EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13/07/2012

Submission of comments on REGULATION (EC) No 1234/2008 ARTICLE 4:REVIEW OF THE VARIATIONS GUIDELINES

Comments from:

Name of organisation or individual
BPI – Bundesverband der Pharmazeutischen Industrie e. V. – German Pharmaceutical Industry Association

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	In homeopathy and anthroposophic medicine, the range of essential remedies is considerably larger compared to other fields of the pharmaceutical industry. Due to the strongly individualised character of the therapeutic approaches homeopathy and anthroposophic medicine need a large range of starting materials (in the range of thousands) and of specific medicinal products. The order of magnitude of dossiers to be maintained per authorisation holder easily can meet the figure of 500 or 1.000 or more, while the turnover gained per product is low to very low (for example less than 50 packages per year). Besides having many different starting materials the large number of products naturally brings a large number of variations with it at all stages of production. In addition, there are numerous characteristics of identical specifications for wide ranges of products: Homeopathic medicinal products of identical dosage form, especially if beyond a certain degree of dilution, share a number of characteristics like composition of excipients, final product specification, primary packaging etc. Hence, a single modification of one of those common characteristics may soon refer to more than 1.000 files	

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	per applicant in one MS. Other frequently identical characteristics of the dossier might be specific for a certain type of starting material, as e. g. the methods for testing impurities in plant materials (one method for testing pesticides could be cited in up to 500 dossiers of one applicant in one MS). **It is extremely important for industry and especially for homeopathic and anthroposohic MAs, that the regulatory and administrative burden linked to variations is restricted to a minimum while guaranteeing the quality and the safety of the products.** These specific characteristiscs were already acknowledged in the considerations of Commission Regulation (EC) No 1234/2008 (consideration 2): …."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 procedures should remain excluded from the scope of the Regulation." In view of the considerations given above, it is just consequent that registrations are excluded from the scope of the Variation Regulation (EC) No. 1234/2008. **However, marketing authorisations of homeopathic**	

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	medicinal products are purely national authorisations for legal reasons; they now will be introduced under the scope of the European variation system. As a matter of principle, the dossier characteristics mentioned above, especially with respect to the content of the quality dossier as well as with respect to safety issues, apply to dossiers of homeopathic marketing authorisations as well as to those of registrations. **In addition, in most Member States of the EU no separate rules exist for registrations and this leads to the fact, that, in practice, the rules of the Variation Regulation and subsequent rules like the classification guideline also are applied to registrations.** Therefore, appropriate rules for handling the variations of these purely national marketing authorisations as well as registrations in countries where the Variation Rules of the EU are applied to registrations are necessary for reasons of proportionality. **A pragmatic system of variations is needed for homeopathic and anthroposophic industry as well as for all other industry in Europe in order to maintain the amount of products required for the**	

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	therapeutic approaches over the life cycle.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Page 7 A.3		Comment: For homeopathic medicinal products changes of name of active substances, already in accordance with pharmacopoeia, in general happen as adaptation to change of name of monograph of the Ph.Eur. or the relevant national (homeopathic) pharmacopoeia. Rationale: The scientific names of the many starting materials used for homeopathic medicinal products are mainly of herbal origin, scientific names use to change rather frequently. With respect to the information of consumers this is of less important relevance. In order to keep the proportionality principle, it should be possible to consider the adaptation of the names in the frame of the periodic reporting. Comment/rationale: The excipients used in production of homeopathic medicinal products generally are well introduced conventional classical pharmaceutical substances like lactose, ethanol, purified water etc where the names are since very longtime in accordance with a pharmacopoeia. In addition, IAIN classification would undermine the transition period acknowledged for implementation of pharmacopoeial changes. Proposed change (if any): A.3 Change in name of the active substance or excipient a) All substances except b)	

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		Conditions to be fulfilled: 1,2 Documentation to be supplied: 1, 2 Procedure type: IA_{IN} b) Homeopathic medicinal products with the active substance/excipient in line with official pharmacopoeia monograph Conditions to be fulfilled: 1,2, 3 Documentation to be supplied: 1, 2 Procedure type: IA New condition: 3. Name and change in line with official monograph (Ph. Eur. or recognised national pharmacopoeia).	
Page 8 A.5 a)		Comment: Proposed change (if any): a) Manufacturer responsible for one or several activities including batch release (**where specified in the dossier**)	
Page 21 B.I.c.1, cond. 2		Comment: Wording should be amended acc. to B.II.a.3, cond. 4, to distinguish between implementation of type IA and type IB changes Proposed change (if any):	

