Revision of the Variations Regulations
European commission Consultation document 'comitology' October 2007

EFPIA/EVM/EBE COMMENTS

GENERAL COMMENTS

The Commission's proposals are a big step forward and have the potential to significantly lower the current regulatory burden on Variations without compromising the quality, safety and efficacy of products on the market.
We strongly support the Commission's proposal for the revised Variation Regulation and broadly agree with its objectives and suggested concepts as outlined in the consultation paper. However, we believe that the implementation of those concepts into the draft legal proposal may need further improvements to the legal drafting to ensure that it fully reflects the Commission's strategy paper.

We also welcome the separation of the guidelines from the Regulation, which will facilitate the more frequent updating of Guidelines to take into account scientific and technical progress, experience with the new system, and the Agency recommendations from Article 5 requests.
It would be helpful that the Regulation contains a provision requiring that yearly statistics on the number and types of variations processed both at European and National level be published.

CHANGES CONCERNING DOSSIERS SUPPORTING ARTICLE 58 SCIENTIFIC OPINIONS

The scope of the Regulation should be extended in Articles 1 and 2 to include the management of the changes proposed to dossiers assessed by the CHMP in accordance with Art. 58 of Regulation (EC) N°726/2004 and which received a positive opinion. The details of the corresponding procedure should be described in a specific section

PHARMACOVIGILANCE

In the absence of any specific inclusion in Annex I (list of minor variations) to the Variations Regulations currently in force, any amendment to the content of the documents referred to in paragraphs (ia) and (n) of Article 8(3) of Directive 2001/83/EC is to be considered a Type II variation. Furthermore, Section 2.2.1 of 'Volume 9A of the Rules governing medicinal products in the European Union: Pharmacovigilance for Medicinal Products for Human Use' reflects this situation in stipulating that 'updates to the information in the detailed description of the pharmacovigilance system should be made as type II variations.

The draft Commission Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use provides that 'all variation pertaining to the pharmacovigilance system' belongs to the categories of changes that can be covered by a single application for a type of a variation of type II or a notification of type IB but it does not currently propose a classification for any type of updates to theses documents.

The legislative proposals to strengthen and rationalise the EU system of pharmacovigilance provides for a simplification of the existing requirement for a detailed description of the pharmacovigilance system to be submitted and kept up to date in the form of a detailed 'Pharmacovigilance System Master File'.

This document is to be maintained on site and is to be submitted on request by the authorities or can be viewed during inspections. This approach is very welcome, particularly as industry very much appreciates the willingness of the Commission to support what will be a significant reduction in administrative burden in the interests of promoting patient safety.

However, until this new pharmacovigilance legislation is implemented, any change to a company pharmacovigilance system will continue to require a variation to the marketing authorisation (for each product and each competent authority). These variations would have to be of a type II category or, at best, a type IB, should the new Variation Regulation comes into force before the legislation on EU pharmacovigilance is adopted. It would therefore be desirable to develop interim measures to start relieving both industry and regulators from a major administrative burden which is not in the interest of public health.

TIMELINES

There should be very clearly defined procedures (incl. timelines) from submission of the variation until the amendment of the MA in order to have predicable timelines for the competent authorities and the applicant.

EXTENSIONS OF MARKETING AUTHORISATIONS (MA)

The classification of extensions of MAs remains unclear. The proposed Regulation states that extensions of MAs are now considered as variations, however art 24.3 (b) suggests that standard review timelines for new MA applications (i.e. 210 days) remain applicable. We believe reduced review times should also apply to extensions of MAs.
We consider that it is not justified that the addition of a new strength (usually only new quality data), or the addition of a pharmaceutical form (generally quality data and bioequivalence data), or a new route of administration (clinical and bioavailability data) justifies a lengthier evaluation time than allocated for a new indication which usually requires the evaluation of a significant amount of new data resulting from a clinical program and maybe additional safety data. As a consequence, we propose that extension applications be assessed within a 90 days assessment period.
In addition the possibility for having accelerated review for innovative extension should follow a timetable of 60 days.

The inclusion of these extension applications as variations must not prevent the marketing authorization holder (MAH) from applying for additional strengths, pharmaceutical forms or route of administration as stand alone MA under separate name. This can be achieved via the inclusion of the original recital 6 of Regulation 1085/2003 and/or Recital 8 of Regulation 1084/2003 in the revised Variations Regulations.

