Public Consultation: Proposal for a Commission Regulation 'Concerning the Examination of Amendments to the Terms of the Marketing Authorisations for Medicinal Products for Human Use and Veterinary Medicinal Products'
(Version 24 October 2007)

Comments from: Wyeth Research

GENERAL COMMENTS
(1) We welcome the principles in the draft regulation, which will significantly contribute to the Commission intention to make the variation system 'simpler, clearer and more flexible'. We also welcome the separation of the guidances from the regulation, which will facilitate the more frequent updating of Guidances to take into account scientific and technical progress, experience with the new system, and the Agency recommendations from Article 5 requests.
(2) Wyeth supports the extension of the Community system to national MAs and would urge the process to be implemented as soon as possible. Assurance is requested that the regulation will if necessary allow the implementation of the new procedures for CP/DP/MRP products in advance of implementation for variations to national MAs.
(3) We consider the new procedures for Type 1A and $1A_{IN}$ variations are extremely positive and simplify the management and supervision of changes which are not expected to have any negative impact on the quality, safety or efficacy of the medicinal product concerned. Although acknowledging that these changes are minor, Article 21 unfortunately appears to allow the option for a CA to reject a Type 1A variation. Unless this option can be removed, it will be important to clarify (i) the limited grounds on which this can happen and (ii) how this would be dealt with for an already-implemented Type 1A change.
(4) The principle that unforeseen variations default to a Type IB is good. However, we are concerned that the guidance might (i) be so comprehensive that there will be few cases of a default to a 1B and (ii) result in too many other cases where a Type II will be required because of an inability to comply with <u>all</u> the conditions for a foreseen variation and (iii) it is unclear how an unforeseen Type 1B variation will be processed as the conditions and required documentation will not be specified. .It is important that the guidance be written in such a way that Type IIs are not required for changes which are also not expected to have any negative impact on the quality, safety or efficacy. [See item 8 – Risk assessment principles should be taken into account]. There should be allowance that, for Type IB changes, if not all of the conditions in the detailed guideline can be met, the applicant should assess the implications using appropriate risk management tools where needed and on the basis of this assessment may consider a change of Type IB is still appropriate. The applicant should justify their assessment in the Type IB

application. The applicant should be encouraged to discuss with the EMEA / RMS to confirm that a Type IB categorisation is still appropriate
(5) The new possibility of 'grouping' is a positive development. As the draft regulation is currently written however, grouping of a single minor variation of Type 1B relating to several MAs in a single member state is not permitted (though it is allowed for these variations to be processed via the Worksharing at EMEA level). We believe that a widened scope for the grouping of minor variations would contribute to an improved efficiency in terms of processing and use of national Competent Authority resources.
(6) The option to use a Worksharing procedure is positive, but we seek assurance that the corresponding EMEA procedures will be designed in the spirit of the consultation document. For example, 'Similarity of Dossiers' was a consideration in the QWP pilot worksharing procedure for PAT variations when considering a variation for the pilot. However the proposed Worksharing procedure should be applicable also to national MAs which have a non-harmonised Module 3/Part II.
(7) The principle of worksharing whereby the EMEA issues a binding decision regarding variations to national MAs without the CAs having an option to contribute to the opinion may be difficult to implement (unless the EMEA issue more detailed guidance on the role of the CHMP in the development of the worksharing opinion).
(8) Incorporation of the 'Design Space' concept into the variation guidance is welcomed. However, the lack of any mention of the principles of Risk Assessment and Quality Systems in the proposed Regulation is an omission. These principles should be included in the Regulation, either in the form of a recital, or in Article 6, as principles to be applied either in the drafting of the initial guidances, or in the further development of the guidances. To avoid any risk for misinterpretation, there should also be a statement that makes clear that a change within an approved Design Space will not trigger a variation.
(9) There will be some changes where it is not possible or appropriate to comply with all of the conditions of the change classification. Such situations may not impact the quality of the product to such an extent that a Type II variation is motivated. There should be allowance that, for Type IB changes, if not all of the conditions in the detailed guideline can be met, the applicant should assess the implications using appropriate risk management tools where needed and on the basis of this assessment may consider a change of Type IB is still appropriate. The applicant should justify their assessment in the Type IB application. The applicant should be encouraged to discuss with the EMEA / RMS to confirm that a Type IB categorisation is still appropriate

