Public Consultation Paper
Review of Commission Regulation (EC) n° 1234/2008

(Final EFPIA/EVM/EBE comments)

General comments

Company	**General comment** (if any)	**Outcome** (if applicable)
	We welcome the opportunity to provide feedback to this Consultation and look forward to realising the full benefits offered by extending the scope of the 'Variations Regulation' (Commission Regulation (EC) No 1234/2008) to national authorisations. In order to put our comments into context, it is worth summarising that the overall objectives of the last revision to the Variations Regulation were: • to make the regulatory framework for the Variations Regulation simpler, clearer and more flexible; • lead to an overall reduction in administrative burden; • harmonisation of procedures and requirements for national authorisations; • accommodation of new ICH quality tools; • without compromising human health.	

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	Whilst the consultation document indicates what changes are needed to extend the scope of the Variations Regulation to purely national authorisations, no indication of the timeframe to accomplish this is indicated. Considering that 'harmonisation of procedures and requirements for national authorisations' was one of the major objectives of the revision, we consider this to be a major omission of this consultation document. Currently the implementation of the principles of the revised Variations Regulation to national authorisations varies significantly across the EU member states: some member states voluntarily implemented the principles of the new Regulation from 1 January 2010; others have implemented in the intervening period since then; whilst other member states have indicated that they will not implement at a national level until there is a mandatory date for implementation. This has created a very complex regulatory environment for Companies to manage variations. We would urge the Commission to progress the comitology step necessary to extend the scope of the Regulation as soon possible, and to consider a mandatory date for implementation of the Variations Regulation to purely national authorisations of no later than 1st July 2012. Although not specifically addressed in this consultation, it is worth noting that approval timelines and implementation timelines are not harmonised across Member States (MS). In light of this, it is proposed that the Commission consider what measures it could take to ensure the timelines set down in the Regulation are adhered to. We note that section 2.2.i of the consultation paper only discusses the Commission decision-making procedure and implementation of variations in respect of centrally authorised products. The same principles should apply to all marketing authorisations, regardless of the route of authorisation. Any amendments to Articles 23 and 24 of	

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	the Variations Regulation to reduce timelines for Commission Decisions and address when variations may be implemented should similarly be applied to national, Mutual Recognition and Decentralised marketing authorisations. With reference to the classification of variations, Article 26 of the Variations Regulation requires that by 1 January 2012 the Commission services shall assess the application of this Regulation as regards the classification of variations, with a view to proposing any necessary amendments to adapt Annexes I, II and V to take account of scientific and technical progress. We request that the Commission clarifies whether a separate consultation will be undertaken in this regard. Important aspects of the Commission classification guideline that need to be addressed are deletion of the DDPS from the classification guideline to reflect the replacement of the DDPS by the Pharmacovigilance Master File (PSMF), and the review of classification of variations for biological products. We understand that changes to the content of the PSMF will not require variations as this is not part of the Marketing Authorisation dossier and that only a change of the qualified person for pharmacovigilance (QPPV) or supervising authority would require submission of a variation application. EFPIA intends to provide proposals with regards to the classification guideline at a later date.	

Consultation item n° 1

Do you agree where dossiers are not harmonised difficulties could raise for worksharing when accepting the assessment carried out by one member state by other member states?

Company	**General comment** (if any)	**Outcome** (if applicable)
	In certain circumstances, there could be difficulties in worksharing where dossiers are not harmonised. However harmonisation of the dossier should not, however, be a prerequisite to apply worksharing to purely national marketing authorisations. The only preconditions to benefit from the worksharing procedure are described in the current Commission procedural guideline: (1) the absence or limited need for assessment of a potential product-specific impact; (2) the absence of individual supportive data sets for each medicinal product concerned. In cases where the two above conditions are met, we believe that an evaluation via worksharing procedures could be performed, regardless of whether or not dossiers are harmonised. In addition: - the CMDh Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure states that "*Harmonisation of the complete initial*	

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	dossier or SmPC, PL and labelling is not a prerequisite for a worksharing procedure" - the CMDh Q&A document on Variations clearly states with reference to *Can harmonisation of Module 3 be done by worksharing?:* "*Module 3 harmonisation is surely an option for worksharing as worksharing does not require product harmonisation in advance. The aim is to have a harmonised result."* All of these existing documents provide adequate guidance and should also apply for national procedures. There is no need to add further conditions. Worksharing should include the flexibility, where the supporting dataset is the same, to harmonize particulars, where the currently approved particulars differ between Marketing Authorisations. Considering that the worksharing procedure is optional, adding an extra hurdle to access this procedure will be detrimental to the ultimate objective of the revised Variations Regulation.	