GUIDELINES

The draft detailed guideline for the conditions for classification of variations needs a thorough revision in accordance with the new thinking, e.g. examples of documentation requirements for a Type IB variation not listed in the guideline would clarify the expected level of information.
The information provided in the guideline should be sufficiently comprehensive to minimize different interpretations of that information.
While detailed review of the “Draft Detailed Guideline Referred To In Article 6(1)(A): Conditions For Classification Of Variations” is generally outside the scope of our comments, we note that additional consideration needs to be given to downgrading the classification of changes for biological products.
Additionally, the Guideline should focus on defining Type II and Type IA variations since the remainder will be Type IB by default. The current guidelines are structured with the intent that a change not meeting conditions for a Type IB change defaults up to a Type II change. In the proposed new system this will no longer be the case, therefore the guidelines will need to be restructured to avoid confusion. If a change does not meet conditions for a Type IB change but yet does not appear on the Type II list, by default it would still remain Type IB under the new default system.

TYPE IB BY DEFAULT

The upgrading of Type IB variations, when the Competent Authority (CA) is of the opinion that the referred variation has a substantial potential to have an impact on quality, safety and/or efficacy (articles 9, 13, 18), seems to leave much discretion and be open for divergent interpretations: clear criteria should be defined to prevent this or a procedure should be identified in order to foresee the possibility for discussing the matter between CAs and applicants.
We welcome the option to seek a scientific recommendation in a variation classification from the Agency according to Article 5.

WORKSHARING

A work sharing procedure as referred to in Article 24 and coordinated by the Agency is welcomed. We recommend that following a positive opinion the Varitions always be processed as a Type IA variation.
We support the present proposal of having the EMEA as the body co-ordinating the work-sharing process,
While we are extremely supportive of the proposals to allow for grouping of variations to simplify procedures, the proposals appear to unnecessarily discriminate between the different variation types and also do not fully address commonplace commercial arrangements in the pharmaceutical sector.

ICH

We highly commend the Commission for considering the implications of ICH Quality developments in the Consultation paper. The introduction of the 'design space' concept into the proposed guideline on conditions for classification of variations is very much welcomed, as is the proposal to revise the guideline as more regulatory experience is gained with the application of the quality tools described within ICH Q9 and Q10. In our opinion, the development of the guideline, which is not an Annex to the Variation Regulations and can be easily updated is key to creating a dynamic legislative framework to take into account developments at the ICH quality level.

In addition, we believe that this proposal would be strengthened by amending bullet 2 under Article 6 Guidelines of the legislative text as proposed in the detailed comments.

FEES

The fees system would have to be adapted to the revised post approval changes system to ensure that the Competent Authority received an income related to the workload involved in the handling of variations.

CONSULTATION PAPER

Key item 1 PURELY NATIONAL AUTHORISATION

We continue to actively support the extension of the scope of the Variations Regulations to national variations, as this will be of tremendous benefit to Industry. In order to facilitate a smooth implementation by Member States at the national level, an appropriate transition period should be factored in.

Key item 2 ICH

Design Space

We welcome the proposal that a change within an approved 'design space' does not require a Variations application; however we believe that changes to an approved 'design space' should be assessed in line with the Variations categories , and should not automatically default to a Type II.
It is important that this provision of the consultation paper is mentioned in the Regulation.

Continuous Improvement of Manufacture

Acknowledgement that ICH developments, namely ICH Q8/Q9/Q10 introduce modern tools, could facilitate continuous improvement over the product lifecycle by providing further flexibility for manufacturers that have introduced modern quality tools, is very much welcomed.
Furthermore we are appreciative of the statement "continuous improvement of manufacture should be supported, e.g. by providing further flexibility to manufacturers who have undertaken the efforts to put in place modern quality tools."
We therefore support the drafting of the detailed guideline to discuss where and how these ICH quality tools could be implemented. We believe this will be critical to creating a dynamic legislative framework in the EU to take into account developments at the ICH quality level.
We also believe that the 'Regulatory Agreement' concept has a key role in enabling flexibility for manufacturers that have introduced modern quality tools and as we gain more experience with implementation of ICH Q8, Q9 and Q10, So the final text of the Variations Regulation should be drafted in such a way as to accommodate the introduction of the 'regulatory agreement' concept in the near future.

Key item 3 “DO & TELL” PROCEDURE

The proposed Do and Tell Procedure will facilitate the rapid implementation of minor changes and is therefore a positive change.
The annual report allows more flexibility in the notification of changes.
Guidance as to what needs to be included in an annual report should be provided, with the documentation requirements being kept as simple as possible, with a content focused on the concerned variations.
The grouping of Type I variations is endorsed, as it will limit the number of submissions. Guidance may be needed to indicate what documentation is needed for grouped variations, other than a description of the change and the products involved, e.g. updated documents per product.

