AESGP
Association Européenne des Spécialités Pharmaceutiques Grand Public
Association of the European Self-Medication Industry
Europäischer Verband der Arzneimittel-Hersteller

AESGP Comments on the review of Regulation (EC) No 1234/2008 Article 4: Review of the Variations Guidelines

AESGP represents the manufacturers of non-prescription medicines of either chemical or herbal origin at European level. It counts 29 national associations and 25 associate members. Through its national and associate members, it represents many small and medium-sized companies operating in the self-care sector.

AESGP appreciates the opportunity to take part in this consultation.

We have the following **general remarks:**

- **For the sake of better regulation principles which motivated the revision of the variation framework, any information which is needed for administrative reasons (e.g. address of MAH, address of QPPV etc.) which is available from EVMPD should not trigger any variation in the future unless the update in EVMPD is not done in the recommended timeframe. The classification of the specific change should remain (unless commented on later with respective arguments) but a footnote should be added similar to the one for C.I.8 b). We have also noticed the change in the classification of a number of variations towards a higher level and the increase in the documentation being requested; this undermines the original intent of the legislator and the main objective of the legislation. We would hence urgently call for more pragmatism in the classification of variations and of the documentation being requested.** To avoid unnecessary variations, updating CEP should trigger a variation only if specific condition(s) are not met e.g. no influence on the product quality.
- We would welcome the **opportunity to meet with the European Commission to discuss our main comments before the revised guideline on classification is finalised**.
- We would also appreciate knowing the timing for the next steps and the possibility for a transition period.
- We observed that the current CMDh recommendations for the classification of unforeseen variations are only partially considered in this revision. We strongly recommend taking advantage of this opportunity to introduce the most frequent changes in quality information. We also became aware that the classification of some variations in the last Quality of Medicines Q&A/ Part 1 and Part 2 (issued in 2012) and in this draft document differ.
- A glossary should give more clarity or links to other current Guidelines for certain definitions of new terms and wording introduced in this revision: e.g. Importer, “Acknowledged enhanced development approach”.
- Throughout the document “Union” is used as either a synonym for “European Union” or for “EU/EEA”. It should be made clear in each case what the correct term is.

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Specific Comments:

A. ADMINISTRATIVE CHANGES		
	Comment and Rationale:	**Proposed Change**
A.3	We do not accept that this change should be classified as a IA In for all excipients, since there are no safety implications in the majority of cases. We propose that the change should be classified as a Type 1A, except in the case of novel excipients.	To add 'change in name of an excipient' as a Type 1A In
A.4	This change results in replication of work since novel excipients are covered by the new variation B.II.c.5.	Change in name and/or address of a novel excipient manufacturer. Please see NTA requirements for initial registration
A.5	The term 'importer' should be defined as being outside the EEA/EU. Otherwise it will create confusion as for example importers between EU countries are e.g. no longer required to be mentioned on new marketing authorisation in the UK [1].	A footnote should be added to clarify the definition of 'importer'
A.5.b)	We reinforce the fact that the supplier of packaging materials is usually not declared if not needed (See CMDh recommendation on unforeseen variation : issue date 22.11.2010) The suppliers of packaging components are not manufacturers of the finished product as per NtA for section 3.2.P.3.1. So a change in name or address of such a supplier should not be filed via IA A.5.b).	Rephrase to say instead: "Any other (as mentioned in "Manufacturer" section of the Module 3)"
A.5.b)	Changes in packaging components and devices should continue to be handled via B.II.e.7 as this takes account of equivalence in specification. The B.II.e.7 variation continues to be present in the revised guideline. This additional administrative variation adds to regulatory burden without contributing to patient safety.	remove

1 http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Variationstolicences/FAQsforvariationssubmittedafter1January2010/Qualitychanges/index.htm#10

