3. For critical dosage form or unstable drug substances

Accelerated	40°C ± 2°C/75% RH ± 5% RH	3 months*	Min. 2 For conventional dosage form and stable drug substances
		6 months	Min.3. For critical dosage form or unstable drug substances

* Example : replacement of an excipient with a comparable excipient, change in the qualitative and/or quantitative composition of the immediate packaging material, change in the batch size of the finished product, minor change in the manufacture of the finished product, change of colouring system or the flavouring system currently use in the finished product, change in coating weight of tablets or change in weight of capsule shells, and any other minor variation in ASEAN Variation Guideline.

4.8. In-use Stability

i. The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

ii. As far as possible the test should be designed to simulate the use of the drug product in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those which occur in practice appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

iii. The physical, chemical and microbial properties of the drug product susceptible to change during storage should be determined over the period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final amount of the drug remaining in the container. Specific parameters, e.g. for liquids and semi-solids, preservatives, per content and effectiveness, need to be studied.

iv. A minimum of two batches, at least pilot-scale batches, should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf- life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

v. This testing should be performed on the reconstituted or diluted drug product throughout the proposed in-use period on primary batches as part of the stability studies at the initial and final time points and, if full shelf-life, long term data are not available before submission, at the last time point at which data will be available.

vi. In general this testing need not be repeated on commitment batches.

4.9. Container Closure System

i. Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

ii. Parameters required to classify the packaging materials as semi-permeable or impermeable depend on the packaging material characteristics such as thickness and permeability coefficient and other relevant parameters. The suitability of the packaging material used for a particular product is determined by its product characteristics. An Example of Types, Thickness and Permeability Coefficient of Packaging Material is provided in Annex 5.4.

iii. When using moisture-permeable containers for packaging, due consideration should be given to the stability of the contents under high humidity conditions.

iv. Moisture may have an undesirable effect on chemical stability (e.g. some antibiotics may undergo hydrolysis) and physical stability (e.g. dissolution rate may change).

v. The issue of the different permeability of various packaging materials should be addressed. Therefore, it will be necessary to specify parameters, such as the material's thickness and permeability coefficient. Discussion should be appropriate made under P2 Pharmaceutical Development and P7 Container Closure System of the ACTD.

vi. The effect of high humidity on solid dosage forms packaged in containers permeable to moisture should be supported by data.

4.10. Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of two or three batches of the drug product (refer 4.7. 'Storage Conditions'), a shelf-life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

The basic concepts of stability data evaluation are the same for single-versus multi-factor studies and for full versus reduced

design studies. Data evaluation from the stability studies and as appropriate, supporting data should be used to determine the critical quality attributes likely to influence the quality and performance of the drug product. Each attribute should be assessed separately and an overall assessment made of the findings for the purpose of proposing a shelf-life. The shelf-life proposed should not exceed that predicted for any single attribute.

The decision tree in Annex 5.5. outlines a stepwise approach to stability data evaluation and when and how much extrapolation can be considered for a proposed shelf-life. Annex 5.6. provides (1) information on how to analyze long term data for appropriate quantitative test attributes from a study with a multi-factor, full or reduced design, (2) information on how to use regression analysis for shelf-life estimation, and (3) examples of statistical procedures to determine poolability of data from different batches or other factors. Additional guidance can be found in the references listed.

In general, certain quantitative chemical attributes (e.g. assay, degradation products, preservative content) for a drug product can be assumed to follow zero order kinetics during long term storage. Data for these attributes are therefore amenable to linear regression and pool ability testing. Although the kinetics of other quantitative attributes (e.g. pH, dissolution) is generally not known, the same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis.

The recommendations on statistical approaches in this guideline are not intended to imply that use of statistical evaluation is preferred when it can be justified to be unnecessary. However, statistical analysis can be useful in supporting the extrapolation of shelf lives in certain situations and can be called for to verify the proposed shelf lives in other cases.

4.10.1. Data Presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application. The values of quantitative attributes at all time points should be reported as measured (e.g., assay as percent of label claim). If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of long term data should be included.

4.10.2. Extrapolation of Data

Extrapolation is the practice of using a known data set to infer information about future data sets. Limited extrapolation to extend the retest period or shelf-life beyond the observed range of available long term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Any extrapolation should take into consideration the possible worst-case situation at the time of batch release.

An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the observed range of available long term data. Hence, the use of extrapolation should be justified in terms of, for example, what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, and the existence of relevant supporting data.

The correctness of the assumed change pattern is crucial if extrapolation beyond the available long term data is contemplated. For example, when estimating a regression line or curve within the available data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve. No such internal check is available

beyond the length of observed data. Thus, shelf-life granted on the basis of extrapolation should always be verified by additional long term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the extrapolated shelf-life.

If the long term data are supported by results from accelerated studies, the shelf-life may be extended beyond the end of long term studies. The extrapolated shelf-life may be up to twice, but should not be more than 12 months beyond, the period covered by long term data, depending on the change over time, variability of data observed, proposed storage conditions and extent of statistical analyses performed.

4.10.3. Data Evaluation for Shelf-Life Estimation for Drug Products Intended for Storage at Room Temperature

For drug products intended for storage at room temperature, the assessment should begin with any significant change at the accelerated condition and progress through the trends and variability of the long term data. The circumstances are delineated under which extrapolation of shelf-life beyond the period covered by long term data can be appropriate. A decision tree is provided in Annex 5.5. as an aid.

4.10.3.1. No significant change at accelerated condition

Where no significant change occurs at the accelerated condition, the shelf-life would depend on the nature of the long term and accelerated data.

a. Long term and accelerated data showing little or no change over time and little or no variability

Where the long term data and accelerated data for an attribute show little or no change over time and little or no variability, it may be apparent that the drug product

will remain well within its acceptance criterion for that attribute during the proposed shelf-life. Under these circumstances, it is normally considered unnecessary to go through a statistical analysis, but justification for the omission should be provided. Justification can include a discussion of the mechanisms of degradation or lack of degradation, relevance of the accelerated data, mass balance, and/or other supporting data.

b. Long term or accelerated data showing change over time and/or variability

If the long term or accelerated data for an attribute show change over time and/or variability within a factor or among factors, statistical analysis of the long term data can be useful in establishing a shelf-life. Where there are differences in stability observed among batches or among other factors (e.g., strength, container size and/or fill) or factor combinations (e.g., strength-by-container size and/or fill) that preclude the combining of data, the proposed shelf-life should not exceed the shortest period supported by any batch, other factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength), different shelf- lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such differences on the product. Extrapolation beyond the period covered by long term data can be proposed; however, the extent of extrapolation would depend on whether long term data for the attribute are amenable to statistical analysis.

- Data not amenable to statistical analysis

  Where long term data are not amenable to statistical analysis, but relevant supporting data are provided, the proposed shelf-life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long term data. Relevant supporting data include satisfactory long term data from development batches that are (1) made with a closely related formulation to, (2) manufactured on a smaller scale than, or (3) packaged in a container closure system similar to, that of the primary stability batches.