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		"Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant ~~at time of implementation~~ (at time of implementation for Type IAs and at time of notification for Type IBs). [...]"	
Page 35 B.II.b.1 c)		Comment: A definition for complex manufacturing processes is missing. However, if extensive knowledge about the formulation could be demonstrated, an exemption could be granted and this variation could be classified as a Type IB under this condition Rationale: Otherwise "complex" would need to be specified further. Proposed change (if any): Proposal: c) (…) pharmaceutical forms not manufactured using standard manufacturing processes.	
Page 38 B.II.b.2.c.2		Comment: A change from variation type IA_{IN} to II seems quite drastic. Replacement/Addition of manufacturer for batch release and control/testing is unnecessary upgraded from Type IA_{IN} (old: B.II.b.2.b.2) to Type II.	

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		Moreover splitting this change in 2 variation as follows: B.II.b.2.a Type IA and B.II.b.2.c.1 Type IA_{IN} allows to avoid this Type II Var. Proposed change (if any): Rephrase to Type IA_{IN}.	
Page 39 B.II.b.3		Comment: In category B.II.b.3 (Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product) changes to biological/immunological medicinal products can only be categorized as follows: c) The product is a biological/immunological medicinal product and **the change requires an assessment of comparability** Any minor changes in the manufacturing process of biological/immunological medicinal products which do not require an assessment of comparability are not reflected in the guideline. Proposed change (if any): Addition of an additional sub-category: h) Minor change in the manufacturing process of a biological/immunological medicinal product (proposed procedure type: IA or IB)	
Page 43		Proposed change:	

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B.II.b.5		Under B.II.b.5 (Change to in-process tests or limits applied during the manufacture of the finished product) we propose to add a type IA: Minor changes to an approved test procedure with the same conditions and documentation requirements as the corresponding variation defined for control of finished product (see B.II.d.2a).	
Page 43 B.II.b.5.b		Addition of a new tests and limits Comment: Editorial mix up of plural and singular Proposed change (if any): Update to: Addition of a new test and limits	
Page 48 B.II.c.5 a)		Comment: a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer If the conditions 1,2,3 are fulfilled, it seems illogical that there is a restriction to a manufacturer who is part of the same pharmaceutical group as the currently approved.	
Page 48 B.II.c.5.b)		Introduction of a new manufacturer of the novel excipient that requires significant update to the relevant novel excipient section(s) of the dossier.	

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		What is the difference to change type B.II.c.4 "change in synthesis"? Comment: What is significant update for dossier sections? Shouldn´t a type II be dependent, whether the change causes significant change to the quality of the novel excipient influencing safety, efficacy and quality of the finished product? Proposed change (if any): Introduction of a new manufacturer of the novel excipient that requires changes with significant impact to the quality of the relevant novel excipient.	
Page 50 B.II.d.1. i)		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) Comment: According to the Q&A on Quality of the CHMP Quality Working Party 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 QWP Internet Link: Link-Q&A QWP Proposed change (if any):	

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		Type IA should be sufficient. 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.	
Page 50 B.II.d.1. h)		Comment/Rationale: Update of a specification parameter for the finished product solely in order to comply with the <u>updated</u> Ph.Eur. monograph should be classified as a Type IA, as it is classified so far within the proposed classification for changes in the "CMDh Recommendation for classification of unforeseen variations acc. to Art. 5 of ... (EC) No 1234/2008". Furthermore following the classification of **B.III.2.b "**Change of a monograph – Change to comply with an update of the relevant monograph of the Ph.Eur. or national pharmacopeia of a Member State", which is also classified as a IA. Moreover: - Condition 7 ("the change does not concern any impurities") should be deleted. As it is the decision of the European Pharmacopoeia to change the specification also in regards of impurities for a certain Ph.Eur. monograph, it should NOT lead to a Type IB by default for updating the relevant monograph in the dossier. - Documentation to be supplied point 2 "Comparative table of current and proposed specifications": this requirement should	

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		be eliminated, at least if the variation submitted includes the sole update of a general monograph and no other change to the specification is introduced by the manufacturer. The workload for compiling and providing a comparative table for a sole update of pharmacopoeial specifications(s) seems unproportional as it is of no additional use for the assessor of the variation, as there is no scope of action both for manufacturers as well as assessors. Proposed change (if any): B.II.d.1 h) Update of the dossier to comply with the provisions of an updated genereal monograph of the Ph.Eur. for the finished product Conditions to be fulfilled: 1,2,3,4, ,8 Documentation to be supplied: 1, Procedure type: IA~~IN~~	
Page 53 B.II.e.1. b)3.		Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form Comment: 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?	