B. QUALITY CHANGES		
	Comment and Rationale:	**Proposed Change**
B.I.a.1 (minor)	Condition 5	replace “are not changing” by “remained identical”
B.I.a.1	Documentation 8	As this change is linked to the drug substance, remove “for the pharmaceutical form or product”... in the first paragraph.
B.I.a.1 g)	According to the new wording, e.g. the change of an extract manufacturer would require a Type II variation. The need for a Type II variation should be restricted to those cases in which important quality characteristics are changed (as described under B.I.a)1.c)).	We propose to add: *"... and which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability."*
B.I.a.2 d)	Raw materials used for the production of herbal medicinal products are often harvested or collected from different sites and/or geographical origins. In general a change of the geographical origin has no impact on the overall quality of the herbal raw material as long as the specification is fulfilled. Furthermore, cultivation, harvesting and collection of the raw material in accordance with the principles of Good Agricultural and Collection Practice (GACP) contribute to a high and consisting quality of the herbal raw material. For these reasons, a change of the geographical source of the herbal raw material should not automatically lead to a Type II variation. The same applies to a change of the manufacturing root or production as long as the specification is fulfilled.	The change relates to a herbal medicinal product *and there is a change having an impact on quality characteristics of the active substance (herbal drug, herbal extract) and the specification is no longer fulfilled.* *The change relates* to any of the following: geographical source, manufacturing route or production.

B.I.a.2 f)	The term "enhanced development approach" should be clarified in a footnote and reference made to ICH Q11. What is the meaning of "acknowledged" for this enhanced development approach in condition 8 and in Documentation 5?	
B.I.a.4	How to address changes such as: - widening of the approved in process test limits which may have **no** significant effect on the quality of the active substance - a translation /moving of a range without widening or tightening e.g. from LOD 0.25 – 0.45% to 0.35 – 0.55% Same comments as above regarding explanation of some terms in Conditions 8 and 9.	
B.I.a.4 c)	The new condition 7 confines Type IA changes to very few cases, although from our experience not every change to the defined parameters "assay, impurities, any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing" are to be regarded as Type IB relevant. E.g. deletion of a test parameter at this process stage due to a new routine test in the release specification, or deletion of an alternatively tested parameter with the same target which would be regarded as obsolete.	Condition no. 7 should be deleted.
B.I.b.1 d)	We recommend to add "taste" as per B.II.b.1 d)	Proposed change: (e.g. odour, **taste**)
B.I.b.1 d)	With reference to our comment under B.I.a.4, condition 8 restricts the possible cases for Type IA variations in such a manner that in practice no Type IA variations will remain. Further we wonder about the meaning of the addition "any request for skip testing".	It should be up to the applicant to identify the "non-significant specification parameters", condition no. 8 should be deleted.
B.I.b.1 f) **B.I.b.1 g)**	Both changes are classified as Type II Variations. In special cases a widening of specification limits might be necessary and unavoidable due to external factors such as e.g. biological fluctuations. The widening of a range for analytical marker substances in herbal	Definition of cases where a type Ib classification is appropriate should be added

	preparations strictly used for batch specific control is an example.	
B.I.b.1 i)	Please define the meaning of 'non official pharmacopoeia'	Change in the specification parameters and/or limits of an active substance – with reference to substances that are not Ph Eur or Ph MS
B.I.c Documentation 3 (minor)		We propose changing 'legislation of the Union' into "EU legislation"
B.I.c.2 c)	Deletion may concern a specification that is not obsolete but not pertinent for the quality itself of the packaging material such as an overall dimension of a plastic bag, or unnecessary details for a drum material if mentioned....	"Deletion of a non critical specification parameter (e.g. deletion of an obsolete **or non-significant** parameter,"
B.I.d.1.c)	Please clarify if the change to an approved stability protocol should be understood as a change in Section 3.2.S.7.2 in EU-CTD format	If our understanding is correct, please add: ..."**as per Section 3.2.S.7.2**"
B.I.d.1.c)		Proposal to add the following change (as per CMDh recommendation on unforeseen variations): Deletion of tests or reduction in the frequency of testing in a previously approved stability protocol of the active substance as a type 1 B with a Condition 3 such as: The change does not concern a widening of the approved specification parameter.
B.I.e.1 a)	It is unclear why a design space variation is restricted to one unit operation. The corresponding change for drug product allows for "One or more"	Add "One **or more** unit operation in the manufacturing process…"
B.I.e.1 Documentation 1	It is unclear what "product" means here. If results from the drug product manufactured with active substance using the proposed design	