- Data amenable to statistical analysis

  If long term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, it can be appropriate to propose a shelf-life of up to twice, but not more than 12 months beyond, the period covered by long term data, when the proposal is backed by the result of the analysis and relevant supporting data.

4.10.3.2. Significant change at accelerated condition

If a “significant change” occurs between 3 and 6 months’ testing at the accelerated storage condition, the proposed shelf-life should be based on the long term data available at the long term storage condition.

Significant Change

In general, “significant change” for a drug product is defined as:

1. A 5% change in assay from its initial value, or failure to meet the acceptance criteria;
2. Any degradation product exceeding the acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality tests (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions and as appropriate for the dosage form.
4. Failure to meet the acceptance criteria for pH;
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units (capsule or tablet).

If the “significant change” occurs within the first 3 months testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug product through 6 months when a “significant change” has occurred within the first 3 months.

This can be applied to products such as ointments, cream or suppositories that are impossible to test at

accelerated condition where only long term testing is required

*Note: The following physical changes can be expected to occur at the accelerated condition and would not be considered significant change that calls for long term testing if there is no other significant change:

a. softening of a suppository that is designed to melt at 37ºC, if the melting point is clearly demonstrated,

b. failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if the failure can be unequivocally attributed to cross-linking.

However, if phase separation of a semi-solid dosage form occurs at the accelerated condition, testing at the long term condition should be performed. Potential interaction effects should also be considered in establishing that there is no other significant change.

4.10.4. Data Evaluation for Shelf-Life Estimation for Drug Products Intended for Storage below Room Temperature

4.10.4.1. Drug products intended for storage in a refrigerator

Data from drug products intended to be stored in a refrigerator should be assessed according to the same principles as described in Section 4.10.3. for drug products intended for room temperature storage, except where explicitly noted in the section below. The decision tree in Appendix 5.5. can be used as an aid.

a. No significant change at accelerated condition

Where no significant change occurs at the accelerated condition, extrapolation of shelf-life beyond the period covered by long term data

can be proposed based on the principles outlined in Section 4.10.3, except that the extent of extrapolation should be more limited.

If the long term and accelerated data show little change over time and little variability, the proposed shelf-life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long term data normally without the support of statistical analysis.

Where the long term or accelerated data show change over time and/or variability, the proposed shelf-life can be up to 3 months beyond the period covered by long term data if (1) the long term data are amenable to statistical analysis but a statistical analysis is not performed, or (2) the long term data are not amenable to statistical analysis but relevant supporting data are provided.

Where the long term or accelerated data show change over time and/or variability, the proposed shelf-life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long term data if (1) the long term data are amenable to statistical analysis and a statistical analysis is performed, and (2) the proposal is backed by the result of the analysis and relevant supporting data.

b. Significant change at accelerated condition

If significant change occurs between 3 and 6 months testing at the accelerated storage condition, the proposed shelf-life should be based on the long term data. Extrapolation is not considered appropriate. In addition, a shelf-life shorter than the

period covered by long term data could be called for. If the long term data show variability, verification of the proposed shelf-life by statistical analysis can be appropriate.

If significant change occurs within the first 3 months testing at the accelerated storage condition, the proposed shelf-life should be based on long term data. Extrapolation is not considered appropriate. A shelf-life shorter than the period covered by long term data could be called for. If the long term data show variability, verification of the proposed shelf-life by statistical analysis can be appropriate. In addition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug product at the accelerated condition for a period shorter than 3 months.

4.10.4.2. Drug products intended for storage in a freezer

For drug products intended for storage in a freezer, the shelf-life should be based on long term data. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

4.10.4.3. Drug products intended for storage below -20°C

For drug products intended for storage below -20°C, the shelf-life should be based on long term data and should be assessed on a case-by-case basis.

4.10.5. General Statistical Approaches

Where applicable, an appropriate statistical method should be employed to analyze the long term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a shelf-life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances. This same method could also be applied to commitment batches to verify or extend the originally approved shelf-life.

In cases where a statistical analysis was employed to evaluate long term data due to a change over time and/or variability, the same statistical method should also be used to analyse data from commitment batches to verify or extend the originally approved shelf- life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a shelf-life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. Usually, the relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. Sometimes a non-linear regression can be expected to better reflect the true relationship.

An appropriate approach to shelf-life estimation is to analyze a quantitative attribute by determining the earliest time at which the 95 percent confidence limit for the mean around the regression curve intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95 percent confidence limit should be compared to the criterion. For an attribute which can either increase or decrease, or whose direction of compared to the upper and lower acceptance criteria.

If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p-values for levels of significant of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life should be based on the minimum time a batch can be expected to remain within acceptance criteria. Any evaluation should consider not only the assay, but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated shelf-life. The approach described above can be used to estimate the shelf-life for a single batch or for multiple batches when combined after an appropriate statistical test. Examples of statistical approaches to the analysis of stability data from design study are included in Annex 5.6.

4.11. Stability Commitment

4.11.1. When available long term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf-life.

4.11.2. Where the submission includes long term stability data on at least the minimum number of production batches required covering the proposed shelf-life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

a. If the submission includes data from stability studies on at least the minimum number of production batches required, a commitment should be made to continue the long term studies through the proposed shelf-life and the accelerated studies for 6 months.

b. If the submission includes data from stability studies on fewer than 3 production batches, a commitment should be made to continue the long term studies through the proposed shelf-life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least the minimum number of production batches required, on long term stability studies through the proposed shelf-life and on accelerated studies for 6 months.

c. If the submission does not include stability data on production batches, a commitment should be made to place the first 3 production batches on long term stability studies through the proposed shelf-life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

4.11.3. Applicant must submit commitment and protocol on post approval stability study if stability study submitted has been conducted under different storage conditions and it cannot be demonstrated that the drug product will remain within its acceptance criteria stated in this guideline. In such cases, the following options should be considered: (1) a reduced shelf-life, (2) a more

protective container closure system, or (3) additional cautionary statements in the labeling.

4.11.4. Post approval stability can be conducted in any ASEAN member country, country of origin, or any country that can meet the required storage condition.

4.12. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instructions should be provided, particularly for drug products that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the label statement and the demonstrated stability characteristics of the drug product.

The storage conditions (temperature, light, humidity) indicated should refer to the relevant national/regional requirements or following the recommendations below. The range should be based on the stability evaluation of the drug product.

Table 1

Recommended labelling statements for Drug Products

Testing condition under which the stability of the drug product has been demonstrated	Recommended labeling statement [a]
30°C/75% RH (long term) 40°C/75% RH (accelerated)	“Do not store above 30°C”
5°C ± 3°C	”Store in a refrigerator (2°C to 8°C)”
-20°C ± 5°C	“Store in a freezer”

[a] During storage, shipment and distribution of the Drug Products, the current good distribution practices (GDP) for pharmaceutical products are to be observed.

If testing conditions different from above table, the recommended labeling statement should justified with supported stability studies.

