Brussels, 13 July 2012

EGGVP's comments to public consultation paper review of the VARIATION GUIDELINES REGULATION (EC) NO. 1234/2008

Category	Subcategory, Documentation, requirement	EGGVP Comm Nº	Comment
General Comments			
-	-	**1**	In general terms, this proposal represents a drastic step back to the principles of simplification, clarification and reduction of unnecessary requirements which are currently the basis of the ongoing process of review of the veterinary medicines' legislation. The current draft seems to propose the contrary, as many new variations are created, while many of the existing simple variations (Type IA/Type IAin) become now Type II variations. This new proposal: • Increases the number of variations. The number of variations that a MAH will have to apply is increased (for example, under the current proposal, adding a production site for a finished product can imply up to 5 variations); the alternative for the MAH would be to choose for a variation that implies a higher cost. • Considerably increases the administrative burden and the pressure on companies (specially on SMEs) • Increase the fees in a way that results unaffordable for companies (at least from the veterinary sector) The current draft is very detrimental for the veterinary medicines' sector, in particular for SMEs. In order to comply with all new requirements, companies will need more resources (staff and economic investment), as they will have to deal with more and more paperwork which at the same time is not contributing to the safety/quality/efficacy of the product (which shall be the real objective of Competent Authorities and of course of industry as well). The proposal is therefore considered to be contrary to the spirit of the fore coming regulation, which is simplification and reduction of the administrative burden. Administrative burden on the veterinary industry side has been estimated at EUR 538 million per year (this is equivalent to 13 per cent of the annual turnover of the animal health sector in Europe), and the second reason for this burden is due to variations. It is inadmissible that under these circumstances, a proposal which is over-complicating the administrative procedures and increasing both the burden and fees (we believe not only at industry but also for Competent Authorities' level) is on the table.

		2	The proposal introduces new terminology; it is therefore necessary that definition to this new terminology is provided. For example: - "*previously approved risk assessment*" (mentioned in variations B.I.a.4, B.I.b.1, B.I.c.2, B.II.b.5, B.II.c.1, B.II.d.1 and B.II.e.2) - "a*n acknowledged enhanced development approach*" (mentioned in variations B.I.A.2., B.I.a.4, B.II.b.3 and B.II.b.5) -"*an already approved monitoring scheme*" (mentioned in variations B.I.A.2., B.I.a.4, B.II.b.3 and B.II.b.5) - "*as part of a previous assessment, where the enhanced development approach in the development and optimisation of the manufacturing process concerned is formally acknowledged*"(mentioned in variations B.I.A.2 and B.II.b.3). - *"already assessed and approved within another procedure*" (mentioned in variations B.II.d.1, B.II.e.2and B.II.f.1) - "*Significant update*" (mentioned in variation B.I.A.1) There is no clarity provided on how these pre-assessments will work on a practical level. Does this mean that MAHs have to liaise with the Authority to get pre-approval for the change before filing the actual variation?
Comments to specific sections of the Guideline			
A.1	-	**3**	At present, MAH shall request a variation for each product and pay IA fee/product as well. It would be recommended just 1 variation (rather than grouping) + 1 fee, being handled and processed at national level.
A.3	-	**4**	This proposal is too demanding, as the same excipient could be used for several medicinal products. As a result, the MAH will have to carry on with higher fees and increased administrative burden.
A.4	-	**5**	This proposal cannot be accepted as suppliers from third countries (*i.e.* China) very frequently change their names. The new requirements will result in higher costs (fees and administrative burden) while not bringing any added value to the safety, quality and efficacy of the medicinal product. EGGVP cannot see the benefits of this proposal.
	-	**6**	Please clarify what is considered as "novel excipient"
A.5	-	**7**	Please clarify if it is referring to importers in third countries.
	Subcategory b)	**8**	Please clarify if it is also referring to supplier of label, leaflet, package etc. It would be a problem if this was the case, because at present, this information is not requested but in case a variation is created it will result in an additional data. This would be a major problem and could not be accepted.
A.7	Subcategory a)	**9**	This proposal is too specific and demanding, an explanation for justification is desirable. EGGVP hardly sees its benefits and it can be interpreted that the new requirements result into higher costs (fees and administrative burden) only, while not bringing any added value to the safety, quality and efficacy of the product.
	Condition 3	**10**	A new condition has been included for active substance manufacturing sites, where at least one batch control/testing site remains within the EU/EEA or where a GMP mutual recognition agreement (MRA) exists. This additional condition is a concern, as currently there would be instances where batch control/testing sites for certain active substances are not within the EU or part of MRA. What will happen for future variations, will we be forced to comply with this condition?