	space is meant this would stop innovation in the dedicated API manufacturing industry.	
B.I.f.4 b) (minor)	The word "data" is missing	…"no further supportive **data** and"…..
B.II.a.1	Removal of imprints, bossing should be considered also in the title as Condition 4 concerns deletion and as change a) refers to Condition 4. In addition, removal of imprints from tablets (should be extended to capsules...) is part of the current CMDh list of unforeseen variations. Further it is not clear why all these changes have been grouped together, since the replacement or addition of an ink may not result in a visible change to the product marking. Such non-visible changes should not fall within the category of an 1A In, but should be handled as a simple excipient change.	Add: "Change, **or deletion** or addition of imprints, bossing or other markings including replacement, deletion of inks **that result in a visible change to the product marking**…."
B.II.b.1	The meaning of 'complex manufacturing process' should be defined.	This might be more precisely mentioned in a Condition to be added or in a glossary.
B.II.b.2	We refer to our comment under A.5 with regard to importers. Please note that importer is not declared in Section 3.2.P.3.1.hence documentation 5 probably needs to be amended	
B.II.b.2.b)	This variation is proposed to be classified as a type II. Assuming no change in approved specifications and analytical method(s), we draw the attention that this classification is certainly too severe. Lower classification (IAIN or IB) may be supported by specific conditions to be fulfilled.	Please amend to IAIN
B.II.b.2 c) 2.	Classification change from type IAIN to type II is unclear. This is a significant shift which could have a huge negative impact on companies.	Change back to Type IAIN The change should be classified - similar to B.II.b.2 c) 1 i.e.

		type IAIN - using the same documentation requested there but - applying the conditions proposed in B.II.b.2 c) 2.
B.II.b.3		Replace: "Including" by "or" in the title as intermediate are not always part of the process.
B.II.b.3	Changes for semi solid (e.g. gel, creams..) delivery forms are not foreseen/mentioned. We recommend introducing the semi solids preparations. Not all unforeseen variations are incorporated We recommend to insert other changes (e.g., but not limited to, the change to allowed bulk/intermediate holding time, minor change in a manufacturing process of a modified release forms) as per CMDh current recommendation for classification of unforeseen variations.	
B.II.b.3 a)	Condition 7 (relevant stability studies) and documentation 3 (dissolution profile data) should be limited to "where appropriate". There are minor changes in the manufacturing process that can clearly be classified as Type IA changes although no new stability/dissolution data are provided as support for the competent authority and the efforts would be disproportional. E.g. exchanging a sieve size for an intermediate sieving step under remaining the last sieving step during granulation.	Condition 7 (relevant stability studies) and documentation 3 (dissolution profile data) should be limited to "where appropriate".
B.II.b.3	Documentation 1: The comparison of the current process and of the new process should not be part of the EU-CTD dossier, but a separate document part of the variation application.	Delete " including a direct comparison of the present process and the new process"

B.II.b.4 c)	Please clarify that this is only foreseen for biological products.	
B.II.b.4 d)	Further clarification on "complex" process would be helpful	This might be more precisely mentioned in a Condition to be added or in a glossary
B.II.b.4 e)	Only immediate release and non-sterile liquid preparations are mentioned. - How to proceed for a scale change without complex manufacturing process for other forms (delayed release / extended release, gel, cream,...) than immediate release and non-sterile liquid preparations (delayed release / extended release, gel, cream)? - How to proceed for non-sterile liquids preparations for more than 10-fold change?	
B.II.b.4 e)	It is not logical that only oral forms are included here, since many simple locally acting dosage forms (topical creams, nasal sprays) could equally be handled in the same way.	Delete "oral"
B.II.b.4.	Documentation 2	Add a definition of conventional immediate release form in the glossary
B.II.b.5	How to address changes such as: - widening of the approved in process test limits which may have **no** significant effect on the quality of the finished product - a translation /moving of a range without widening or tightening of specifications e.g. from Hardness 3 – 5 kP% to 4 to 4 kP Same comments as above are valid regarding explanation of some terms in Conditions 8 and 9.	
B.II.b.5 b) (minor)	Editorial mix up of plural and singular	Update to: Addition of a new test and limits
B.II.c.1 c)	Add odour and taste as done for finished product, as parameters that might trigger safety hazards In addition, the new condition 8 confines Type	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter, **odour, taste**). Condition no. 8 should be