In principle, Drug Products should be packed in containers that ensure stability and protect the Drug Product from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labeling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table 2 below.

Table 2

Additional labeling statements for use where the result of the stability testing demonstrates limiting factors

Limiting factors	Additional labeling statement, where relevant
Drug Products that cannot tolerate refrigeration	"Do not refrigerate or freeze"[a]
Drug Products that cannot tolerate freezing	"Do not freeze"[a]
Light-sensitive Drug Products	"Protect from light"
Drug Products that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic Drug Products	"Store in dry conditions"

[a] Depending on the pharmaceutical form and the properties of the Drug Product, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semi-solids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

1. The use of terms such as "ambient conditions" or "room temperature" is unacceptable.
2. If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, e.g., an antibiotic injection or suspension supplied as a powder for reconstitution.

5. ANNEXES

5.1. Protocol of Stability Study (example)

5.1.1. PARACETAMOL TABLET 500 MG PACKED IN PVC BLISTER OF 10 TABLETS

1. Purpose

   To evaluate stability of product due to the scaling up from the Research and Development to the Manufacturing Site.

2. Test Design

   The product is packed in PVC blister and will be stored according to the storage condition mentioned in the manufacturing instruction

   2.1. Test Material

   - Push-through foil
     Alufoil of 20 micron thickness, heat-seal lacquered, PVC layered (8 g/m^2), hard temper, bright side finish silver-tinted.
     Forming foil
     PVC foil of 250 micron thickness.

Batch No.	Packaging type	Storage Condition/Period
001	PVC Blister	Long term (60 months); Accelerated (6 months)
002	PVC Blister	Long term (60 months); Accelerated (6 months)
003	PVC Blister	Long term (60 months); Accelerated (6 months)

2.2. Testing Plan

2.2.1. Storage condition and sampling intervals

Paracetamol tablet is filled and sealed in PVC blister, 10 blisters are packed in carton folding box and stored at the following storage condition:

Storage Condition	Sampling Intervals
Long term 30°C/75% RH	0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months
Accelerated 40°C/75% RH	0, 1, 3, 6 months

The detailed schedule is attached.

2.2.2. Testing and Test Criteria

QA/QC Dept. is responsible for storing and testing the sample in accordance with the storage condition and the valid test method.

The samples are taken out of the storage prior to the planned testing date, and kept at 5°C until the time for analysis.

The analytical work should be concluded not later than 4 weeks after the samples have been out of storage.

The testing procedure is: No. XXXX and the parameters to be tested are as follows:

a. Physical test
   - appearance
   - average weight
   - dissolution
   - disintegration time
   - hardness
   - friability
   - water content

b. Content : Paracetamol
c. Degradation Product : p-aminophenol

3. Number of Samples (of one batch / storage condition)

Accelerated Test

- Appearance	:	0*	tablets
- water content	:	10	tablets
- disintegration	:	6	tablets
- dissolution	:	6	tablets
- content & impurity	:	10	tablets
- hardness	:	10	tablets
- friability	:	50	tablets
	→	= 92	tablets ~ rounded to 100 tablets

Number of testing : 4 times

Quality needed

= 4 x 100 tablets

= 400 tablets

= 40 blisters of 10 tablets

= 4 boxes

Long Term Stability Study

- Appearance	:	0*	tablets
- water content	:	10	tablets
- disintegration	:	6	tablets
- dissolution	:	6	tablets
- content & impurity	:	10	tablets
- hardness	:	10	tablets
- friability	:	50	tablets
	→	= 92	tablets ~ rounded to100 tablets

* = observation made on tablets allocated for other tests

Number of testing: 9 times

Quality needed

= 9 x 100 tablets

= 900 tablets

= 90 blisters 0f 10 tablets

= 9 boxes

Total for long term and accelerated stability studies = 4 boxes + 9 boxes = 13 boxes of 10 blisters

4. Report Content :
    1. Responsibility
    2. Summary
    3. Objective
    4. Test Material
    5. Composition
    6. Packaging
    7. Storage condition and testing materials (Schedule)
    8. Analytical Procedures
    9. Reference Standard
    10. Results
        - 10.1. Physical Stability
        - 10.2. Chemical Stability
            - 10.2.1. Stability under long term storage condition
            - 10.2.2. Stability under accelerated storage condition
    11. Discussion/Conclusion
    12. Test result in tabular form

Approved by: Checked by: Prepared by:

5.1.2. Schedule for Stability Study

Paracetamol Tablet 500 mg

Dated:
02.07.1997

Storage		Schedule		
		Batch No.	Batch No.	Batch No.
Period	Condition	001	002	003
Initial	Accelerated	July 02, 1997	July 09, 1997	July 16, 1997
	Long term	July 04, 1997	July 12, 1997	July 18, 1997
1 Month	Accelerated	Aug 02, 1997	Aug 09, 1997	Aug 16, 1997
3 Months	Accelerated	Oct 02, 1997	Oct 09, 1997	Oct 16, 1997
	Long term	Oct 04, 1997	Oct 12, 1997	Oct 18, 1997
6 Months	Accelerated	Jan 02, 1998	Jan 09, 1998	Jan 16, 1998
	Long term	Jan 04, 1998	Jan 12, 1998	Jan 18, 1998
9 Months	Long term	Apr 04, 1998	Apr 12, 1998	Apr 18, 1998
12 Months	Long term	Jul 04, 1998	Jul 12, 1998	Jul 18, 1998
18 Months	Long term	Jan 02, 1999	Jan 12, 1999	Jan 18, 1999
24 Months	Long term	Jul 04, 1999	Jul 12, 1999	Jul 18, 1999
36 Months	Long term	Jul 04, 2000	Jul 12, 2000	Jul 18, 2000
48 Months	Long term	Jul 04, 2001	Jul 12, 2001	Jul18, 2001
60 Months	Long term	Jul 04, 2002	Jul 12, 2002	Jul 18, 2002

Remarks :

Accelerated : 40°C ± 2°C/75% RH ± 5% RH
Long term: 30°C ± 2°C/75% RH ± 5% RH

Approved by: Checked by: Prepared by:

5.2. Report Format

DRUG PRODUCT:	**PARACETAMOL TABLET**	
STRENGTH:	500 mg	Date: 23/07/02
Doc. No.:	XXXX.	Page 1 of 20

Study Type:	Pre- and post-market Stability
Objective:	Stability profile of the drug product for storage under long term and accelerated conditions
Period of Investigation:	60 Months
Packaging:	PVC Blister
Originating Site :	MMM Ltd Jakarta – Indonesia

Stability Study Unit :	R&D Dept. John Doe
Quality Assurance :	Tom Smith

1. RESPONSIBILITY

Persons in Charge	Site / Department	Responsibility
John Doe	R&D	Physical and chemical tests
John Doe	R&D	Microbiological tests

2. SUMMARY

This report presents the stability data on Paracetamol tablet 500 mg stored up to 60 months in the primary packaging used for marketing.