Page, Section title, article	Relative Importance	COMMENT AND RATIONALE	PROPOSED CHANGE
Page 5, Article 4	Critical	The principle that the classification of a change and the assessment should be related to the risk that the change may have a negative impact on the quality, safety or efficacy of the medicinal product concerned, should be included in a recital in this section	

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Page 5, Article 5 (1), 2nd paragraph		Sixty days is too long a period to provide a recommendation on an unforeseen variation. Considering that the outcome of an Article 5 process is only a recommendation, and that an alternative procedure exists (i.e., to submit an unforeseen variation as a Type 1B and await the CAs decision that a Type II process may be appropriate) the delay should be shorter and the recommendation simpler for the new procedure to become attractive. The recommendation should be limited to a) the type of variation that is required (Type 1A, Type 1B, Type II or Extension) b) The documentation required for the variation if it is a Type I variation c) A statement on whether this recommendation is general, and can be applied to other medicinal products. We believe that 30 days should be sufficient for this.	Specify that: *"The Agency shall deliver this recommendation within 30 days following receipt of the request, taking into account the guidelines referred to in point (a) of Article 6(1), Article 29(2) of Directive 2001/83/EC and Article 33(2) of Directive 2001/82/EC."* *"The recommendation should include the Type of Variation appropriate to the proposed changes, the documentation required in the case that the proposed variation is a Type 1 variation, and a statement whether the recommendation is applicable to other medicinal products."*

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Page 5, Article 5		In view of the fact that an Agency recommendation may be requested for a variation to product licences for which the Agency has not been previously responsible, guidance will be needed on the documentation to be provided by the Marketing Authorisation holder in this case.	Consider adding paragraph stating that the Agency shall issue guidance
Page 5, Article 5 (1)	Critical	Considering that the outcome of an Article 5 process is as currently written only a recommendation, and that an alternative procedure exists to submit an unforeseen variation as a Type 1B and await the CAs decision that a Type II process may be appropriate, we instead propose that the Agency should deliver a binding decision (but with an option for the MAH to request a re-examination of the decision). Details should further be provided as to how the EMEA decision will be reached. The CAs and MAHs should be included and should have an opportunity to give their position in particular when they are not in agreement with the EMEA's (CHMP's) opinion	Add to the end of the 2nd paragraph: *"(…) Directive 2001/82/EC, in association with the marketing authorisation holder and the competent authorities of the Member States."* Add a new paragraph at the end of 5 (1): *"Within 15 days after receipt of the decision referred to in paragraph 1, the applicant may give written notice to the Agency that he wishes to request a re-examination of the decision. In that case, the applicant shall forward to the Agency the detailed grounds for the request within 30 days after receipt of the decision."* *"Within 30 days following receipt of the grounds for the request, the Agency shall re-examine its decision. The reasons for the conclusion reached shall be annexed to the final decision."*

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Page 5, Article 5(2)	Critical	The MAH should be able to review the agency recommendation before it is published. This could be a similar process to that for preparation of EPARs.	
Page 6, Article 6		While Article 6(2) refers to the necessity for European guidelines to be updated regularly to take account of "scientific and technical progress", an explicit reference in the Regulation to important new ICH Quality concepts (the importance of which is mentioned in the public consultation paper) is deemed important.	Add a new Article 6 (3): *"(3) In particular, the guidelines shall be updated to reflect new, internationally agreed, concepts (e.g., ICH; International Conference for Harmonisation Guidelines) introducing new tools, or developing existing tools (e.g. risk management, quality systems, design space) to the extent these concepts may facilitate continuous manufacturing improvements while ensuring satisfactory authority control and high quality standards."*
Page 6, Article 7 (2)	Critical	We propose that a single minor variation of Type 1B relating to several MAs in a single member state should be eligible for grouping. Furthermore the option of processing such variations via the Worksharing at EMEA level appears to add unnecessary regulatory complexity to the process. This should be allowed as a single application to be processed at the appropriate level (member state or MRP/DP)	Add a new paragraph 7 (2) c: "(…) where a single minor variation of Type 1B relates to changes that concern several marketing authorisations submitted at once to a relevant authority, all such variations may be covered by a single application as referred to in Articles 9, 13 and 18."

