Proposal for alignment of comparative dissolution profile in ASEAN Variation Guideline with SUPAC IR and MR Guidelines

1. Background

During the ASEAN Variation Guideline (AVG) Training Workshop which was conducted on 20-21 August 2013 in National Pharmaceutical Control Bureau (NPCB), Malaysia, there was a proposal to align comparative dissolution profile (CDP) in AVG with SUPAC IR and MR Guidelines. The draft on proposed alignment was subsequently circulated on 29 May 2014 along with the ASEAN Variation Guideline 1st Edition.

Following the Technical Working Group on AVG during the 21st ACCSQ PPWG Meeting in Bandar Sunway, Malaysia; the Meeting agreed to maintain the adopted AVG draft 7.2 and any proposals for changes or amendments which includes proposed CDP requirement aligned with SUPAC IR and MR guidelines will be included in an appendix to the adopted guideline. The Chair further requested Member States to provide feedback on the proposed alignment on CDP to Malaysia by 31 July 2014.

2. CDP requirements in AVG

In the AVG draft 7.2 2012, there are 5 major variations (MaV) and 5 minor variation prior approval (MiV-PA) that require CDP as per Appendix 1. It is generally stated as below:

Example of CDP (MaV-4 Addition or replacement of the manufacturing site of the drug product):
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.

The CDP requirement in AVG is not standardized in terms of number of batches and does not provide details on number of buffers required. Therefore there is a need to harmonize according to technical aspects of CDP as per SUPAC IR and MR Guidelines.

3. CDP requirements in SUPAC IR and MR Guidelines

A post-approval change is generally categorized into 3 levels of changes according to SUPAC IR and MR Guidelines. CDP is not required in level 1 change but required in level 2 and 3 changes in terms of different number of dissolution profiles and medium. Not all variations in AVG are listed in SUPAC.

3.1 CDP requirements in SUPAC IR Guideline

CDP requirement for post-approval change of immediate release dosage forms can be categorized as:

Dissolution Testing

Case A:	Dissolution of Q = 85% in 15 minutes in 900 milliliters (mL) of 0.1N hydrochloride (HCl), using the United States Pharmacopeia (USP) <711> Apparatus 1 at 100 revolutions per minute (rpm) or Apparatus 2 at 50 rpm.
Case B:	Multi-point dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation.
Case C:	Multi-point dissolution profiles performed in water, 0.1N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

CDP requirement for level 3 change is less stringent than level 2 change due to bioequivalence report as one of the supporting documentations for level 3 change.

SUPAC IR Guideline specifically outlines the use of Biopharmaceutical Classification System (BCS) for post-approval quantitative change of excipients as below:

Level I – no CDP

Level II – according to Bioppharmaceutical Classification System (BCS):

- High solubility, high permeability: Case A
- High solubility, low permeability: Case B
- Low solubility, high permeability: Case C

Level III: Case B

3.2 CDP requirements in SUPAC MR Guideline

According to SUPAC MR Guideline, the CDP requirements for a modified release dosage form are different depending on whether the excipients are release or non-release controlling and whether it is extended release (ER) or delayed release (DR).

Generally, CDP requirements for level 2 changes are as below:

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional

test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation , only application/compendial dissolution testing need be performed (i.e., only in vitro release data by the correlating method need to be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles . Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

Generally, CDP requirements for level 3 changes are less stringent than level 2 changes due to BE report submission. The CDP requirements for level 3 changes are as below:

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter, until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

4. Basis for alignment of CDP in AVG with SUPAC IR and MR Guidelines

- Generally in SUPAC, the CDP technical requirements for level 3 change is less stringent than level 2 due to BE report as one of the requirements. In AVG, this is covered under the document "Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable)".