Any storage-related changes occuring in the finished product were monitored by means of stability-specified control tests. The test design was based on the stability profile of the drug substance paracetamol and on the specific requirements of the dosage form.

Shelf-life:

The product has a shelf-life of five years

Storage Directions:

The finished product is not labelled with any storage directions.

3. OBJECTIVE

The objective of the present study on Paracetamol tablet 500 mg is the assessment of the stability profile for storage under long term and accelerated conditions. The samples were in inverted position to ensure contact with the container closure system.

4. TEST MATERIAL

The batches under stability testing are listed in the following table with further details:

4.1. Starting Material

MATERIAL	PRODUCT BATCH NO			SOURCE
	#01	#02	# 03	
Paracetamol	**Note: Batch API**	.....	.....	.....
Lactose $1H_2O$	.....	.....	.....	.....
Maize Starch	.....	.....	.....	.....
Pregelatinized Maize Starch	.....	.....	.....	.....
Talc	.....	.....	.....	.....
Colloidal Anhydrous Silica (Aerosil 200)	.....	.....	.....	.....
Magnesium Stearate	.....	.....	.....	.....

4.2. Drug Product

Dosage	Batch No.	Manufacturing		Scale	Batch Size (Unit)
		Date	Site		
500 mg/tab	001	July 02, 1997	Jakarta	Production	280000
500 mg/tab	002	July 09, 1997	Jakarta	Production	280000
500 mg/tab	003	July 16, 1997	Jakarta	Production	280000

5. COMPOSITION

1 tablet of Paracetamol contains :

Composition	Weight [mg]	Source (API produsen)
Paracetamol	500.00	
Lactose $1H_2O$	79.00	
Maize Starch	65.50	
Pregelatinized Maize Starch	5.00	
Talc	3.00	
Colloidal Anhydrous Silica (Aerosil 200)	2.00	
Magnesium Stearate	0.50	
Total	655.00	

6. PACKAGING

The stability tests on the batches listed above are performed in the following primary packaging:

The product is packed in PVC blister consisting of:

- Push-through foil : Alufoil of 20 micron thickness, heat-seal lacquered, PVC layered (8 g/m^2), hard temper, bright side finish silver-tinted.
- Forming foil : PVC foil of 250 micron thickness.

7. STORAGE CONDITIONS AND TESTING INTERVALS

The various samples of the packaged drug product have been / will be tested according to the following schedule:

Storage Condition	Months										
	0	1	3	6	9	12	18	24	36	48	60
30°C ± 2°C/75% RH ± 5% RH	X	-	X	X	X	X	X	X	X	X	X
40°C ± 2°C/75% RH ± 5% RH	X	X	X	X	-	-	-	-	-	-	-

8. ANALYTICAL PROCEDURES

The stability tests on Paracetamol were performed according to the control tests of USP.

In the course of the stability testing the main emphasis was put on the stability-relevant test items as listed below:

Test Item	Control Test No.	Specification
Hardness	USP	≥ 70 N
Friability	USP	≤ 2%
Degradation Product • p-aminophenol	USP	≤ 0.005%
Microbial Contamination	USP	Total count ≤ 10^2 CFU E.coli : absent
Content (LC)	USP	95.0. – 105.0 %

Note: As mentioned in 2.1.2, 3.1 and 3.2, Disintegration Time and Dissolution should be added.

9. REFERENCE STANDARD

Standard Paracetamol USP, 99.5%, was used.

10. RESULTS

The test results of the study are presented in the tables attached.

Physical Stability

The physical stability of Paracetamol tablet 500 mg proved to be unchanged after storage up to 60 months at 30°C/75% RH and after 6 months under accelerated conditions at 40°C/75% RH.

The result obtained for the test item's "appearance" was not changed significantly.

Chemical Stability

Stability under Long term Conditions

Storage for up to 60 months at 30°C/75% RH had no significant effect on the chemical stability of the drug product. With regard to test item “Organic Impurity” only slight changes were observed. The p-aminophenol concentration was below 0.005%.

The content of Paracetamol did not change significantly after storage under long term conditions compared to initial assay of the batches.

Stability under Accelerated Conditions

Storage under accelerated conditions for 6 months did not affect the chemical stability. The content of paracetamol was not significantly changed compared to the initial value of the batches.

11. DISCUSSION / CONCLUSIONS

Storage under long term testing conditions causes insignificant change of assay results of paracetamol. Significant changes in physical and chemical stabilities were not observed. Since the long-term data and accelerated data show little or no change over time and little variability, a statistical analysis is considered unnecessary.

Shelf-life:

Based on the resulting data the shelf-life has been established for five years.

Storage Directions:

The product can be labelled with ”Store below 30°C”

Summary of Stability Study Result

Table 1

Drug Product :	Paracetamol	Batch No. : 001
Dosage :	500 mg/tablet	
Packaging :	PVC Blister	

Storage		Appearance	Hardness [N]	Friability [%]	Content : Paracetamol 500 mg	Degradation Product p-aminophenol [%]	Microbial Contamination
Time [Months]	Conditions						
Specifications		White, round-flat tablet	≥ 70 N	≤ 2 %	95.0–105.0%	≤ 0.005%	Total count ≤ 10^2 CFU **E.coli: absent**
Initial	-	Complies	80	1	98.8	0.001	Complies
3	30°C ± 2°C/ 75% RH ± 5%RH	Complies	80	1	101.4	0.002	Complies
6		Complies	85	0.5.	98.3	0.004	Complies
9		Complies	90	0.5.	99.6	0.001	Complies
12		Complies	85	1	98.9	0.003	Complies
18		Complies	97	1	99.0	0.003	Complies
24		Complies	94	0.5.	98.9	0.004	Complies
36		Complies	87	1	99.1	0.002	Complies
48		Complies	98	1	99.5	0.001	Complies
60		Complies	93	0.5	99.3	0.001	Complies
1	40°C ± 2°/75% RH ± 5%RH	Complies	98	0.5	100.9	0.004	Complies
3		Complies	96	0.5	100.5	0.004	Complies
6		Complies	80	0.5	99.6	0.004	Complies

Note: - More data on disintegration time or dissolution are required for each batch.
- For batch number 002 and 003, study results are provided in the same format as batch number 001

5.3. Reduced Design (Bracketing and Matrixing)

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination is not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the shelf-life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter shelf-life than could be derived from a full design due to the reduced amount of data collected.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

Applicability of Reduced Designs

Reduced designs can be applied to the stability study of most types of drug products, although additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions.

Bracketing

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Design Example

An example of a bracketing design is given in Table 1.

This example is based on a product available in three strengths and three container sizes (P1, P2 and P3). In this example, it should be demonstrated that the 15 ml (P1) and 500 ml (P3) high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

Table 1: Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container size	**15 ml**	**T**	**T**	**T**				**T**	**T**	**T**
	100 ml									
	500 ml	**T**	**T**	**T**				**T**	**T**	**T**

Key: T = Sample tested

The bracketing design assumes that the stability of the intermediate strengths or sizes is represented by the stability at the extremes. If the statistical analysis indicates that the stability of the extreme strengths or sizes is different, the intermediate strengths or sizes should be considered no more stable than the least stable extreme. For example, if P1 from the above bracketing design is found to be less stable than P3, the shelf-life for P2 should not exceed that for P1. No interpolation between P1 and P3 should be considered.