Consultation item n° 2

Which option a) or b) mentioned above do you consider that should be adopted to allow worksharing?

Company	**General comment** (if any)	**Outcome** (if applicable)
	We do not support option a), as such an approach would be overly restrictive and not in line with current guidance or the objectives of the Variations Regulation. It is not quite clear how option b) should be interpreted. As outlined in our answer to consultation item #1, the state of harmonisation of dossiers should not be a prerequisite for worksharing. As long as the current conditions (no separate product specific assessment and no need for individual supportive data), are fulfilled, worksharing can be a valuable and resource-saving option. If the intent of option b) is to reflect these current conditions, then we support option b).	

Consultation item n° 3

Do you agree with the principle that the deadline for adoption of Commission Decisions amending marketing authorisations must be driven by public health considerations?

Company	**General comment** (if any)	**Outcome** (if applicable)
	It is our understanding that the Commission's proposals in section 2.2.i may be summarised as follows: • The possibility for the MAH to implement variations following a favourable EMA committee opinion, without having to wait for adoption of the corresponding Commission Decision, should be extended to more categories of variations than presently described in the Regulation. The update of the Decision may be adopted up to 6 months after the committee opinion. • If the concept of implementation prior to the adoption of Commission Decision is extended, it is essential that that the EMA issues Certificate of Pharmaceutical products (CPPs) prior to Commission Decision (i.e. at CHMP opinion) for all relevant variations. The EMA's processes for issuing of CPPs will need to be modified slightly, to correspondingly extend the situations in which they can reflect revised product information in the CPP based on EMA endorsement, without awaiting the revised Decision. In the situation where the EMA would not agree to issue CPPs prior to Commission Decision, this would lead to delays in the implementation of changes to the Product Information in CPP depending countries.	

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	• A Commission Decision would only be required prior to implementation of certain "crucial changes", such as new indications or changes in the composition of vaccines. • The timelines for adoption of the Commission Decision for these "crucial changes", and for other changes identified as critical for public health, would be shortened to 2 months. Further clarity is required on what is meant by "public health considerations." MAHs should have the opportunity to contribute to the discussion to define what is considered a public health consideration. Subject to further clarification, we support the principle that the deadline for adoption of Commission Decisions amending marketing authorisations must be driven by public health considerations: Decisions on variations that are important to public health should be adopted in a shorter timeframe than for those that are not critical. It should be noted, however, that not all "public health critical" changes should await a Commission Decision, even if adopted more rapidly, prior to implementation. For example, the addition of important new safety information to the product information should be implementable following adoption of the EMA committee opinion. Furthermore we support that other changes to the marketing authorisation, which would not have such public health implications, could be implemented without a Commission Decision.	

Consultation item n° 4

Which category of variations do you consider that should be adopted within shorter deadlines?

Company	**General comment** (if any)	**Outcome** (if applicable)
	Further clarification is also needed on the meaning of "critical for public health" and "crucial changes", with regard to the proposed 2 month deadline for adoption. We believe that Commission Decisions on the following categories of variations should be adopted within shorter deadlines and should require adoption of the Decision prior to implementation. These should be detailed in a guideline to facilitate updating: • new indications; • new contraindications • any variation which requires the assignment of a new marketing authorisation number (e.g. new pharmaceutical strengths; new routes of administration; new presentations); • changes in composition of vaccines. Commission Decisions on the following categories of variations should be adopted within shorter deadlines, but implementation should be permitted following adoption of the EMA committee opinion: • addition of important new safety information to the product information;	

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	• restrictions to the indications or changes to posology in the product information that may be critical for public health; • quality changes impacting on the use of the product.	

Consultation item n° 5

Do you agree to extend the current system that allows holders to implement certain variations prior to the adoption of the Commission Decision (to the exclusion of those changes with most impact for public health)?