5. Proposed amendments to be made in AVG draft 7.2 in relation to CDP alignment with SUPAC IR and MR Guidelines.

5.1 Malaysia proposes to align CDP requirements in AVG with SUPAC IR and MR Guidelines as per Appendix 1. The CDP requirement should be standardized as below:

Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the currently approved and proposed changes for oral solid dosage forms as per level of change in SUPAC IR or MR Guidelines

5.2 Malaysia proposes to

a) Add additional document "Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable)" to MaV-4 since BE documentation for the new site should be submitted.

6. Feedback on proposed alignments on (5.1) CDP in AVG with SUPAC IR and MR Guidelines and (5.2) amendments to AVG draft 7.2.

No.	Member State/ Pharmaceutical association	Agree/Disagree	Comments
1.	Brunei Darulssalam	No response	
2.	Cambodia	No response	
3.	Indonesia	Agree	- Indonesia agrees with the alignment of CDP AVG with SUPAC since it is also in accordance with our regulation. - Propose to change "MaV-11" in the column of "proposed alignment in AVG" in point 5 and 7, to "MaV-10", to be consistent with point 4 that previously described. Malaysia: Error corrected.
4.	Laos	No response	
5.	Malaysia	Agree	As proposed in Appendix 1.
6.	Myanmar	No response	
7.	Philippines	Agree	MIV-PA26 – Clarification on the proposed alignment to follow same CDP requirements with MaV-10 considering that there will be no Qualitative/Quantitative change in the composition and mean mass. Malaysia: Pls refer to Appendix 1
8.	Singapore	Agree	
9.	Thailand	5.1- Disagree with Appendix 1. - Agree with	5.1 In order to avoid the misinterpretation in some variation type, we propose not to refer to the CDP alignment as proposed in Appendix 1 but to refer to "as stated in SUPAC

		The CDP requirement to be standardized as proposed. 5.2 – a) Agree with Malaysia - proposes to Add additional document. - b) Disagree to remove CDP requirement.	Guidelines". Malaysia: Not all variations that require CDP are found in SUPAC Guidelines. 5.2 b) Please refer to WHO Guidance on Variations to a Prequalified Product Dossier "no. 37. Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass" in which the Comparative dissolution data is required.
10.	Vietnam	Agree	Also accept Comparative Dissolution Profile compliance SUPAC Guidelines with appropriate justifications.
11.	APRIA	Agree	Hyperlink for APRIA's general comments.
12.	APC	No response	

APPENDIX 1: Proposed alignment of Comparative Dissolution Profile in AVG with SUPAC IR And MR Guidelines

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
1.	MaV-4[#]	Addition or replacement of the manufacturing site of the drug product	D7	I	None	I	none	Same as non-release controlling		IR: Level III, B ([#]added new document justification for not submitting BE report) MR: Level III Singapore and Thailand agree with the proposed addition of supporting document. Vietnam: SUPAC-IR and ASEAN BE GL do not require BE report in this variation. Malaysia (New): As per SUPAC IR or MR[#]
				II	None	II	ER: 4 media			
							DR: 0.1N HCL, (acid stage), USP buffer media (pH4.5-7.5)			
				III	B	III	ER: a multipoint profile			
							DR: multipoint, at buffer stage			
2.	MaV-8	Change of batch size of non-sterile drug product	D1					Same as non-release controlling		IR: Level II, B MR: Level II Malaysia (New): As per SUPAC IR or MR
				II (>10times)	B	II (>10times)	ER: 4 media			
							DR: 0.1N HCL, (acid stage), USP buffer media (pH4.5-7.5)			

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
3.	MaV-9	Major change in the manufacturing process for drug product	D2	III	B	III	ER: a multipoint profile DR: multipoint, at buffer stage	Same as non-release controlling		IR: Level III, B MR: Level III Singapore: For D2, may consider including the option to provide BE study in addition to the current justification for BE waiver. APRIA: Suggest including Level 2 SUPAC process change in Item 3. Revise the proposed alignment to read: Level 2 IR: Case B dissolution with CDP Level 3 IR: Case B dissolution with CDP; plus BE (except BCS 1) Level 2 MR: CDP in 4 media (buffer stage for DR) Level 3 MR: Dissolution profile in application/compendial medium; plus BE (unless waived based on IVIVC)
4.	MaV-10	Qualitative or quantitative change of excipient	D4	II	BCS: case A, B or C	I II	None ER: 4 media	I II (non-narrow	None ER: 4 media	IR: BCS (even though BE is in D section)

