Comments of the association of the Austrian pharmaceutical industry (PHARMIG) regarding the public consultation paper on the REVIEW OF THE VARIATIONS GUIDELINES (Brussels, Sanco.ddgl.d.5(2012)817838)

PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank for the opportunity to comment on the consultation paper on the REVIEW OF THE VARIATIONS GUIDELINES. Please find our comments following.

General comments

The variation Regulation (EC) No 1234/2008 indicates in the preamble (2)

> The procedures laid down in Regulations (EC) No 1084/2003 and (EC) No 1085/2003 should therefore be adjusted, without departing from the general principles on which those procedures are based. For reasons of proportionality, homeopathic and traditional herbal medicinal products which have not been granted a marketing authorisation but are subject to a simplified registration procedure should remain excluded from the scope of the Regulation.

The classification guideline takes this statement of the regulation into account and does not list any changes, conditions or document requirements for homeopathic or traditional herbal medicinal products.

However, it is industry's experience that most NCA follow the same rules for changes to registrations. Therefore, proportionality is not given.

We suggest to provide clarification or including a separate procedure type for each classified change for registered products that takes the preamble of the regulation into account.

Fees are calculated by submitted change and there is no reduction of fees when grouping or worksharing is used. However, grouping reduces the administrative work at the agencies' side. Therefore it is not understandable why this reduced workload is not considered in the fees system.

Detailed comments

Var. No.	Change	Proposal	Rationale / Comments
B.II.d.1. h) and i) and B.II.d.2. c) and d)	Change in the specification parameters and/or limits of the finished product; Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product >> type IA_{IN} Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass. or Ph. Eur. 2.9.6 (Uniformity of content) >> type IB Change in test procedure for the finished	To change classification to type IA	Any update in accordance to the Ph. Eur. shall be classified as type IA. The manufacturer is obliged by the premises of the Ph. Eur. to adapt its methods and specifications within 6 months after revision of the pharmacopoeia. Therefore, NCAs should be aware of the change.

	product; Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol >> type II Other changes to a test procedure (including replacement or addition) >> type IB		
B.II.d.1.i	Change in the specification parameters and/or limits of the finished product; Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass. or Ph. Eur. 2.9.6	"Documentation to be supplied" items 3, 4, 5 are not relevant	By introducing general method 2.9.40 no new analytical method is applied which needs to be validated, other specification parameter are not affected and the dissolution does not change.

	(Uniformity of content)		
B.II.d.2.e	Change in test procedure for the finished product; Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	To add "if relevant" for the conditions 2, 3 and 5	The conditions 2, 3 and 5 proposed do not fit to all possible changes, e.g. the updating of the microbial test procedures to be in line with the current Pharmacopoeia (culture media as well as incubation temperatures and times) or the introduction of Ph. Eur. 2.9.40 Uniformity of dosage units. "if relevant" could be added in these cases
B.II.i.1.b.1	Update to the “Adventitious Agents Safety Evaluation” information (section 3.2.A.2); Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier; with modification of risk assessment >> type II	To delete this category	We do not agree to this new category. In fact, the assessment of revised Viral Validation Studies, which may modify the risk assessment, is already part of the assessment of the underlying change in the manufacturing process. Thus this is to be considered as redundant categorisation/assessment.
B.III.1	Submission of a new or updated Ph. Eur.	To change classification to type IA	The proposed differences in the

	Certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient		classifications are not justified. An EDQM CEP has been approved by a body of the EU.
C.I.3.a	Implementation of change(s) requested by the EMA/National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report(*), Risk Management Plan, Post-Authorisation Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC;	To change classification to type IA_{IN}	The change refers to the "Implementation of agreed wording… " which means that NCA has already assessed the change and wording, therefore type IAin would avoid redundant work on the agencies' side. (Please compare to C.I.1.a)

	Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH >> type IB		
C.I.8 a and C.II.7.a	Introduction or changes to a summary of pharmacovigilance system for medicinal products for human use; Introduction of a summary of the pharmacovigilance system >> type IA_{IN} **In conjunction with** Introduction of a new Pharmacovigilance system; Which has not been assessed by the relevant national competent	To provide clarification	Category C.I.8 a) seems to be in contradiction with C.II.7.a). In fact, it is unclear which category a MAH should submit in case he had not submitted previously any DDPS for a specific medicinal product in the respective country/procedure.

	authority/EMA for another product of the same MAH >> type II		