Annexure 1 (Draft 1): Proposed changes to ASEAN Variation Guideline Draft 7.2 July 2012 and inclusion into ASEAN Variation Guideline Revision 1

Background

The ASEAN Variation Guideline 7th draft was presented in the 19th ACCSQ-PPWG Meeting in Bangkok, Thailand and adopted in principle with proposed implementation latest within one year of adoption ie. by 31 July 2013. Following the adoption of 7th draft of AVG, minor amendments were made and circulated as draft 7.1. It was further commented and finalized as draft 7.2

In the Technical Working Group discussion on AVG during 21st ACCSQ PPWG Meeting in Bandar Sunway, Malaysia, the Meeting agreed to maintain AVG draft 7.2 as the adopted guideline and any proposals for changes or amendments will be included in an annexure which will be circulated to AMS, APRIA and APC by 31 August 2014.

The proposed changes have been previously discussed either at the TWG level or through circulation (as in AVG 1st Edition) and should be included in ASEAN Variation Guideline Revision 1 upon achieving consensus. Proposed changes are categorized into 6 categories as below:

1) **Proposed addition of new variations** (where a new variation number will be assigned)
2) **Proposed amendment to existing variations** (where existing variation number remains unchanged)
3) **Proposed addition of new conditions and/or supporting documents**
4) **Proposed amendment to existing conditions and/or supporting documents**
5) **Proposed deletion of condition or document**
6) **Proposed renumbering of variations due to addition of new variations**

1) Proposed addition of new variations

This may include addition of a totally new variation or as a result of splitting or re-categorization of existing variation which will lead to a new variation number being assigned. New set of conditions and supporting documents are created.

1.1) Major change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]

One of the conditions for MiV-PA7 of AVG draft 7.2 is that the synthetic route of drug substance remains the same. Hence, this new major variation is created for cases where the synthetic route is different.

Discussed and agreed during AVG Training Workshop. Brought up in the TWG Meeting during 21st ACCSQ PPWG. This new variation is proposed for consensus to be included in AVG Revision 1 as a new MaV.

New MaV	**Major 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. The synthetic route is different. Refer to MiV-PA if the synthetic route remains unchanged. 3. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Stability performance of drug substance remain unchanged.
D	1. Relevant 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 approved and new processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. 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. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed 6. 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). 7. Batch analysis data and/or certificate of analysis (in a comparative tabulated format) for at least two pilot/production batches of drug product manufactured with the drug substance according to the currently approved and proposed processes.

1.2) Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product

MaV-5 of AVG draft 7.2 is for both sterile and non sterile products. Since the risk in stability of non-sterile product is less than sterile product, it has been proposed that addition or replacement of alternative site for primary packaging for non-sterile product be downgraded to MiV-PA. A letter of commitment to conduct stability study is proposed in lieu of stability data for this variation. MaV-5 will be applicable for sterile product only and the stability data requirement remains unchanged.

Circulated and agreed by most Member States and APRIA. Brought up in the TWG Meeting during 21st ACCSQ PPWG. This new variation is proposed for consensus to be included in AVG Revision 1 as a new MiV-PA.

New MiV-PA	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product, please refer to MaV.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. 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. 3. 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). 4. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 5. A letter of commitment from marketing authorization holder to conduct real time and accelerated stability studies for the drug product packed at the proposed site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

1.3) Change of specifications and/or test procedure of excipient, following updates in the compendium

MiV-PA22 of AVG draft 7.2 does not cover change of test procedure of compendial excipient. Since change of specifications of excipient due to updates in compendium is considered as MiV-Notification, similar categorization should be applied for change of test procedure of compendial excipient.

Circulated and included in AVG 1st Edition. Brought up in the TWG Meeting during 21st ACCSQ PPWG. This new variation is proposed for consensus to be included in AVG Revision 1 as a new MiV-N.

New MiV-N	**Change of specifications and/or test procedure of excipient, following updates in the compendium**
C	1. Applicable to compendial excipients only. 2. Change is made exclusively to comply with an update of the relevant monograph of the compendium.
D	1. Revised specifications of the excipient. 2. Description of the analytical methodology with a comparative tabulation of the changes. 3. CoA of excipients (where applicable)

2) Proposed amendment to existing variations

Amendment to existing variation that does not lead to creation of a new variation number. This includes a wider variation that covers more aspect or editorial changes due to splitting of variation. Current set of conditions or supporting documents remain principally the same with minor amendments to suit the change in variation title.

2.1) MiV-PA3 - Addition of quality control testing site to existing MiV-PA3 (change of batch release site)

Change of quality testing site was previously not covered in AVG draft 7.2. This is added to existing MiV-PA3 in view of similar conditions and supporting documents required for change of site responsible for batch release and/or quality testing.