Matrixing

Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for

example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems. Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

Design Examples

Examples of matrixing designs on time points for a product with two strengths (S1 and S2) are shown in Table 2. The terms “one-half reduction” and “one-third reduction” refer to the reduction strategy initially applied to the full study design. For example, a “one-half reduction” initially eliminates one in every two time points from the full study design and a “one-third reduction” initially removes one in every three. In the examples shown in Table 2, the reductions are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points. These examples include full testing at the initial, final, and 12- month time points. The ultimate reduction is therefore less than one-half (24/48) or one-third (16/48), and is actually 15/48 or 10/48, respectively.

Table 2: Examples of Matrixing Designs on Time Points for a Product with Two Strengths

"One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
STRENGTH	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

Key: T = Sample tested

"One-Third Reduction"

Time point (months)			0	3	6	9	12	18	24	36
STRENGTH	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	S2	Batch 1	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

Key: T = Sample tested

More details are described in ICH Q1D.

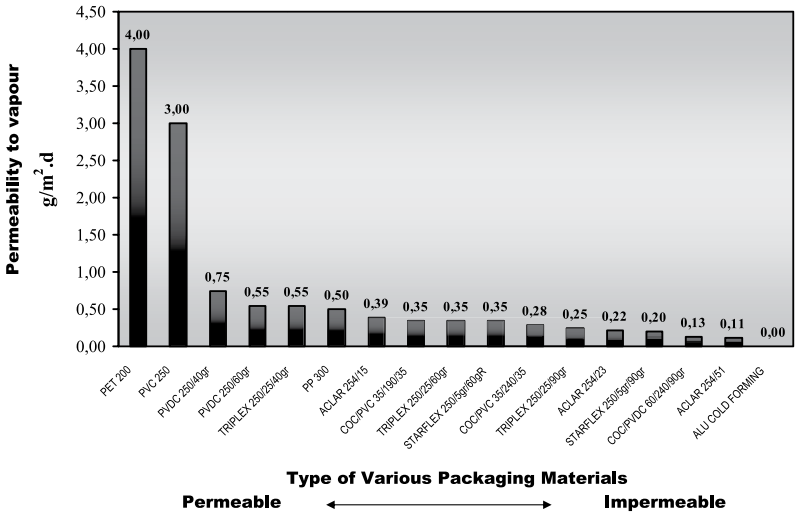
5.4. **Example** of Types, Thickness and Permeability Coefficient of Packaging Materials can be seen in Table-1 and Permeability to Vapour of Various Packaging Materials can be seen in Figure-1.

Table-1: Example of Types, Thickness and Permeability Coefficient of Packaging Materials

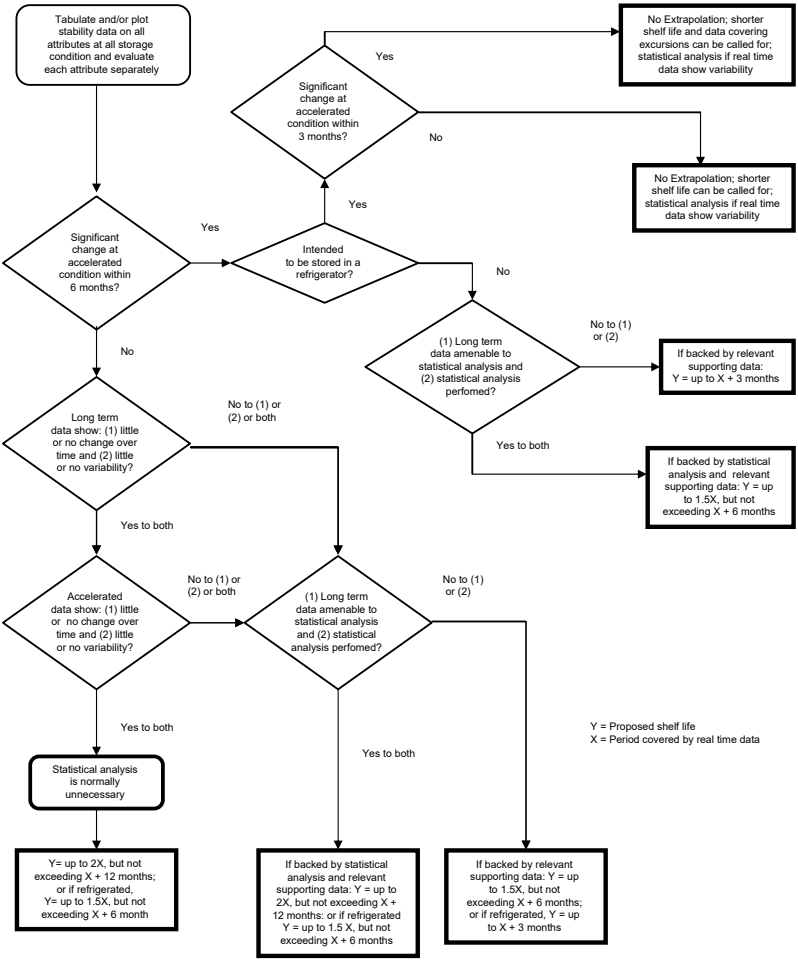
No.	Material	Thickness	**Thickness Commonly Used** (µm)	SPECIFICATION PERMEABLITY		Thermo-formability
				At 23°C / 85%RH (g/m².d)	**At 38°C /** 90%RH (g/m².d)	
1	**PVC** (Polyvinyl Chloride)	250 µm	200 - 250 µm	1,6 - 1,8	3,0 - 3,2	Good
2	**Duplex (PVC + PVDC) PVC** (Polyvinyl Chloride) **PVDC** (Polyvinylidene Chloride)		270 µm			Good / Excellent
		200 – 250 µm				
		5 µm for spread of 10 g/m² (40 - 60 - 80 g/m²)	40g/m²	0,15	0,6	
			60g/m²	0,1	0,4	
			80g/m²	0,05	0,3	
3	**Triplex (PVC + PE + PVDC) PVC** (Polyvinyl Chloride) **PE** (Polyethylene) **PVDC** (Polyvinylidene Chloride)		300 µm			Good/ Excellent (according to thickness)
		200 – 250 µm				
		25 µm				
		5 µm for spread of 10 g/m² (40 - 60 - 90 g/m²)	40g/m²	0,12	0,55	
			60g/m²	0,06	0,35	
			90g/m²	0,02	0,2	
4	**Starflex (PVC + TE + PVDC) PVC** (Polyvinyl Chloride) **TE** (Thermolast) **PVDC** (Polyvinylidene Chloride)		Max. 300 µm			Good/ Excellent (according to thickness)
		200 - 250 µm				
		Spreading TE (coating) 5 g/m²				
		5 µm for spread of 10 g/m² (60 - 90 - 120 g/m²)	60g/m²	0,06	0,35	
			90g/m²	0,03	0,2	
			120g/m²	0,01	0,15	
5	**PVC + ACLAR PVC** (Polyvinyl Chloride) **ACLAR** (Polyfluor Carbonat)		270 µm			Excellent
		200 - 250 µm				
		15-23-51 µm	15g/m²	-	0,39	
			23g/m²	-	0,22	
			51g/m²	-	0,11	
6	**PVC/PE/ACLAR PVC** (Polyvinyl Chloride) **PE** (Polyester) **ACLAR** (pfc)		280 µm			Excellent
		200- 250 µm				
		25 µm				
		15 - 51 µm	15 µm	-	< 0.32	
			51µm	-	< 0.11	