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
								therapeutic range drugs)	DR: 0.1N HCL, (acid stage), USP buffer media (pH4.5-7.5)	MR: Level III (for both release and non-release controlling) Singapore: IR: As per level II or III MR: As per level II or III (according to release and non-release controlling sections) APRIA: Recommend moving Level I information for SUPAC-MR non-release and release-controlling to MiV-PA15 (no. 6). It is not required for Level I component composition changes For MR products should require extensive dissolution testing. Malaysia (New): As per SUPAC IR or MR (according to release and non-release controlling sections)
							DR: 0.1N HCL, (acid stage), USP buffer media (pH4.5-7.5)	II (narrow therapeutic range drugs)	ER: a multipoint profile	
									DR: multipoint, at buffer stage	
				III	B	III	ER: a multipoint profile	III	ER: a multipoint profile	
							DR: multipoint, at buffer stage		DR: multipoint, at buffer stage	
5.	MaV-11	Quantitative change in the coating weight of tablets or weight and/or size and/or	D3	NA		Not in SUPAC		Not in SUPAC		Should follow MaV--10 MR: Level III (for both

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
		colour of capsule shell for modified release oral dosage form								release and non-release controlling) Singapore: For change of colour of capsule shell only: None beyond application / compendial requirements (routine method) MR: As per level II or III (according to release and non-release controlling sections) APRIA: MR: As per level II or III (according to release and non-release controlling sections) Malaysia (New): Similar approach as MaV-10, as per level II or III of SUPAC MR (according to release and non-release controlling sections)
6.	MiV-PA15	Qualitative or quantitative change of excipient	D5	I	None	NA		NA		IR: BCS Singapore: None beyond

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
										application / compendial requirements (routine method) APRIA: Recommend moving Level I information for SUPAC-MR non-release and release-controlling from MaV-10 (no. 4) to MiV-PA15 (no. 6). It is not required that for Level I component composition changes for MR products should require extensive dissolution testing. Malaysia (New): None beyond application / compendial requirements (routine method)
7.	MiV-PA16	Quantitative change in coating weight of tablets or weight and/or size and/or colour of capsule shell for immediate release oral dosage form	D4	Not in SUPAC		NA		NA		Should follow MaV-10 IR: BCS (even though BE is in D section) Singapore: For change of colour of

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
										capsule shell only: none beyond application / compendial requirements (routine method). Suggest to follow item 6 (or item 4, as appropriate) APRIA: None beyond 1-point application/compendial dissolution test Malaysia (New): Similar approach as MaV-10 (level II or III) or MiV-PA15 (level I) where appropriate. For change of colour of capsule shell only: none beyond application / compendial requirements (routine method).
8.	MiV-PA20	Minor change of the manufacturing process for non-sterile product	D1	I	None	I	None	Same as non-release controlling		IR: Level II, B MR: Level II APRIA: Define MiV-PA20 as a Level 1 SUPAC process
				II	B	II	ER: 4 media			
							DR: 0.1N HCL, (acid stage), USP buffer media (pH4.5-			

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
							7.5)			change and delete Level 2 SUPAC process change from Item 8 Revise the proposed alignment to read: IR: None beyond application/compendial requirement MR: None beyond application/compendial requirement Malaysia (New): IR: Level I or II MR: Level I or II
9.	MiV-PA23	Change in the source of empty hard capsule	D4	Not in SUPAC		Not in SUPAC		Not in SUPAC		IR: BCS Singapore: IR and MR: None beyond application / compendial requirements (routine method) MR may be applicable too, where enteric-coated or modified release pellets are contained within. APRIA: IR: Case B with CDP There is only a