Agreed by the TWG Meeting during 21st ACCSQ PPWG. This amendment is proposed for consensus to be included in AVG Revision 1.

MiV- PA3	**Addition or replacement of the company or party responsible for batch release and/or quality control testing site**
C	1. Only applicable for batch release and/or quality control testing site. 2. The manufacturer of the drug product remains the same. 3. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (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. Otherwise in the case where the proposed site is only responsible for quality control testing, documentary evidence that the proposed site has been appropriately accredited and audited to be qualified for such activity should be submitted. 3. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable). 4. Analytical method transfer data (where applicable).

2.2) Due to splitting of non-sterile product from MaV-5 to become a MiV-PA, existing MaV-5 is amended as below:

MaV-5	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product, please refer to MiV-PA.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. 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. 3. 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). 4. ~~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. 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. 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).

2.3) MaV-11 Quantitative and/or qualitative change in coating weight of tablets or weight and/or size and/or colour of capsule shell for modified release oral dosage form

MaV-11	**Quantitative and/or qualitative change in coating weight of tablets or weight and/or size and/or colour 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 and/or quantitative change in coating weight of tablets or weight and/or size and/or colour of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA16.
	1. Comparative dissolution profile data of at least one pilot/production batch of

D	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). 8. Certificate of analysis of capsule shell of the proposed size and/or colour.

2.4) MiV-PA7 Minor change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]

2.5) MiV-PA9 Change of the test procedure of ~~non-compendial~~ drug substance

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. Appropriate verification/validation data of the proposed test procedure. 3. Specification of the drug substance. 4. Batch analysis data (in a comparative tabulated format) for two pilot/production batches of the drug substance for current and proposed test.

2.6) MiV-PA16 Quantitative change in coating weight of tablets or weight and/or size and/or colour of capsule shell for immediate release oral solid dosage forms Condition to be amended as well.

MiV–PA16	**Quantitative and/or qualitative change in coating weight of tablets or weight and/or size and/or colour 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 and/or colour. 3. For quantitative and/or quantitative change in coating weight of tablets or weight and/or size and/or colour 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. 8. Certificate of analysis of capsule shell of the proposed size and/or colour.

2.7) MiV-PA21 Change of specifications of an excipient

a) Specification limits are tightened/widened

b) Addition/replacement/deletion of ~~new~~ test parameter and limits

2.8) MiV-PA35 Change of storage conditions of the drug product (Increasing from the current approved storage condition and/or addition or removal of general precautionary statements such as “Protect from light” and/or “Store in a dry place”).

MiV-PA35	a) **Change of storage conditions of the drug product (Increasing from the current approved storage condition and/or addition or removal of general precautionary statements such as “Protect from light” and/or “Store in a dry place”).** **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. 4. General precautionary statements on storage conditions in product labeling may be included but should not be used to conceal stability problems.
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. 4. Data on light and/or moisture sensitivity test on drug product (where applicable).

2.9) MiV-N9 Change of release and shelf-life specifications of the drug product, and/or drug substance ~~and/or excipient~~, following updates in the compendium

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 and/or drug substance with changes highlighted. 2. Batch analysis of the drug product and/or drug substance for all tests in the new specification of at least two batches. 3. Revised release and shelf-life specifications of the drug product and/or drug substance.

3) Proposed addition of new conditions and/or supporting documents

This includes addition of a new condition and/or supporting document under existing variation title or as a result of a new variation.

3.1) MaV-4 (new document) - Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

3.2) MaV-8 & MiV-PA13 (new condition) - The product formulation remains unchanged.

3.3) MaV-10, MiV-PA15, MiV-PA17 (new document) - Data to show that the new excipient does not interfere with the drug product release and shelf life specifications test method (where applicable).

3.4) MaV-10 & MiV-PA15 (new document) - For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).

3.5) MaV-11 & MiV-PA16 (new document) - Certificate of analysis of capsule shell of the proposed size and/or colour.

3.6) MiV-PA3 (new document) –Added in to D2 “Otherwise in the case where the proposed site is only responsible for quality control testing, documentary evidence that the proposed site has been appropriately accredited and audited to be qualified for such activity should be submitted.”

3.7) MiV-PA3 (new document) - Analytical method transfer data (where applicable).

3.8) MiV-PA9 (new document) – Validation data separated from current D1 and made as a new document “Appropriate verification/validation data of the proposed test procedure.”

3.9) MiV-PA9 (new document) – Analytical results removed from current D1 and made as a new document “Batch analysis data and/or certificate of analysis (in a comparative tabulated format) for two pilot/production batches of the drug substance for current and proposed test protocol.”