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Page 6, Article 7(2)		In the case where one or more Type 1A changes have been implemented, but not reported to the relevant authorities as they are still within the 12 month period, and a non-consequential and unrelated Type II or Type 1B variation is to be submitted, *and where the amended documents will include the Type 1A changes,* the Type 1A changes should be included in the single application. This option should be included in either Article 7 or in Annex II	
Page 7, Article 9 (2), 2nd paragraph	Critical	Different CAs currently apply different validation times for Type 1B variations. It is very important that the new procedure provides consistent assessments and approval times across member states. For this reason, we believe it is critical that the time for validation be included in the regulation. Fifteen (15) days is proposed.	Change 9(2), 2nd paragraph to: *"The relevant authority shall acknowledge receipt of a valid notification within 15 days if the notification fulfils the requirement laid down in the first subparagraph."*

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Page 7, Article 9 (4) [Also applies to 13.4 and 18.4]		The second paragraph states *"the holder may submit to the relevant authorities an amended notification …".* More detail is needed. Does this mean resubmission of the full notification submission or only the amended sections of the notification? It potentially represents a significant workload for the Marketing Authorisation Holder and the proposed timeline should therefore be allowed to exceed 30 days when justified.	
Page 8, Article 10 (4) [Also applies to 14.4 and 19.4]		After submission of the supplementary information requested by the competent authority, the 60-day evaluation may be *"(…) extended for a further period to be determined by the relevant authority."* The extension of the procedure should not exceed 60 days and following discussion with the MAH.	The last sentence of the Article 10 (4) should be reworded as follows: *"In this case the period laid down in paragraph 3 may be extended for a further period to be determined by the relevant authority in consultation with the MA holder. This extension of the procedure should not exceed 60 days."*

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Page 8, Article 10 (5)	Critical	Our experience is that competent authorities do not always hold to the timelines, and this can often include lengthy delays in issuing a decision on Type II variations. We therefore propose that if, following a Type II process for a national MA, an opinion is not issued by the authority within the specified timelines, the variation can be considered approved, as with Type 1B variations.	Revise text as follows: *"Within the period laid down in paragraphs 3 and 4, the relevant authority shall reach a final opinion on the application, and close the procedure in accordance with Article 21(1). If within the period laid down in paragraph 3, the relevant authority has not sent the holder its opinion, the variation shall be deemed accepted."*
Page 8, Article 11(5) [Also applies to 13(5) and 18(5)]	Critical	Where a relevant authority is of the opinion that a Type 1B variation submitted for an unforeseen variation should instead be evaluated as a Type II variation, the clock should not be restarted (the original start date should be maintained). Further documentation should not be required (as both Type 1B and Type II variations follow the list of documents in Annex III paragraph 2 with the exception of (2) (e)).	
Page 14		A footnote should confirm that reference to MAs granted in accordance with regulation 726/2004 is applicable to those MAs granted in accordance with the previous regulation 2309/93	

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Page 17, Article 21 (1) (a) [And also 21 (2) (a) and 21 (3) (a)]		The grounds for retroactively 'rejecting' a Type 1A notification need to be specified. 'Rejection' is in addition not the correct term, as a notification of a change that should not have any negative impact on the quality, safety or efficacy of a product should only fail on validation (i.e. if it is incorrectly classified as a Type 1A).	
Page 17, Article 21 (1), (2) and (3)		A statement should be inserted on how to manage the situation where a Type 1A variation that has already been implemented is judged to fail validation (see above comment).	
Page 17, Article 21 (1) (b), (2) (b), (3) (b)		Six months to amend the particulars of a MA seems excessive, particularly where the change may have been implemented 12 months previously and only notified via the annual reporting. Three (3) months is proposed.	Revise to read: *"(…) within 3 months after sending the information referred to in point (a) in the other cases."*

