Revision of the Variations Regulations
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GENERAL COMMENTS
The move towards simplified processes, grouping, worksharing, submission of changes with no impact on efficacy, safety or quality by an annual report mechanism, etc is greatly appreciated and the majority of the changes are well thought-out and transparently presented. Notwithstanding these congratulations, there are a few points which we feel require further attention and/or a rethink on detail. In particular, we are concerned that the principles and processes of worksharing are inadequately described. Also, some of the proposed timelines are unnecessarily lengthy and will lead to delays representing an *increase* over the situation today. These points are addressed more fully in the pagewise comments below..
With regard to the scope of the legislation apart from products registered via centralised, mutual recognition or purely national procedures, also those products of one MAH need to be included which have been registered via both a mix of national and mutual recognition procedures in the transition period of implementation of the MRP and CP in the years 1995-1998.
It is acknowledged that the worksharing will require EMEA and CA's to redeploy resources, but assumed that the overall savings offered by the new strategies will more than compensate.
It is also acknowledged that the coming election of the European Parliament (EP) in 2009 may impact on the timelines of the legislative procedure. It would be appreciated if an indication would be given of what should be ready before EP election in 2009 and what is independent of this date.
It is appreciated that the Commission has stated the intention for generation of detailed guidance on procedures, such as grouping, worksharing as well as for different situations which lead to up- and downgrading. This is felt especially necessary for providing information on detailed procedures incl. timelines, need of additional documentation and fees. It should be ensured that overall timelines are not extended compared to the current procedures and that fees are not substantially increased.

Page, Section title, article	Relative Importance	COMMENT AND RATIONALE	PROPOSED CHANGE
page 4, Article 3, points 3 and 6	high	Major variation of Type II means …, which has a substantial potential to have a negative impact on…. Not only those changes, which have a negative	Change sentence to: 3. 'Minor variation of Type IA' means a variation which is not expected to have any ~~negative~~ ***substantial potential*** impact on the quality, safety or efficacy of the medicinal

		impact but also positive impact (e.g. new indication) will be classified as Type II variations.	product concerned. 6. Major variation of Type II means …, which has a substantial potential to have a ~~negative~~ impact on….
page 5, Article 4, point 2	medium	It is **highly** appreciated that changes unforeseen by the guideline may be submitted as Type IB by default, and it would be expected that the majority of unforeseen changes would fall into this category. And we welcome the increased flexibility achieved by the replacement of the Annex by guidelines. A switch to Type II, if deemed necessary, would invoke an added dimension of complexity involving further activity (submission of extra fees, update of Expert Report/Summaries etc), and it is unclear at this stage how this would be handled. Particularly, would the clock be restarted, and perhaps only after all these items were received? In order to avoid this added complexity and potential delay arising unnecessarily owing to submission as IB of changes which are expected to be judged to have a substantial potential for impact (perhaps because of the nature of the product, or previous history), we suggest that the applicant may himself decide to classify a change as Type II and submit it as such.	Add the following text: ….shall be considered a minor variation of Type IB, **unless the Applicant judges the change to meet the criteria of Type II and chooses to submit it as such**.
page 5, Article 5.1, 1st paragraph	high	The facility to obtain an agency opinion on the classification of a change unforeseen by the guideline is a welcome option and is an excellent route for bringing a change initially unforeseen, but likely to recur in the future, into the public domain in a consistent fashion. We propose that a holder wishing to approach the Agency with an unforeseen change would *propose* a classification for confirmation, rather than make a neutral request for a judgement.	Add the following text: … potential impact on the quality, safety or efficacy of the referred variation on the medicinal products concerned. **The marketing authorisation holder may also request the Agency to confirm a classification of a variation proposed by the holder.** The Agency shall deliver this recommendation **or confirmation** within ….