B.I.a.1	-	**11**	It is not clear how to do the addition of a new manufacturer of an active substance with DMF if previously you had a Certificate of Suitability? Because B.I.a) is meant when there is no Certificate of Suitability and a DMF is added, but if there is a Certificate of Suitability and you add a DMF would it then be a IB by default?
	Subcategory g)	**12**	Introducing a new manufacturer of the active substance that is not supported by its own ASMF should be classified as Type IB.
B.I.a.2	Subcategory f)	**13**	How does the new category (f) differ from category (a) for minor changes in the manufacturing process where these changes to non-critical process parameters are currently captured? Could an example be provided of a change under this new category that would be different from a change filed via category (a)? In addition, as we do not have visibility of all changes made in the restricted/closed part of the DMF and we may not be notified of same. What happens in this instance? What happens when CEP holders make non-critical process parameter changes, will there be a minor update to the CEP?
	Conditions 8 & 9, Documentation 5	**14**	There is a need to clarify what these additional conditions / requirements are meant for. The new conditions and documentation required cannot be accepted unless the new terminology is defined (please refer to EGGVP comment nr. 2). The same comment applies to: - Variation B.I.a.4: Subcategory g), Conditions nr. 7, 8 and 9, Documentation requirement nr. 5 and 7 - Variation B.I.b.1: Documentation requirement nr. 6 - Variation B.I.c.2: Documentation requirement nr. 5 - Variation B.II.b.3: Subcategory g), Conditions nr. 8 and 9, Documentation requirement nr. 5 - Variation B.II.b.5: Subcategory g), Conditions nr. 8 and 9, Documentation requirement nr. 6 - Variation B.II.c.1: Documentation requirement nr. 7 - Variation B.II.d.1: Condition nr. 1, Documentation requirement nr. 6 - Variation B.II.e.2: Condition nr. 1, Documentation requirement nr. 5 - Variation B.II.f.1: Condition nr. 1 - Variation B.I.a.1: Subcategory g)
B.I.a.4	Subcategory g)	**15**	This is not a critical issue; the creation of this new category is therefore not considered necessary. EGGVP cannot see the benefits of this proposal; an explanation for justification is desirable.
B.I.b.1	Subcategory i)	**16**	EGGVP would propose to create this new category as a IAIN variation instead of a type IB, since it is moving to a better status from a quality point of view.
	-	**17**	We suggest the addition of a new category: j) Administrative update of the specification, where the content itself is not affected (i.e. addition of the programme of testing, if it was already approved as part of any other part of the dossier like Justification of Specification, correction of typing mistakes,…). Such change should be classified as Type IA.
B.I.d.1	Subcategory c)	**18**	A new category (c) is included to change an approved stability protocol (type IA). We would like clarification on what this means and what it relates to with an example of same.
B.I.f.3.	-	**19**	This is not a critical issue. EGGVP cannot see the benefits of this proposal; an explanation for justification is desirable.
B.I.f.4.	-	**20**	This is not a critical issue. EGGVP cannot see the benefits of this proposal; an explanation for justification is desirable.
	-	**21**	Please clarify: if the foreseen change is within the approved management protocol and no supportive data are needed, does it have to be reported at all?