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
										recommendation for IR, not MR. MR recommendation should be included. Malaysia (New): Similar approach as MaV-10. Specifically, IR: level II MR: level II (according to release and non-release controlling sections) (since justification for not submitting BE is not required as supporting document for this variation)
10.	MiV-PA26	Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass	D3	NA		Not in SUPAC		Not in SUPAC		MR: Level III (for both release and non-release controlling) Singapore: None beyond application / compendial requirements (routine method). This does not constitute a change in SUPAC. Philippines: Clarification on the

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
										proposed alignment to follow same CDP requirements with MaV-10 considering that there will be no Qualitative/Quantitative change in the composition and mean mass. Thailand: Please refer to WHO Guidance on Variations to a Prequalified Product Dossier "no. 37. Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass" in which the Comparative dissolution data is required. APRIA: IR: Case B with CDP if BCS 2, BCS 4, or narrow therapeutic MR: CDP in 4 media Malaysia (New):

No.		Variation title	AVG	SUPAC (IR)		SUPAC (MR, non-release controlling)		SUPAC (MR –release controlling)		Proposed alignment in AVG
				Level	Case	Level	Case	Level	Case	
										Similar approach as MaV-10. Specifically, IR: level II MR: level III (due to justification for not submitting BE is required)

Note:

[#] For MaV-4, Malaysia proposes to include a new supporting document "Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable)".

APRIA's Comments
(30 July 2014)

GENERAL Comments and/or Concerns
It is technically difficult, if not impossible, to align comparative dissolution profiles (CDP) in AVG with those in SUPACs when the types and levels of change are not aligned between AVG and SUPACs. Thus, in addition to the CDP requirement and associated f2 criteria, the level of change should be aligned with that in the SUPAC wherever possible.
A distinction should be made between dissolution profiles and comparative dissolution profiles (CDP). The latter requires a comparison using a statistical test such as the similarity factor (f2), while the former does not. It should be clearly indicated in the proposal and, more importantly, in the AVG when CDP is necessary and when dissolution profiles (without statistical test) is sufficient if alignment with SUPACs is to be achieved. Specifically, • In SUPAC IR, CDP is necessary for Level 2 (Case B dissolution) and Level 3 (Case C dissolution) changes even where BE is required (i.e., Level 3 components/composition change and Level 3 process change). • In SUPAC MR, (1) CDP is required, and BE is not, for Level 2 changes (excluding Level 2 components/composition changes to narrow therapeutic drugs); and (2) dissolution profile (without statistical test), in lieu of CDP, is sufficient where BE is required for Level 3 changes and Level 2 components/composition changes to narrow therapeutic drugs.
Although SUPAC IR and MR guidance documents (issued in 1995 and 1997, respectively) have withstood the test of time and still provide value, they are not fully aligned with modern QbD development principles where product knowledge can allow for product-specific approaches. In some instances, increased process knowledge/understanding and controls resulting from QbD can identify the factors that impact dissolution. Such knowledge (e.g., understanding of critical raw material attributes, defined relationship between process parameters and their impact on dissolution, modelling) may eliminate the need for performing dissolution testing and allow the use of alternative in-vitro quality attributes such as disintegration (in lieu of dissolution) for low risk products. It would be desirable if the AVG can afford such flexibility in the requirements for dissolution testing when these instances exist.
Usually the phrase "requires dissolution *as per compendium*" would mean BP, Ph. Eur. or USP. Sometimes for innovator, dissolution medium can be different from that stated in the compendium. Therefore, application medium used should also be acceptable in these cases.
If CDP in AVG will be aligned with SUPAC Guidelines, suggest to delete *Appendix 1* in Malaysia's proposal. Some alignments in Appendix 1 are more stringent than SUPAC. Should read: *Malaysia proposes to align CDP requirements in AVG with SUPAC IR and MR Guidelines.*

*In case Appendix 1 will be maintained, APRIA is also providing comments.