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		Proposed change (if any): Remove "new"; replace "pack size" with "container" : 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	
Page 66 B.III.1 a)		Comment: The addition of the alternative (point 6) concerning non-sterile APIs to be used in sterile product, where water is used in the final step and the material is not claimed to be endotoxin free, may have an significant impact on the PN products both concerning the cost effectiveness as well as potential supply risks. It is important to be able to find new suppliers and this proposal would have an impact on cost and time. First what is the relevance if water is used in the last step or not if the API is non-sterile: for products with a CEP the file is reviewed by EDQM and there should be quality specifications for water included in file which should comply with the defined requirements in addition to the specification for the API. In addition endotoxins as well as bioburden is a parameter checked on each API batch both by supplier and internally prior it is approved for use. If water is used in the final step it will in the future be included in CEP. Proposed change (if any): We are of the opinion this change could be defined as a Type IA provided the above mentioned conditions are fulfilled: 1) the CEP includes a specification for water, 2) endotoxins as	

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		well as well as the bioburden are specified	
Page 68 B.III.2		Comment: Title should clearly indicate, that this applies only to active substance / excipient and not finished product. Proposed change (if any): Clarify title to: Change 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"	
Page 69 B.III.2, Documentation #5		Comment: We think that submitting a copy of the Ph. Eur. Monograph is redundant. Proposed change (if any): "A copy of the ~~Ph.Eur. monograph /~~Member State national pharmacopoeia monograph for the concerned material as appropriate."	
Page 73 B.V.a. 1d)		The PMF is updated at least annually by a separate variation procedure at the EMA. Comment: According to category B.V.a.1 (Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation	

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		dossier of a medicinal product. (PMF 2nd step procedure))Sub-category d), all updates of the Plasma Master File must be additionally included in the dossiers of all affected products (by variation procedures) even if the changes do not affect the properties of the finished product (condition of this sub-category). Proposed change (if any): As this variations is of purely administrative nature for MAHs and authorities, this sub-category should be deleted. We consider a notification of the NCAs outside a variation procedure as sufficient.	
Page 75 B.V.b.1		Comment: Update of the quality dossier of a homeopathic medicinal product Rationale: Because of the national competence, renewal and dossier update procedures frequently still are to be done. Often, these procedures include a complete revision of the quality dossier including transfer to the CTD formate for the following reasons (1) The CTD formate for homeopathic medicinal product was introduced later than for conventional medicinal products, and this revision still remains to be done. (2) Since some years, since the harmonisation efforts of HMPWG become visible in the EU, the dossier requirements are increasing. This frequently may imply a need to completely revise the quality	

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		dossier. On the other hand, the quality dossiers are less dense, comparatively simple, using generic well-known active substances and excipients as well as classical dosage forms, all of them described in official pharmacopoeias. The big amount of medicinal products with low to very low turnover is particular for this niche of the pharmaceutical business while the quality variations use to be simple. Therefore a revision of the quality dossier would be far from complex and comparable to the extent of a revision of the quality dossier in the frame of a referral procedure (case B.V.b.1.b). Proposed change (if any): New: B.V.d) Homeopathic medicinal products B.V.d.1 Update of the quality dossier of a purely national homeopathic medicinal product: The update of the quality dossier Conditions to be fulfilled: Documentation to be supplied: Procedure Type: II	
Page 82 C.I.12		Comment: Initial inclusion should not be implemented by means of a variation procedure. The increase in workload for industry and authority is too high.	

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		In this respect a general Type IA variation would be welcome for formal adaptations to the latest QRD templates.	
Page 84 C.II.7		The Pharmacovigilance system should be introduced on a company basis not on a product level	

Please add more rows if needed.