B.II.a.3	Subcategory a.3)	**22**	This variation has changed from Type IA to Type II and EGGVP would like to know the reasons and justification for this change (the benefits of such a proposal remain unclear). Is it up to the applicant to decide if the flavour/colour is important? How can the colour impact the uptake by the target animal species?
	Condition 11	**23**	Please clarify: why is this change relevant to veterinary pharmaceuticals only? Surely a change or introduction of a flavour will have a greater impact on uptake of human medicines.
B.II.b.1.	Subcategory c)	**24**	The replacement or addition of manufacturing site for pharmaceutical forms manufactured by complex manufacturing process should be type IB, instead of restricting to Type II. We suggest amending the section under required documentation (page 36, no.2) to state that for pharmaceutical forms manufactured by complex manufacturing process the results of process validation are required.
	Subcategory f), Condition 3	**25**	Subcategory f) reads: Site where any manufacturing operation takes place, except batch release, batch control, and secondary packing, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products. Condition 3 reads: Product concerned is not a sterile product. The variation B.II.B.1 is absolutely necessary when a second manufacturer must be established, because there might be e.g. a fire in original production plant. The condition 3 must therefore be deleted.
B.II.b.2.	-	**26**	Please clarify what is meant by "importer".
	Subcategory c) 2.	**27**	It is noted that category (c.2) (formerly b.2) has been changed from a type IAIN variation to a type II variation. This change results in a significant increase in fees. What is the purpose of changing to a type II variation? There is no concern regarding a safety risk which may be a reason for this type of change. By upgrading to a type II, there is an additional increase in workload as will now have to provide an expert report. Therefore EGGVP would like to know the justification for going from a Type IAIN to a Type II?
	Subcategory c) 2.	**28**	EGGVP cannot agree with the re-classification of this change. The replacement or addition of a manufacturer responsible for importation and /or batch release including batch control testing should not be Type II change. The method transfer should be required, as it is according to the current guidelines; the type of change IAIN should also remain for this change.
B.II.b.3	Documentation 5	**29**	It is not clear what type of documentary evidence could be provided for this variation.
	-	**30**	We would like to highlight that there is no category for minor changes to sterile products or parenteral products. Currently, they default to a type IB perhaps we could use this opportunity to include them as an additional category.
B.II.b.4	Subcategory c)	**31**	Please clarify: is this only applicable to biological/immunological products?
	Condition 7	**32**	This is of concern, as currently clinical trials use lab scale pilot batches of typically 1-10 liters to perform bioequivalence studies. If this condition is introduced, it would mean that bioequivalence studies would have to be performed on batches that are 10% of the commercial batch size, which would have significant and non-acceptable cost implications. Furthermore, the purpose of the additional text is not clear; what is the difference between human and veterinary medicines in this regard?
B.II.b.5	Subcategory g)	**33**	This is not a critical issue. EGGVP cannot see the benefits of this proposal; an explanation for justification is desirable.

B.II.c.1	Subcategory g)	**34**	New subcategory (g) has been included where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country (Type IB). For Veterinary Medicinal Products there are instances where for both APIs and excipients, they are not monograph substances and for certain 'old' products the raw material specifications would require updating when changing suppliers. Currently this is a type IA but with the introduction of this new category, this type of variation may be restricted to a type II. EGGVP believes a Type IAin should be applied.
B.II.c.5	-	**35**	There are several variations covering "excipients", EGGVP does not see the need and benefit to create a new one. Please provide a defintion of "novel excipient"
B.II.d.1	-	**36**	We propose the inclusion of another category (j) for a change in description of the finished product to more accurately describe the appearance of the product. Currently, this change is captured under article 5. We propose the introduction of this type of change as a type IA.
	Subcategory h), Condition 8	**37**	EGGVP considers condition number 8 is not a "condition" (it is for information only). Also it is not clear why this variation is required as the current guideline states 'There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product.'
B.II.d.2	Subcategory f)	**38**	This variation seems unnecessary and will add non-value added work in terms of safety/quality/efficacy of the product to both industry and the authorities
B.II.f.1	Documentation 4	**39**	If a justification of the change is required, the variation should not be considered Type IA. Stability protocols should be considered GMP issue rather than regulatory.
B.II.h.4	-	**40**	Please clarify: if the foreseen change is within the approved management protocol and no supportive data are needed, does it have to be reported at all?
B.III.1	-	**41**	Where a new version of the CEP is issued by EDQM due to changes requested by the manufacturer or because the previous CEP has already expired, the changes updating of CEP should not be needed since CEP has already been authorized by EDQM and updates are made by producer who has received the CEP.
	-	**42**	This guideline does not define 'sterile medicinal product'. Therefore we need clarification on whether this condition would apply to sterile, intra-mammary products?
	-	**43**	The following text is to be deleted: "For and intermediate used" and "for an excipient" For a reagent: CEP is only required for Active Ingredients at present. Therefore all the others should be canceled.
	Subcategory b)	**44**	The following text is to be deleted: "for a starting material"
	Subcategory a) 6.	**45**	Please define "last steps of the synthesis"?
	Documentation 6	**46**	Please define "suitable evidence"?
	Documentation 6	**47**	This information, if relevant, should be provided as part of the CEP assessment by the EDQM and not as part of the variation application.