page 5, Article 5.1, 2nd paragraph	high	Having in mind that the assessment of minor variations and many type II variations need 60 days or less, 60 days for delivering a recommendation on the type of the variation appears to be excessively long.	The agency shall deliver this recommendation within **3**0 days following receipt of the request,…
page 5, Article 5.1, new additional 2nd paragraph	medium	The recommendation delivered in accordance with the first subparagraph shall be sent to the MA holder and to the competent authorities of all Member States. In case the applicant does not agree with the recommendation, there should be a formal process to object in order to achieve a revision.	Add the following text: Prior to submission of a variation … on the medicinal products concerned. **The Agency shall provide the applicant with the draft recommendation on the request of the applicant referred to in paragraph 1. If the applicant does not object within 15 days after receiving the draft recommendation, the recommendation shall be considered final.** The Agency shall deliver this recommendation ….
page 5, Article 5.1, 3rd paragraph	high	To strengthen the opinion made by the agency on the classification of the variation as well as to prevent a prolongation of the overall timelines (comprised by scientific recommendation plus assessment of the variation), the Member States should be encouraged to follow this recommendation unless new knowledge about the medicinal product lead to a modified benefit-risk assessment.	Add the following text: The recommendation delivered in accordance with the first subparagraph shall be sent to the holder and to the competent authorities of all Member States. **The Member States should follow this recommendation unless new knowledge about the medicinal product require a re-assessment of the classification.**
p 7, Art 9.2, 2nd paragraph p 8, Art 10.2, 2nd paragraph p 9, Art 11.2, 2nd paragraph p 10, Art 13.2, 2nd paragraph p 11, Art 14.2, 2nd paragraph p 12, Art 15.2, 2nd paragraph p 14, Art 18.2, 2nd paragraph p 15, Art 19.2, 2nd paragraph p 16, Art 20.2, 2nd paragraph	high	There should be a timeline for the validation of a variation (“acknowledge receipt of a valid notification”) of 14 days.	For Art. 9 and 10: If the notification fulfils the requirement laid down in the first subparagraph the relevant authority shall acknowledge receipt of a valid notification **within 14 days**. For Art. 11: If the notification fulfils the requirement laid down in the first subparagraph the relevant authority shall acknowledge receipt of a valid notification **within 14 days** and inform the holder…

			For Art. 13: If the notification fulfils the requirement laid down in the first subparagraph the competent authority of the reference Member State shall acknowledge receipt of a valid notification **within 14 days**. For Art 14 and 15: If the notification fulfils the requirement laid down in the first subparagraph the competent authority of the reference Member State shall acknowledge receipt of a valid notification **within 14 days** and inform the holder… For Art 18 and 19: If the notification fulfils the requirement laid down in the first subparagraph the Agency shall acknowledge receipt of a valid notification **within 14 days**. For Art 20: If the notification fulfils the requirement laid down in the first subparagraph the Agency shall acknowledge receipt of a valid notification **within 14 days** and inform the holder…
p.8, Article 9, point 5 p.11, Article 13, point 5 p.15, Article 18, point 5	medium	For unforeseen changes submitted as Type IB, it is unclear how the switch from Type IB to Type II is to be made when deemed necessary. It is noted that detailed guidance on procedures is yet to be drawn up. Nevertheless, it is felt that the Regulation should address this point. A clock-stop whilst necessary extra documentation is submitted would be acceptable, but the procedure should *not* be set back to zero and/or resubmission required. This would be particularly unacceptable, if the MA holder did not initially have the option to submit directly as a Type II.	Add to Art 13, point 5 the following paragraph: **The competent authority of the reference Member State shall inform the relevant competent authorities of the concerned Member States of its decision. The procedure shall be suspended for [*time for clockstop*].**
page 8, Article 10.4	High	A suspension of the procedure is foreseen in case of questions. However, it is not mentioned how long this clock stop may be. A definition of a	Add the following text:

page 12, Article 14.4 page 15, Article 19.4		window for questions and a time frame for the clock stop period is necessary similar to as it is now in the current system. In national, MRP/DCP and CP Type II procedures it is foreseen that the CA may request for additional documentation at any time during the 60 days period.	4. ... the procedure shall be suspended until such supplementary information has been provided. In this case the period laid down in paragraph 3 may be extended ~~for a further period to be determined by the relevant authority~~ **by maximum 60 days.**
page 10, Article 13.2 new third paragraph	high	In case the applicant does not agree with the recommendation, there should be a formal process to object in order to achieve a revision.	Add the following text: **The reference Member State shall provide the applicant with the draft opinion on the application referred to in paragraph 2. If the applicant does not object within 15 days after receiving the draft opinion, the opinion shall be considered final.**
page 10, Article 13.3	low	Typo	If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph ~~13~~ **2**,
page 10, Article 13.4	low	Typo	Where the competent authority of the reference Member State is of the opinion that the notification referred to in paragraph ~~13~~ **2** cannot be accepted,
page 10, Article 13.4a	High	When the reference Member State comes to the conclusion that the classification of the variation needs to be changed from Type IB to Type II a) this should be only possible if there is a defined and important reason, such as a potential serious risk to public health connected with the variation in question as defined by the Commission guideline 2006/C 133/05 b) it shall be clarified in the procedural guidance what additional documentation will be required for the upgraded variation and timelines for its submission need to be defined. Will the procedure be stopped or just continue? Which time lines does the transition from Type IB to Type II follow?	Add the following text: **b) + c**) to second paragraph: "Within 30 days following the receipt of ….. in order to take due account of the grounds laid down in that opinion. **A guideline will specify the timelines of the transition to the following Type II procedure as well as the additional information needed to be submitted by the holder."**

		c) The assessment time for upgrading the variation type from IB to II should be taken into account in the overall assessment timeline in order not to prolong the entire process compared to the current procedures.	
page 11, Article 13.5	high	As above, not only those changes, which have a negative impact but also positive impact (e.g. new indication) will be classified as Type II variations.	Change the text as follows: 5. By way of derogation from …. is of the opinion that the referred variation has a substantial potential to have a**n** ~~**negative**~~ impact on the quality, safety or efficacy of the ….
page 13, Article 16.1	High	In case not all CAs support the conclusion of the RMS it should be foreseen to bring the matter to the CMD. An attempt should be made first to solve the issue between RMS and CMSs during the procedure before involving the CMD. In case of involvement of the CMD there is a need to define details and time lines of the procedure, which may be done as a reference to Article 29 of Directive 2001/83/EC.	Add the following text: … Within the coordination group, all Member States shall use their best endeavour to reach agreement on the action to be taken **according to the procedure and timelines laid down in Article 29 of Directive 2001/83/EC**.
page 15, Article 18.5	high	As above, not only those changes, which have a negative impact but also positive impact (e.g. new indication) will be classified as Type II variations.	Change the text as follows: 5. By way of derogation from …. is of the opinion that the referred variation has a substantial potential to have a ~~**negative**~~ impact on the quality, safety or efficacy of the ….
page 17, Article 21.1a		We support that changes submitted as Type I and II variations can be implement before the marketing authorisation is amended. In order to get more legal clarity we see a need to add a time frame to the text, in which the CA shall inform the marketing authorization holder.	Add the following text: 1. Where reference is made to this paragraph, the following provisions shall apply: (a) The relevant authority shall forthwith provide the holder with the following information **within 7 calendar days:** - whether the variation or notification is accepted or rejected; - where the variation or notification is rejected, the

			grounds on which that rejection is based; …
page 17, Article 21.1b	high	The amendment of marketing authorisations regarding the addition of a new paediatric indication via Type II variation should be amended within 30 days after sending the information referred in point (a) in order to enable the timely application for the 6-month SPC extension according to the paediatric regulation. Therefore, a new paragraph should be added.	Add the following text: Where necessary, the relevant authority shall amend the marketing authorisation in accordance with the accepted variation or notification: – within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification; - **within 30 days after sending the information referred to in point (a) in case of major Variations of Type II according to Article 8 of Regulation (EC) No 1901/2006.** - within 6 months after sending the information referred to in point (a) in the other cases.
page 17/18, Article 21.2b	high	As above, the amendment of marketing authorisations regarding the addition of a new paediatric indication via Type II variation should be amended within 30 days after sending the information referred in point (a) in order to enable the fast application for the 6-month SPC extension according to the paediatric regulation. Therefore, a new paragraph should be added.	Add the following text: Without prejudice to Article 16, each relevant authority shall, where necessary, amend the marketing authorisation in accordance with the accepted variation or notification: – within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification; **- within 30 days after sending the information referred to in point (a) in case of major Variations of Type II according to Article 8 of Regulation (EC) No 1901/2006.** - within 6 months after sending the information referred to in point (a) in the other cases.
page 18, Article 21.3c	high	As above, the amendment of marketing authorisations regarding the addition of a new paediatric indication via Type II variation should be amended within 30 days after sending the	Add the following text: The amendment of the marketing authorisation referred to in point (b) shall be made:

		information referred in point (a) in order to enable the fast application for the 6-month SPC extension according to the paediatric regulation. Therefore, a new paragraph should be added	– within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification; **- within 30 days after sending the information referred to in point (a) in case of major Variations of Type II according to Article 8 of Regulation (EC) No 1901/2006.** - within 6 months after sending the information referred to in point (a) in the other cases.
page19., Article 23 new paragraph refer also to: page 23, Annex I items 2 c, d, and e	medium	The assessment time for line-extensions (new strength, dosage form or route of administration) shall be reduced to 90 days under certain conditions, which are: • no change in bioavailability or pharmacokinetic (PK) (new dosage form or route of administration) • linear dose-PK-response in investigated dose ranged (additional strength)	Add the following text: **1.** An application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as for the granting of the marketing authorisation to which it relates. **2. An extension to a marketing authorisation should be assessed within 90 days if the following conditions apply:** • **The extension has no impact on bioavailability or pharmacokinetic of the product (in case of a new dosage form or route of administration).** • **The marketing authorisation is extended by an additional dosage strength, which demonstrates a linear dose-pharmacokinetic response.**
page 19, Article 24.1	high	Where a minor variation of Type IB, a major variation of Type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations, the holder of such authorisations may follow the procedure laid down in paragraphs 2 to 6. *Text needs to be added as outlined on the right site in order to specify the scope according to the*	Add the following text: Where a minor variation of Type IB, a major variation of Type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations, the holder of such authorisations may follow the **'work sharing'** procedure laid down in paragraphs 2 to 6. **The work sharing procedure is optional; the choice is with the marketing authorisation holder. It applies in**

		public consultation paper of 24 Oct 2007.	**the following two cases:** **(a) where the change concerns one given medicinal product that is authorised at purely national level or a mixed registration status, i.e. registered via national and mutual recognition procedure in several Member States;** **(b) where the change is common to several, distinct medicinal products, which are registered via purely national, mutual recognition or decentralised or centralised procedures.**
page 20, Article 24.3	high	An introduction of a fixed validation period is needed in order to ensure a timely start of the procedure.	Add the following text: The Agency shall **validate the application referred to in paragraph 2 within 14 days and shall** issue an opinion ….
page 20, Article 24.6	high	Before a final opinion is reached the applicant should be informed about the draft opinion and should have the chance to formally object to it in order to achieve a revision.	Add a new second paragraph: **The Agency shall provide the applicant with the draft opinion on the application referred to in paragraph 2. If the applicant does not object within 15 days after receiving the draft opinion, the opinion shall be considered final.** Where it reaches a final opinion on the application ….
page 20, Article 24 new subparagraphs 8 and 9	high	In the Consultation Paper a positive Agency opinion leads to a downgrading of the variation. This is an acceptable approach, which should be included into the Regulation. The proposal for worksharing, with the enormous potential for efficiency gain, is laudable. The draft Regulation, however, *omits to address the immediate subsequent steps*, and additionally, some of the timelines are questionable. a) Further guidance is needed on what are the next steps in the case the Agency issues a	Guidance needed for the next steps in case of a positive or negative opinion, respectively. The addition of the following text may clarify as well: **8. Where the Agency assessment results in a positive opinion, this results in a downgrading of the classification of the change at national level.** **9. Following receipt of the notification referred to in paragraph 8, the relevant authority(ies) shall close the procedure in accordance with Article 21.**