Company	**General comment** (if any)	**Outcome** (if applicable)
	The definition of "changes with most impact for public health" is unclear. Assuming this refers to the changes as outlined above under Item #4, then we believe there is a further opportunity to extend the current system to allow MAHs to implement certain variations prior to the adoption of the Commission Decision. See also the responses to consultation items 3 and 4 above. If the Commission does extend the number of cases where a variation can be implemented prior to adoption of the Commission Decision, it is important that the EMA promptly makes the revised product information publicly available on their website following the committee Opinion. This is necessary to avoid confusing patients and healthcare professionals, who may receive or access revised product information from the MAH or other sources, such as medicines compendia. It may also be important for products which are typically placed on the market in tender environments, such as vaccines. Calls for tender occur only at fixed moments in time, and certain product characteristics that appear in the SmPC, even if they may seem less important for	

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	public health, can be crucial as they may be part of the tender specifications (e.g. shelf life, time that a product can be kept out of the fridge).	

Consultation item n° 6

Do you consider appropriate to introduce a deadline for the implementation of changes to product information significant from a public health standpoint?

Company	**General comment** (if any)	**Outcome** (if applicable)
	We assume that item #6 refers to the implementation into the market of revised product information. In our view, a deadline for implementation of safety related changes, is already reflected in the Commission Procedural Guideline, namely that "*Variations related to safety issues must be implemented within a time-frame agreed between the Commission/ reference Member State and the holder*." This aspect should remain a case-by-case decision agreed between MAH and Authority/ Commission and in our view does not require an amendment to the Variation Regulation. In addition it is in the interest of the MAH to implement important public health changes as soon as possible. Flexibility of implementation should be maintained and be consistent with the current guidance.	

Consultation item n° 7

More stable summary of product characteristics. Do you agree with the analysis?

Company	**General comment** (if any)	**Outcome** (if applicable)
	From the MAH viewpoint, it is important not to delay communication of new safety or efficacy information to healthcare professionals. Delaying small changes to allow a stable SmPC has potential legal implications and changes outside of those affecting public health could have impact on individual patient care. We agree that there are frequent changes to SmPCs. It should be noted that the current proliferation of variations (especially Type II) is largely due to the fact that under the previous regulations multiple safety subjects could be combined into one variation. Now this is no longer possible, unless all safety changes are based on one dataset. We also believe that multiple changes to the QRD template over the past few years contributed to the increase of changes to the Product Information, with only little benefit for patients and healthcare professionals. Consequently, we suggest avoiding such frequent changes in the future.	

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	In addition, in the current system there is sometimes little or no incentive to group variations (which in any case is difficult for Type II Variations). In some cases, separate variations may incur less work or complications compared to grouped variations. We believe that allowing more flexible criteria for grouping of variations, when not delaying the submission and implementation of important safety and efficacy changes, would greatly contribute to reduce the number of changes to the SmPC. Consequently, we suggest the Commission considers further groupings to be included in Annex III (e.g., unrelated changes to differences sections of the SmPC). In addition, more flexibility in implementation of changes could help to address the proliferation by grouping implementation of changes. Furthermore, healthcare professionals should be educated on the role of 'Summary of Product Characteristics' and encouraged to use them. Flagging changes with serious implications for public health could be achieved through the use of electronic information.	

Consultation item n° 8

Do you consider appropriate to extend the time limits for assessment of complex grouped applications to enable a larger amount of cases where grouping under one single application could be agreed by the competent authority?

Company	**General comment** (if any)	**Outcome** (if applicable)
	We believe that the introduction of the grouping concept into the new Variations Regulation offers a major benefit for MAHs. Extending the time limits for assessment of complex grouped variations would not foster the use of grouping but rather stimulate the submission of several single variations, especially if applicants cannot anticipate the timetable that would apply to a given grouping. Therefore we believe that any extension of time limits should be carefully considered before introducing changes at this time. This is particularly true since we have less than 24 months experience of applying the new Variations Regulation. It is quite difficult to provide a definite answer to the posed question without the knowing the following: • What will be the scope of grouped applications being considered as complex? • What extension of time limits is being considered?	

Company	**General comment** (if any)	**Outcome** (if applicable)
	We do not believe that the number of changes in a grouped application is a criterion to extend the time limits. The Variations Regulation does not include any restriction on numbers of variations to be included in a grouping. For grouped variations we favour harmonization and predictability so that all Competent Authorities have the same requirements/interpretation on implementation for grouping.	

Consultation item n° 9

Do you think that changes to the procedure in Article 21 of the Variations Regulation are necessary?

Company	**General comment** (if any)	**Outcome** (if applicable)
	The answer to this consultation item will be provided by the specialised vaccine group EVM within EFPIA, these comments are provided as an annex to this document".	