B.III.2	Documentation 3	**48**	The documentation for all 4 changes described in these paragraphs require the document nr 3 – batch analysis data on API and in addition also, where appropriate, the dissolution data on the finished product (or disintegration for herbal product). Such change – changing the reference of the API from internal standards to EP or any other standards- could not have the influence on the dissolution profile. The API itself remains unchanged, only the reference (standard) is changed, therefore the influence on the finished product is in this case not anticipated.
	Documentation 3	**49**	If the relevant conditions for the variation are met, it should not be necessary to provide batch data.
	Documentation 5	**50**	A copy of the Ph. Eur. Monograph should not be provided. This will become obsolete once the next version of the pharmacopoeia is published. Monographs are not included in the dossier and so should not be required for a variation.
	Footnote	**51**	It should be highlighted that it is very important that all CAs understand and agree with this point.
C.I.8	-	**52**	Introduction of a summary of the pharmacovigilance system should not be made by a variation and should not be charged on a product basis. MAH has responsibility to prepare PSMF and should be available upon request of competent authorities. Data about the PSMF location and QPPV contact details are being reported in the EudraVigilance database due to Article 57. There is no need for variations to all MAs, which will only result in very high increase in efforts and costs, with no impact on patient's safety. The QPPV system should be linked to the company, thus, only one variation each time applies (not one variation for each product in each country).
C.I.9	-	**53**	It has to be assured that not all changes of the DDPS does affect MAs. Only major changes related to QPPV name and contact details and other important information (as minimum as possible) are reported as Type IA or IA IN, all other changes should not have influence on MAs. It should be somehow taken for granted that for all MAs of one MAH, the last version of DDPS is valid.
C.I.10	-	**54**	Procedure type II: Communication to the Pharmacovigilance Unit. Precise changes in either quality, safety of efficacy parts of the file would be Type II
C.I.11	-	**55**	EGGVP believes a variation is unnecessary (communication to Pharmacovigilance Unit should be enough)
C.II.6	-	**56**	It is noted that this category of variation has been amended from a type IB to a type IA, this is a welcomed change.
C.II.7	-	**57**	In the veterinary sector, variations applicable are II and IB; we could perhaps propose a IA? Again, the QPPV system should be linked to the company, thus, only one variation each time would apply (not one variation for each product in each country).
	-	**58**	Please clarify: why is this considered to be a Type IB variation for veterinary products when the corresponding change for a human DDPS is considered to be a Type IA
Additional Comments			
-	-	**59**	We would like to have a variation included, when a new part II has been fixed. A new part II might be necessary, when e.g. new impurities are included in the monograph of European pharmacopoeia or when a substance included in a formulation is not available any more, etc. A new part II documentation could be handled in the past during renewal of a product. If a company fix a new part II today, there have to be multiple variations to be initiated – an intense work and considerable increase in costs. May we suggest a variation, procedure type II for a complete new part II of a product?
-	-	**60**	We noticed different acceptance of possible grouping especially in case of C.I.3.a and C.I.2 a variations.
		61	If there are concerns in relation to certain existing type IA variations instead of over-complicating the issue by including additional conditions and documentation requirements, the variations could instead be re-categorised as a Type IB variations.