		positive opinion. b) It is unclear what steps need to be done in the case of a negative opinion. Does it mean that the product is non-approvable or can it just not be down-graded?	
page 20, Article 24	High	The current timeline proposals would lead in most scenarios to delays in approval (60-day EMEA assessment plus resubmission by traditional route represents a doubling for Type IB and an increase from 60+ to 90+ days for a standard Type II). Therefore, it is suggested that a Type IB change can be assessed in 30 days, as is currently the case In case (A), single product with "purely" national licences, the increased timelines are offset only by reduction in fees payable (assuming that an appropriate change to fee structures is achieved), the administrative workload not being reduced at all (EMEA submission in addition to individual CMS submissions). Real gains to offset the increased timelines are only to be seen in case (B), change affecting multiple products – assuming that the subsequent submission to CMS may also be made as a single application following to the preceding EMEA submission. This last point should be clarified..	Add the following text: 3. The Agency shall issue an opinion…. **(a) 30 days following receipt… Type IB** (b) 60 days…….. Type II (c) 210 days……. extensions
page 23, Annex I	high	Add text (bold and underlined) before “1. Changes to the active substances”.	Annex I: Extensions of marketing authorizations **These changes, listed below, will be regarded as an ‘extension’ application.** **The MA holder has the option to propose a new invented name that may contain a modifier to specify the variation.** Changes to the active substance(s): (a) replacement of a chemical active substance by a different salt/ester complex/derivative, with ….

			(b) replacement of a different isomer, a different ….
page 24, Annex II	low	The addition may make the purpose of this Annex clearer.	Annex II: **Cases for grouping of variations**
page 24, Annex II	high	It is not completely clear how to group different variations for one product, in particular in the case when a product is purely nationally registered in some Member States and at the same time registered via mutual recognition procedure in some other member states.	Detailed guidance on grouping is needed.
page 24, Annex II, point 5	high	In order to provide consistency with currently discussed legislative proposals on pharmacovigilance, changes to the pharmacovigilance system master file should be subject of grouping as well.	Add the following text: 5. All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File, Plasma Master File **or Pharmacovigilance System Master File.**
page 24, Annex II, point 6	High	The opportunities for grouping of variations are welcomed. For changes to chemistry, manufacturing and controls, however, these opportunities are restricted to consequential variations or to changes within a process/quality improvement project. It should be clear that other changes made (as required by European Directives) in order to maintain processes and controls within "state of the art" can also be included, even if no measurable "improvement in quality" can be demonstrated, and other projects, for example site changes, should also be within scope as long as there is no deterioration in product quality.	Add the following text: 6. All variations in the group relate to **one of the following**: • a project intended to improve **or update** manufacturing process, controls or quality of the medicinal product concerned. • **a project to transfer manufacture or controls to a new or additional site, where no negative change in quality or performance is demonstrated**
page 24, Annex II introduction of new points 14 and 15.	medium	In the context of simplification and enhancement of flexibility, we suggest additional possibilities for grouping in certain cases: - combination of points 8 and 9. - combination of points 10 and 11.	The following points should be added: **14. All variations in the group are consequential to a given urgent safety restriction, which relate to the implementation of a given class labeling and submitted in accordance with paragraph 3 of Article**

			26. **15. All variations in the group are consequential to the assessment of a given periodic safety update report as well as to a given post-authorisation study conducted under the supervision of the holder.**
page 25, Annex III	low	The addition may make the purpose of this Annex clearer.	Annex III: **Documentation for the variation applications (Type IA, IB, II and Extension)**
page 25, Annex III, 1(d)	High	This item requires the date of implementation of Type IA variations to be given. This should be accepted in general terms, with sufficient flexibility that country-specific reports or lists need not be generated.	Point 1(d) needs to be modified as follows: (**d) the approximate date of implementation for each variation described;**
page 47 Draft Detailed Guideline introduction of a new paragraph 6	High	It is understood that the guideline will go through a thorough development process at a later stage and comments are not expressly sought at present. Nevertheless we would like to propose that a change to an established Design Space need not default to Type II. Straightforward changes resulting from, for example, a widening of the knowledge base on account of increased data collection or wider ranges of input variables, or a change in scale if the process is not claimed as scale-independent, could be classified as Type IB, leaving Type II for fundamental changes in approach, cases where extensive data need be assessed, or changes made as a result of data indicating that the previously allocated Design Space may not yield product of the appropriate quality under all foreseen circumstances. The Type IB submission still allows the CA the option to reclassify if it considers the company is being too ambitious (akin to the default IB for unforeseen changes).	Add the following text: **6. Modification of an approved design space** **a. Incremental changes in design space resulting from the generation of additional data – Type IB (Condition – the data are satisfactory and lead to an extension of design space with no increased risk to quality)** **b. Change in design space arising from the generation of new data, where data indicate that a tightening of the design space is warranted – Type II** **b. Fundamental changes in design space resulting from generation of new types of data, different approach – Type II**