3.10) MiV-PA21 (new document) - Technical justification for the change.

3.11) MiV-PA33 (new document) - Data on test of uniformity of delivered dose as per pharmacopoeia.

3.12) MiV-PA35 (new condition) - General precautionary statements on storage conditions in product labeling may be included but should not be used to conceal stability problems.

3.13) MiV-PA35 (new document) - Data on photosensitivity and/or moisture sensitivity test on drug product (where applicable).

4) Proposed amendment to existing conditions and/or supporting documents

General amendments for better clarity and improving consistency.

4.1) MaV-6, MiV-PA8, PA21, PA24 & PA27 (Condition) – The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified.

There are circumstances where specifications are revised due to stability concern, eg. widening of specifications of preservative due to consistent OOS in the stability study as a result of interaction between preservative and rubber closure. It may be justified with results of Preservative Efficacy Test appropriately.

4.2) MaV-4 (Document) – Product formula and/or batch manufacturing formula.

4.3) MaV-8 (Document)- Comparative tabulated format of proposed and currently approved batch manufacturing formula.

4.4) MaV-10 & MiV-PA15, PA17, PA23 (Document) - For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant competent authority of the issuing country and/or documentary evidence from the supplier (where applicable).

4.5) MaV-15 & MiV-PA34 (Document) - Justification letter for the proposed change ~~of shelf-life of the drug product~~ (where applicable).

4.6) MaV-16 & MiV-PA35 (Document) – ~~Technical~~ Justification letter for the proposed change.

4.7) MaV-16 & MiV-PA35 (Document) - 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
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 microbiological testing should be included (where appropriate).

4.8) MiV-PA7 (Condition) - The synthetic route remains the same (for example, intermediates remain the same). Refer to MaV if synthetic route is different.

4.9) MiV-PA15 (Condition) - Release and shelf-life specifications of the drug product remain unchanged; excluding product description.

4.10) MiV-PA22 (Condition) - This applies for non-compendial excipient. For compendial excipients, please refer to MiV-N.

4.11) MiV-PA25 (Document) - Data on test of ~~content~~ uniformity of the subdivided parts of the tablets at release as conformed to compendial requirement ~~should be submitted~~.

4.12) MiV-PA25 (Document) - Certificate of analysis of two production/pilot batches of the drug product.

4.13) MiV-PA26 (Document) - For scored tablets, 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).~~

4.14) MiV-PA26 (Document) - Release and shelf-life specifications of the drug product with new dimension and/or shape.

4.15) MiV-PA28 (Condition) - The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties; unless otherwise justified.

4.16) MiV-PA28 (Document) - 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). Stability data covering at least 6 months should be submitted for the proposed primary packaging material which is not equivalent or better than the approved material in respect of its relevant properties.

4.17) MaV-(3, 4, 6, 7, 8, 9 & 10), MiV-PA(4-9, 12, 13, 14, 15, 19, 20, 21, 24 & 27) & MiV-N9 (Document) - Standardization of batch analysis data and/or certificate of analysis for consistency throughout the guideline

Batch analysis data and certificate of analysis can both be combined as appropriate to the variation.

4.17a) For drug substance:
Batch analysis data and/or certificate of analysis (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed (subject).

4.17b) For drug product:

Batch analysis data and/or certificate of analysis (in a comparative tabulated format) for at least two pilot/production batches of drug product manufactured with the drug substance according to the currently approved and proposed (subject).

or

Batch analysis data and/or certificate of analysis (in a comparative tabulated format) for at least two production batches of the drug product manufactured according to currently approved and proposed batch sizes.

or

Batch analysis data and/or certificate of analysis (in a comparative tabulated format) for at least two production batches (or one production batch and two pilot batch) of the drug product from the current and proposed (subject). Batch analysis data and/or certificate of analysis on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).

4.18) MaV(4, 8, 9, 10 & 11) & MiV-PA(15, 16, 20, 23 & 26) (Document) - Standardization of comparative dissolution profile data for consistency throughout the guideline

Comparative dissolution profile data is proposed to be standardized as:
Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the currently approved and proposed (subject) for oral solid dosage forms as per compendium and/or validated dissolution test method; as per SUPAC IR or MR Guideline.

5) Proposed deletion of condition or document

Certain condition that is confusing or document that is no longer relevant due to better understanding of the variation.

5.1) MiV-PA28 (Condition) – C2 The change only concerns the same packaging type (for example from blister to blister).

Propose to delete as the sentence is confusing since the change should cover change to another type of container.

6) Proposed renumbering of variations due to addition of new variations

There will be 17 MaV, 36 MiV-PA and 11 MiV-N in AVG Revision 1.