	IA changes to extremely few possible cases, although from experience not every change to the defined parameters is to be regarded as Type IB relevant.	reconsidered
B.II.c.1 d)	This change is classified as a Type II variation. This classification is not appropriate in cases such as change of specifications for excipients like flavours or colorants without technical consequences to the finished product. E.g. the range of a colorant content in a colouring preparation from 9-10 % to 7-11 % which might be imposed by the supplier's specification.	Exemptions from Type II classification should be defined
B.II.c.1 g)	Cf. our comments under B.1.b.1 i)	
B.II.c.5 b)	What is significant update for dossier sections? Type II should only be for change that causes significant change to the quality of the novel excipient influencing safety, efficacy and quality of the finished product.	Introduction of a new manufacturer of the novel excipient **that bears significant influence on the safety, efficacy and quality of the finished product**
B.II.d.1	Not all unforeseen variations are incorporated	We recommend to insert them as per CMDh current recommendation for classification of unforeseen variations.
B.II.d.1	Condition 1: It remains unclear which other procedures are meant. Agreements during the mentioned Type II variation or MA application procedures? These changes do usually not need to be notified separately but are submitted with the documentation of these procedures only. I.e. this condition is obsolete and leads to misunderstandings.	Condition no. 1 should be deleted
B.II.d.1 d)	The new condition 9 confines Type IA changes to extremely few possible cases, although from experience not every change to the defined parameters are to be regarded as Type IB relevant. Hardness is not a significant parameter for effervescent tablets and mentioning it as example of critical parameter for uncoated	Reword condition no. 9

	tablets can be misleading.	
B.II.d.1.e)	The text should specify that a Type II procedure should only apply when the change is expected to have a significant impact on the overall quality of the finished product.	Add: "substance, **which may have a significant effect on the overall quality of the finished product**"
B.II.d.1 h)	The procedure type should refer to IA as per B.III.2. We recommend there should be a note at the end stating that there is no need to notify when reference is made to "current edition" of Pharmacopoeia and in case of implementation with the updated monograph/chapter within 6 months of publication" (see B.II.2).	Change to IA Add footnote. Add in the definition of the change "with the corresponding test method(s)" by analogy with other changes in this section. Replace "finished product" by "dosage form" as there is no specific monograph for finished product in Ph. Eur.
B.II.d.1 i)	The change will be obligatory and the methods are described in the Ph. Eur. and are regarded as validated. From our point of view this change should be a Type IA variation according to B.III.2.b). According to the Q&A[2] on Quality of the CHMP QWP, Uniformity of dosage units (2.9.40) is considered equivalent to what was previously required in the Ph. Eur. Nevertheless it is categorised as Type IB here. Furthermore, the documentation to be provided is not justified. It is unclear what effect an analytical method change should have on the	Reclassify as Type IA

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	dissolution profile. Setting a condition not using the 2% relative-standard-deviation clause would be possible. Using the clause would by default result into a Type IB variation. The documentation required should be reconsidered. The title should clearly indicate that this applies only to active substance / excipient and not finished product.	
B.II.d.1 i)	The request for documentation 5 (comparative dissolution) does not make sense for the introduction of Ph. Eur. 2.9.40 specifications.	Remove it
B.II.d.2 f)	We recommend there should be a note at the end stating that there is no need to notify when reference is made to "current edition" of Pharmacopoeia and in case of implementation with the updated monograph/chapter within 6 months of publication" (see B.II.2).	Add footnote
B.II.e.1 b)	The mention “addition of a new container” may be unclear if it refers to size or type. Add “or deletion” in the title as case B.II.e.1.b.3 is mentioned underneath	Change in **or addition or deletion of new** type of container
B.II.e.1 b) 3.	Documentation 8 – only used for this variation - refers also to *new pack sizes* which is not applicable for a deletion. Or was it the intention to allow deletion of packaging container AND pack size in one variation?	Remove “new”; replace “pack size” with “container” as such: 8. Declaration that the remaining container(s), is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics
B.II.e.5	Documentation 4: The request for documentation 4 should not to the EU-CTD module 3 as this is not a quality requirement.	