No.	Material	Thickness	Thickness Commonly Used (µm)	SPECIFICATION PERMEABLITY		Thermo-formability
				At 23°C / 85%RH (g/m².d)	At 38°C / 90%RH (g/m².d)	
7	**Aluminum Cold Forming** Aluminum PVC rigid OPA		130 µm	-	0	Excellent
		40 µm - 45 µm		-	-	
		60 µm		-	-	
		25 µm		-	-	
8	Aluminum Foil Hard Temper (Lidding Foil)		20 µm	-	-	
	Alublister for PVC Foil - Aluminum - PVC			-	-	
		20 µm		-	-	
		min. 7 g/m²		-	-	
	Alublister for PVC - PVDC Foil - Aluminum - PVDC		30 µm	-	-	
		20 µm		-	-	
		15 g/m²		-	-	
9	**Aluminum Foil for Soft Temper** - Aluminum - PVDC		40 µm	-	-	
		30 µm				
		15 g/m²				

Figure 1 Permeability to Vapour of Various Packaging Materials (Method ASTM F1249, 38°C/90%RH)



5.5. Decision Tree for Data Evaluation for Shelf Life Estimation for Drug Products (excluding Frozen Products)



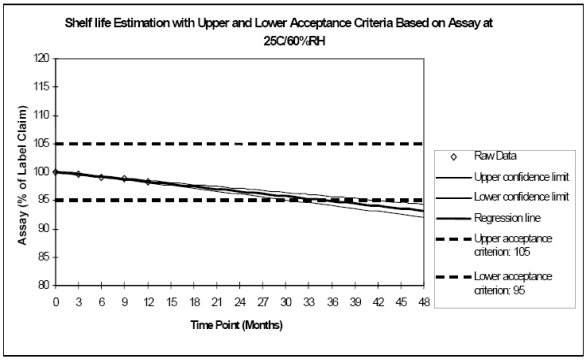
5.6. Examples of Statistical Approaches to Stability Data Analysis

Linear regression, poolability tests, and statistical modeling, described below, are examples of statistical methods and procedures that can be used in the analysis of stability data that are amenable to statistical analysis for a quantitative attribute for which there is a proposed acceptance criterion.

Data Analysis for a Single Batch

In general, the relationship between certain quantitative attributes and time is assumed to be linear[1]. Figure 1 shows the regression line for assay of a drug product with upper and lower acceptance criteria of 105 percent and 95 percent of label claim, respectively, with 12 months of long term data and a proposed shelf-life of 24 months. In this example, two-sided 95 percent confidence limits for the mean are applied because it is not known ahead of time whether the assay would increase or decrease with time (e.g., in the case of an aqueous-based product packaged in a semi-permeable container). The lower confidence limit intersects the lower acceptance criterion at 30 months, while the upper confidence limit does not intersect with the upper acceptance criterion until later. Therefore, the proposed shelf-life of 24 months can be supported by the statistical analysis of the assay, provided the recommendations in Sections 4.10.1 and 4.10.2 are followed.

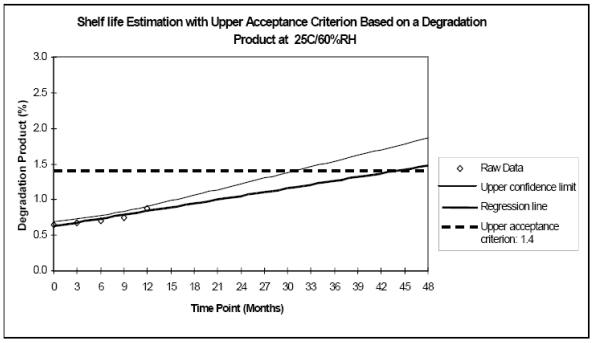
Figure 1



When data for an attribute with only an upper or a lower acceptance criterion are analyzed, the corresponding one-sided 95 percent confidence limit for the mean is recommended. Figure 2 shows the regression line for a degradation product in a drug product with 12 months of long term data and a proposed shelf-life of 24 months, where the acceptance criterion is not more than 1.4 percent. The upper one-sided 95 percent confidence limit for the mean intersects the acceptance criterion at 31 months. Therefore, the proposed shelf-life of 24 months can be supported by statistical analysis of the degradation product data, provided the recommendations in Sections 4.10.1 and 4.10.2 are followed.

If the above approach is used, the mean value of the quantitative attribute (e.g., assay, degradation products) can be expected to remain within the acceptance criteria through the end of the shelf-life at a confidence level of 95 percent.

Figure 2



6. GLOSSARY

Accelerated Testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. (Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated condition and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes**;** see also Stability and related terms)

Batch

A defined quantity of starting material, packaging material or Drug Product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. (The design assumes that the stability of any intermediate level is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition [e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling

different plug fill weight of the same basic composition into different size capsule shell]. Bracketing can be applied to different container sizes or different fills in the same container closure system).

Climatic Zones

Climatic Zone	Definition	Long-term testing conditions
I	Temperate climate	21 °C / 45% RH
II	Subtropical and Mediterranean climate	25 °C / 60% RH
III	Hot and dry climate	30 °C / 35% RH
IVA	Hot and humid climate	30 °C / 65% RH
IVB	Hot and very humid climate	30 °C / 75% RH

Commitment batches

Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container Closure System

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage Form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug Product/Pharmaceutical Product

Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Drug Substance

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.(See also Active Pharmaceutical Ingredient in the Glossary of Terms of ACTD Quality)

Excipient

An ingredient, added intentionally to the drug substance, which should not have pharmacological properties in the quantity used.

Expiry Date

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions. (After the expiry date, there is no guarantee that the product will remain within the approved specifications and, therefore, it may be unsuitable for use and should not be used).

Formal Stability Studies

Long term and accelerated studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the shelf-life of a drug product.

Impermeable Containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms.

Long Term Testing

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

Major Variation (MaV)

Variation to authorized pharmaceutical product affecting one or more of the following aspects :

• route of administration
• strength, posology
• indication, or
• or that does not fall within the definition of minor variation

(Applications for major variations usually require the submission of data necessary to establish quality, safety and efficacy of the new formulation resulting from the variation).