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Page 18, Article 22 (2)	Critical	Article 22.2 states that a variation may be implemented once the relevant authority has accepted it and informed the holder accordingly. Clarification is required on the implementation of SmPC, PIL and labelling changes since changes could occur between acceptance and receipt of updated MA documentation, particularly where translations are required in the case of centrally authorised products.	
Page 19, Article 24 (1)		The first paragraph should make it clear that the Worksharing procedure can be used where a single variation is submitted to national MAs in more than one country, or where the products concerned are authorised by different procedures (MRP/DP/National)	Revise as follows: *"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* - *concern several marketing authorisations, in a single member state or in more than one member state, or,* - *to marketing authorisations authorised by different regulatory procedures* *the holder of such authorisations may follow the procedure laid down in paragraphs 2 to 6."*

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Page 20, Article 24 (3) (a)	Critical	The 'Worksharing' procedure should operate according to the same timetable as for variations via the CP, so that an opinion on a Type 1B variation should be issued within 30 days	Revise to read: *"(a) 30 days following receipt of the valid application in the case of minor variations of Type IB or 60 days following receipt of the valid application in the case of major variations of Type II;"*
Page 20 Article 24		It is important that the regulation includes the mechanism for translating the Worksharing opinion into approvals at the national member state level. At present this is only contained in a guideline which can be modified independently of the regulation. Member states should not be able to disagree with the Worksharing opinion except on major grounds of risk to public health (guidance specified in 2001/83 Article 29 (2) defining a potential serious risk to public health).	Add new paragraph 7: *"Where the worksharing concerns nationally authorised MAs, the MAH should then submit a variation to each CA for the MAs listed in Annex III para 2 (g) (1). A variation which has already been evaluated in accordance with the procedure in para 2-5 above shall be classified as a minor variation of Type 1A $_{IN}$ unless the variation applied to more than one MA and prior to evaluation by the Agency pursuant to Article 24, the variation was considered as a major variation of Type II or an extension."*

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Page 21, Article 27		This is an extension of the current requirements and seems to have arisen from a statement in a consultation paper from October 2006 stating that "From the date of its implementation, all regulatory information related to a given "Do and Tell" change would be available without delay to the concerned competent authorities, upon request to the marketing authorisation holder". We would propose to delete Article 27 as the implementation of approved variations should continue to be managed through the company's change control process and GMP inspections. However, if this is not acceptable, a revised text to better reflect the original intent is proposed.	Revise as follows: *"At any time, and with notification of the reason to the MAH, the relevant authority may request the holder to provide the information required for an already implemented Type 1A variation as specified in the Guideline referred to in Article 6 (1) (b) in advance of the notification of that variation by annual report. The holder shall supply this information without delay."*
Page 23, Annex I	Critical	It is proposed that a new strength or a new route of administration should no longer be considered an extension application with a 210 day review period. It is proposed that these be 90-day Type II variations as are variations for new indications.	

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Page 26, Annex III		It is not clear to us why for a Type 1A variation, it would not be required to submit *'all documents amended as a result of the variation'.* For example, if the drug product batch size is changed, it seems reasonable for the Type 1A variation to include an amended section 3.2.P.3.2. This could be different to the 'documents demonstrating that the conditions laid down in the detailed guidelines referred to in point (a) of Article 6(1) for the referred variations are met'.	Add a new bullet: *(d) all documents amended as a result of the variation(s);*
Page 30, 11 ("Change of batch size of active substance or intermediate")		Although detailed comments are not requested at this time, we want clarification on whether the change in several of the Type 1 conditions, from *'Active substance is not a biological substance' to The 'product concerned is not a biological medicinal product*' has any significance or consequences.	