B.II.e.7 b)	Condition 1 seems to be independent from the described change.	Condition 1 should be deleted.
B.II.f.1 e)	Please clarify if the change to an approved stability protocol should be understood as a change in Section 3.2.P.8.2 in EU-CTD format	If so, it would be useful to add the following "as per Section 3.2.P.8.2".
B.III.1 (minor)	Condition 2	Proposed change: "additional (to Ph. Eur.) specification for.. " by "additional specification to Ph. Eur. for..".
B.III.1	The scientific rationale for the categorisation of the change with respect to condition 3 is not clear: An updated certificate due to administrative change or manufacturing process changes not affecting the risk evaluation for adventitious agents safety is now a type IB by default because condition 3 is not fulfilled (see also a recent publication by AIFA regarding this variation, where by default in addition to the variation type IB, an unforeseen variation B.I.z type II is required to (re-)assess the adventitious agents safety), whereas these changes would be type IA if the information was part of the MA dossier.	1.New certificate from **a new or** an already approved manufacturer **(replacement or addition)** 3. delete Condition 3: reword as follows: "where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier or changed manufacturing process for which a new assessment is required of viral safety data or compliance with the current note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products."
B.III.1 b).2	The variation also addresses new CEP for excipient but condition 3 only applies to active substance.	
B.III.1 a) 5)	This new change will significantly increase the administrative burden and is contrary to better regulation practices.	Delete variation 5

B.III.2	The title should clearly indicate that this applies only to active substance / excipient and not finished product.	Change title to: Change **of active substance/excipient** to comply with Ph. Eur. or with a national pharmacopoeia of a Member State Main title of BIII should be rephrased to "CEP/TSE/monographs for active substances/excipients"
B.III.2	Condition 1: How to proceed if partial update to comply to Ph. Eur. is proposed? Will it be a Procedure Type IB? Documentation 5: We consider that the copy of the Ph. Eur. monograph should not be added to the Module 3, but part of the additional document in the application if needed.	
B.III.2.b)	This category does not clearly state that it is also relevant for products registered with an "in-house" specification and who now wish to upgrade to Ph.Eur. Some national competent authorities have advised to use this category for these types of change, despite the category suggesting that it only applies to products which are already registered with a Ph.Eur. or National Pharmacopoeia specification.	
B.IV.1 a) 3	Clarification is required regarding other device which may have a significant impact on the delivery of the active substance. The fact that nebulizer is mentioned as an example opens the door to a lot of other systems such as metered dose spray pump...Would a metered dose spray pump considered as a medical device as well as a dropper for nasal solutions with a required CE marking? We recommend that a more precise list (or exclusion list) of foreseen devices is provided in a glossary.	

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES		
C.I.	Currently changes concerning all **non-substantial changes** in the SmPC, Package leaflet and the labelling, which are not covered by the Article 61(3) notification procedure, need to be submitted under the category C.I. z) "other variation". Due to the frequency of these changes an own category including various sub-categories would be very much appreciated.	A new category C.I.x. should be created for all non-substantial changes in the SmPC, Package leaflet and the labelling, which are not covered by the Article 61(3) notification procedure.
C.I.1 / C.I.4	Could Article 5(3) of Regulation (EC) No 726/2004 be added? Otherwise, it may be classified as a C.I.4 which is typified as a Type II. If Article 5(3) of Regulation (EC) No 726/2004 cannot be added, then could it be feasible to add another Explanatory Note to C.I.4 to exclude the Type IB variation that could be agreed for amending the product information after an Article 5(3) of Regulation (EC) No 726/2004?	
C.I.3 a)	Classification is inappropriate as no assessment should take place. If the applicant deviates from the agreed wording the requirements of this classification would not be met and the applicant is required to submit a type IB by default.	Classification as type IA
C.I.3 b)	It would be worth adding a note clarifying that in case the post-authorisation change requested by the EMA/NCA following an assessment of an Urgent Safety assessment, class labelling, RMP, PAM, etc. has its own variation type, that variation type will apply and not C.I.3.	
C.I.8	Terminology used is confusing. We would suggest the following: Introduction of a Pharmacovigilance System Master File (PSMF) or changes to the existing pharmacovigilance system as described in the PSMF	
C.I.8 a)	We would suggest the following: Introduction of a Pharmacovigilance System Master File (PSMF)	
C.I.8 a)		Please add an additional case: aa) Introduction of a summary of the

		pharmacovigilance system IA Condition: 1. (As given) 2. (As given) 3. (As given) 4. PSMF and QPPV are updated in EVMPD in time
C.I.9	This should be updated to reflect that the DDPS is being phased out and will be replaced by the PSMF at the latest by 2/21 July 2015.	
C.I.10	It is not clear why this is type II given that the change should come as an outcome of an evaluation by regulators	Downgrade to type IB

16 July 2012