Mass Balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factors combinations is tested at a specified time point. (At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point; the differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems).

Minor Variation (MiV)

Variation to authorized pharmaceutical product not affecting one or more of the following aspects :

• route of administration
• strength, posology

• indications, and
• active ingredient(s)

(Applications for minor variations usually require the submission of data necessary to establish quality of the new formulation resulting from the variations).

Pilot Scale Batch

A batch of a drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. (For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger unless otherwise justified).

Primary Batch

A batch of a drug product used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life, respectively. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch).

Production Batch

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

Semi-Permeable Containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi- rigid, low-density polyethylene

(LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles and vials.

Shelf-life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the condition defined on the container label.

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. (It establishes the set of criteria to which a drug substance, drug product or material at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval).

Specifications – Release

The specifications that determine the suitability of a drug product at the time of its release. (See also Specification)

Specifications – Shelf-life

The specifications that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf-life.

Stability

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. (The chemical, physical, microbiological and biopharmaceutical aspects of stability must be considered).

Stability Studies

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or shelf-life of a drug product.

Storage Condition Tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. (The equipment should be capable of controlling the storage condition within the ranges defined in the current relevant guidelines. The actual temperature and humidity - when controlled - should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed).

Stress Testing (Drug Product)

Studies undertaken to assess the effect of severe condition on the drug product. (Such studies include photo-stability testing; - see ICH Q1B - and specific testing on certain products, e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting Data

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf-life, and the label storage statements. (Such data include (1) stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales).

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ASEAN GUIDELINES FOR VALIDATION OF ANALYTICAL PROCEDURES

Adopted from ICH Guidelines

ICH Q2A: Validation of Analytical Methods: Definitions and Terminology, 27 October 1994.

ICH Q2B: Validation of Analytical Procedure: Methodology, 6 November 1996.

TABLE OF CONTENTS

VALIDATION OF ANALYTICAL PROCEDURES

1. Introduction

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose.

This guideline is to provide the guidance and recommendation of validation of the analytical procedures for submission as part of registration applications within ASEAN. The document mainly adopts two ICH guidelines “Q2A: Validation of Analytical Methods: Definitions and Terminology, 27 October 1994” and “ICH Q2B: Validation of Analytical Procedure: Methodology, 6 November 1996. The methodology applied for biological and biotechnological products may be approached differently than chemical entities.

All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate. Well-characterized reference materials, with document purity, should be used throughout the validation study. The degree of purity depends on the intended use.

In practice, it is usually possible to design the experimental work such that the appropriate validation characteristics can be considered simultaneously to provide a sound, over all knowledge of the capabilities of the analytical procedure, for instance: specificity, linearity, range, accuracy and precision. The compendial methods are not required to be validated, but merely verify their suitability under actual conditions of use.

For Asean requirement : All data related to the validation characteristics should be submitted to the Drug Regulatory Authority together with the respective acceptance criteria.

2. Types of Analytical Procedures to be Validated

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests.
- Quantitative tests for impurities' content.
- Limit tests for the control of impurities.
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard.
- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.
- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated.

Typical validation characteristics which should be considered are listed below:

Accuracy
Precision
    Repeatability
    Intermediate Precision
    Reproducibility
Specificity
Detection Limit
Quantitation Limit
Linearity
Range
Robustness

Each of these validation characteristics is defined in the Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- changes in the synthesis of the drug substance;
- changes in the composition of the finished product;
- changes in the analytical procedure;

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

Type of analytical procedure Characteristics	Identification	Testing for Impurities		Assay - dissolution (measurement only) - content/potency
		Quantitative	Limit	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm. Precision	-	+(1)	-	+(1)
Specificity (2)	+	+	+	+
Detection Limit	-	-(3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

- signifies that this characteristic is not normally evaluated
+ signifies that this characteristic is normally evaluated
(1) in cases where reproducibility (see glossary) has been performed, intermediate precision is not needed
(2) lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)
(3) may be needed in some cases

3. Analytical Performance Characteristics

3.1. SPECIFICITY

An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and the assay. The procedures used to demonstrate specificity will depend on the intended objective of the analytical procedure. It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination). In this case a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination.

3.1.1. Identification

Suitable identification tests should be able to discriminate between compounds of closely related structures which are likely to be present. The discrimination of a procedure may be

confirmed by obtaining positive results (perhaps by comparison with a known reference material) from samples containing the analyte, coupled with negative results from samples which do not contain the analyte. In addition, the identification test may be applied to materials structurally similar to or closely related to the analyte to confirm that a positive response is not obtained. The choice of such potentially interfering materials should be based on sound scientific judgement with a consideration of the interferences that could occur.

3.1.2. Assay and Impurity Test(s)

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity and individual components should be appropriately labelled. Similar considerations should be given to other separation techniques. Critical separations in chromatography should be investigated at an appropriate level. For critical separations, specificity can be demonstrated by the resolution of the two components which elute closest to each other. In cases where a non-specific assay is used, other supporting analytical procedures should be used to demonstrate overall specificity. For example, where a titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used. The approach is similar for both assay and impurity tests:

3.1.2.1. Impurities are available

For the assay , this should involve demonstration of the discrimination of the analyte in the presence of impurities and/or excipients; practically, this can be done by spiking pure substances (drug substance or drug product) with appropriate levels of impurities and/or excipients and demonstrating that the assay result is unaffected by the presence of these materials (by comparison with the assay result obtained on unspiked samples).

For the impurity test, the discrimination may be established by spiking drug substance or drug product with appropriate levels of impurities and demonstrating the separation of these impurities individually and/or from other components in the sample matrix.

3.1.2.2. Impurities are not available

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure e.g.: pharmacopoeial method or other validated analytical procedure (independent procedure). As appropriate, this should include samples stored under relevant stress conditions:

light, heat, humidity, acid/base hydrolysis and oxidation.

- for the assay, the two results should be compared.
- for the impurity tests, the impurity profiles should be compared.

Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g., diode array, mass spectrometry).

3.2. LINEARITY

A linear relationship should be evaluated across the range (see section 3.3) of the analytical procedure. It may be demonstrated directly on the drug substance (by dilution of a standard stock solution) and/or separate weighings of synthetic mixtures of the drug product components, using the proposed procedure. The latter aspect can be studied during investigation of the range. Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by

appropriate statistical methods, for example, by calculation of a regression line by the method of least squares. In some cases, to obtain linearity between assays and sample concentrations, the test data may need to be subjected to a mathematical transformation prior to the regression analysis. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity.

The correlation coefficient, y-intercept, slope of the regression line and residual sum of squares should be submitted. A plot of the data should be included. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity.

Some analytical procedures, such as immunoassays, do not demonstrate linearity after any transformation. In this case, the analytical response should be described by an appropriate function of the concentration (amount) of an analyte in a sample.

For the establishment of linearity, a minimum of 5 concentrations is recommended. Other approaches should be justified.

3.3. RANGE

The specified range is normally derived from linearity studies and depends on the intended application of the procedure. It is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure. The following minimum specified ranges should be considered:

- for the assay of a drug substance or a finished (drug) product: normally from 80 to 120 percent of the test concentration;
- for content uniformity, covering a minimum of 70 to 130 percent of the test concentration, unless a wider more appropriate

range, based on the nature of the dosage form (e.g., metered dose inhalers), is justified;

- for dissolution testing: +/-20 % over the specified range; e.g., if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0-110% of the label claim.
- for the determination of an impurity: from the reporting level of an impurity[1] to 120% of the specification; for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the detection/quantitation limit should be commensurate with the level at which the impurities must be controlled.

Note: for validation of impurity test procedures carried out during development, it may be necessary to consider the range around a suggested (probable) limit;

- if assay and purity are performed together as one test and only a 100% standard is used, linearity should cover the range from the reporting level of the impurities[1] to 120% of the assay specification;

1 see chapters "Reporting Impurity Content of Batches" of the corresponding ICH- Guidelines: "Impurities in New Drug Substances" and "Impurities in New Drug Products"

3.4. ACCURACY

Accuracy should be established across the specified range of the analytical procedure.

3.4.1. Assay

3.4.1.1. Drug Substance

Several methods of determining accuracy are available:

a) application of an analytical procedure to an analyte of known purity (e.g. reference material);

b) comparison of the results of the proposed analytical procedure with those of a second well-characterized procedure, the accuracy of which is stated and/or defined (independent procedure, see 3.1.2.);

c) accuracy may be inferred once precision, linearity and specificity have been established.

3.4.1.2. Drug Product

Several methods for determining accuracy are available:

a) application of the analytical procedure to synthetic mixtures of the drug product components to which known quantities of the drug substance to be analysed have been added;

b) in cases where it is impossible to obtain samples of all drug product components, it may be acceptable either to add known quantities of the analyte to the drug product or to compare the results obtained from a second, well characterized procedure, the accuracy of which is stated and/or defined (independent procedure, see 3.1.2.).

c) accuracy may be inferred once precision, linearity and specificity have been established.

3.4.2. Impurities (Quantitation)

Accuracy should be assessed on samples (drug substance/ drug product) spiked with known amounts of impurities. In cases where it is impossible to obtain samples of certain impurities and/ or degradation products, it is considered acceptable to compare results obtained by an independent procedure (see 3.1.2.). The response factor of the drug substance can be used.

It should be clear how the individual or total impurities are to be determined e.g., weight/weight or area percent, in all cases with respect to the major analyte.

3.4.3. Recommended Data

Accuracy should be assessed using a minimum of 9 determinations over a minimum of 3 concentration levels covering the specified range (e.g. 3 concentrations/3 replicates each of the total analytical procedure).

Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals.

3.5. PRECISION

Validation of tests for assay and for quantitative determination of impurities includes an investigation of precision.

3.5.1. Repeatability

Repeatability should be assessed using:

a) a minimum of 9 determinations covering the specified range for the procedure (e.g. 3 concentrations/3 replicates each) or

b) a minimum of 6 determinations at 100% of the test concentration.

3.5.2. Intermediate Precision

The extent to which intermediate precision should be established depends on the circumstances under which the procedure is intended to be used. The applicant should establish the effects of random events on the precision of the analytical procedure. Typical variations to be studied include days, analysts, equipment, etc. It is not considered necessary to study these effects individually. The use of an experimental design (matrix) is encouraged.

3.5.3. Reproducibility

Reproducibility is assessed by means of an inter-laboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. These data are not part of the marketing authorization dossier.

3.5.4. Recommended Data

The standard deviation, relative standard deviation (coefficient of variation) and confidence interval should be reported for each type of precision investigated.

3.6. DETECTION LIMIT

Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

3.6.1. Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods.

The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected .

3.6.2. Based on Signal-to-Noise

This approach can only be applied to analytical procedures which exhibit baseline noise. Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit.

3.6.3. Based on the Standard Deviation of the Response and the Slope

The detection limit (DL) may be expressed as: $DL = 3.3 \sigma/S$

where σ = the standard deviation of the response

S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of S may be carried out in a variety of ways, for example:

3.6.3.1. Based on the Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

3.6.3.2. Based on the Calibration Curve

A specific calibration curve should be studied using samples containing an analyte in the range of DL. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

3.6.4. Recommended Data

The detection limit and the method used for determining the detection limit should be presented. If DL is determined based on visual evaluation or based on signal to noise ratio, the presentation of the relevant chromatograms is considered acceptable for justification.

In cases where an estimated value for the detection limit is obtained by calculation or extrapolation, this estimate may subsequently be validated by the independent analysis of a suitable number of samples known to be near or prepared at the detection limit.

3.7. QUANTITATION LIMIT

Several approaches for determining the quantitation limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

3.7.1. Based on Visual Evaluation

Visual evaluation may be used for non-instrumental methods but may also be used with instrumental methods. The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

3.7.2. Based on Signal-to-Noise Approach

This approach can only be applied to analytical procedures that exhibit baseline noise. Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and by establishing the minimum concentration at which the analyte can be reliably quantified. A typical signal-to-noise ratio is 10:1.

3.7.3. Based on the Standard Deviation of the Response and the Slope

The quantitation limit (QL) may be expressed as: $QL = 10\ \sigma/S$

where σ = the standard deviation of the response

S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of S may be carried out in a variety of ways for example:

3.7.3.1. Based on Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

3.7.3.2. Based on the Calibration Curve

A specific calibration curve should be studied using samples, containing an analyte in the range of QL. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

3.7.4. Recommended Data

The quantitation limit and the method used for determining the quantitation limit should be presented. The limit should be subsequently validated by the analysis of a suitable number of samples known to be near or prepared at the quantitation limit.

3.8. ROBUSTNESS

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters. If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system suitability parameters (e.g., resolution test) is established to ensure that the validity of the analytical procedure is maintained whenever used. Examples of typical variations are:

- stability of analytical solutions,
- extraction time

In the case of liquid chromatography, examples of typical variations are

- influence of variations of pH in a mobile phase,
- influence of variations in mobile phase composition,
- different columns (different lots and/or suppliers),
- temperature,
- flow rate.

In the case of gas-chromatography, examples of typical variations are

- different columns (different lots and/or suppliers),
- temperature,
- flow rate.

3.9. SYSTEM SUITABILITY TESTING

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. They are especially important in the case of chromatographic methods. See Pharmacopoeias for additional information.

4. GLOSSARY

1. ANALYTICAL PROCEDURE

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

2. SPECIFICITY

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s). This definition has the following implications: Identification: to ensure the identity of an analyte. Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc. Assay (content

or potency): to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

3. ACCURACY

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.

4. PRECISION

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

4.1. Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

4.2. Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

4.3. Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

5. DETECTION LIMIT

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

6. QUANTITATION LIMIT

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

7. LINEARITY

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

8. RANGE

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

9. ROBUSTNESS

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

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