We are also supportive that no annual report needs to be filed if no changes are implemented and there is no fixed date for submission.
We consider the new procedures for Type IA and IA_{IN} variations are extremely positive and simplify regulation of changes which are not expected to have any 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 possibility could be removed, it would be important to clarify the limited grounds on which this can happen.
The Regulation should specify that rejection of Type IA variations may only occur where any of the elements listed in paragraph 1 of Annex III is missing.

Key item 4 WORKSHARING

EFPIA strongly supports the introduction of the worksharing proposal considering that it has the potential to significantly lower the administrative burden and redundancy of evaluation for changes to medicinal products.
It is important that the worksharing procedure remains optional for the Marketing Authorisation Holder (MAH). This is stated in the consultation paper, but this should also be clearly mentioned in the Regulation.

The Regulation should stipulate that the worksharing procedure applies to all medicinal products, independently of the evaluation procedure used.

We support the single evaluation co-ordinated by the Agency resulting in an opinion, knowing that the review process will be performed by the Member States. We believe this will ensure consistency across variations themselves, products, and companies.
It will be important that NCAs play an active role in the worksharing procedure to ensure a consistent outcome across the Member States involved. We also believe there must be legally binding timelines for this procedure to be successful.

We would like to emphasize that the worksharing procedure should not trigger duplication of evaluation and delays in approval. The downgrading provision should be included in the Regulation.
In accordance with the current proposal if a Type II variation concerning several products (case (b)) is downgraded to a Type IB, this will result in a second and unnecessary further evaluation at national level; there is always a risk that the discussion in the second step is re-opened at that time. It must be made clear that downgrading the variation should not lead into a request for change in the supportive documentation. The downgrading of the classification of the change to Type IA notification at national level should be applicable to all cases, independently of the number of medicinal products involved in the worksharing procedure.

We believe that all concerns must be raised during the worksharing procedure and that only major grounds of potential serious risk to public health should be the basis of a negative opinion. In addition, special provisions should be added to address the case of a negative opinion with the possibility for the MAH to request a re-examination of the opinion.

Harmonisation of the initial dossier should not be a pre-requisite for the worksharing procedure, although the outcome of a worksharing procedure will result in a harmonised sub-set of the dossier. Additionally, harmonisation of the entire Summary of Product Characteristics should also not be a pre-requisite for labelling changes of a specific section of the SmPC under the worksharing procedure (e.g. addition of a paediatric indication).

The development of detailed guidelines on the practical implementation of the worksharing procedure will be welcome for better defining each step of the procedure, particularly to clarify:
-- who conducts the assessment and how is this recognized by other relevant Competent Authorities;
-- details on the closure procedure, and implementation of the changes.

It would be important to better clarify the combination of the grouping and the worksharing procedure.

Special attention should be paid to the compatibility with the e-CTD requirements. If e-CTD dossiers must be kept up to date by adaptation of the original dossier, this may involve more regulatory burden than the submission of the variation itself, and in particular in the worksharing procedure and/or grouped variations the e-CTD related administrative requirements should be carefully considered.

Key item 5 TYPE IB BY DEFAULT

The principle of Type IB by default, for changes not anticipated in the detailed guideline on classification of changes, is supported. However this proposal raises a concern: the preamble to the detailed guidelines stipulates that where all of the conditions prescribed per change cannot be met, the change defaults to a Type II. This principle is contradictory to the overall aims of the Commission Proposal to simplify the variations system. There will be some changes where it is not possible or appropriate to comply with all of the conditions of the change classification, but such situations may not all have a potential impact on the quality of the product to such an extent that a Type II variation is always needed. 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.

- **There should be a complete, as is feasible, list of Type II variations published as part of the guidance. This list is to be dynamic and should be updated regularly to include the outcome of consultations processes regarding classification of variations.**
- The safeguard clause provides the assessor with the possibility, in exceptional cases, to upgrade the variation to Type II if the applicant has not discussed and agreed the appropriate categorisation in advance, or if the assessor disagrees with the applicant's risk assessment.

Additional points would require further clarification:

A) <u>Use of Safeguard clause</u>

- **Circumstances for upgrading to Type II:** The conditions for reverting a Type IB to a Type II Variation, namely 'substantial potential to have a impact on quality, safety or efficacy ' are open to a wide interpretation .

B) **<u>Timelines</u>**

The potential cumulative timeline of 60 days for EMEA advice plus 30 days for the Type IB Variation which might result in upgrading to the Type II

process (60 days total) is of significant concern to industry.

- **Timeline to obtain an EMEA opinion on classification:** it is considered that the EMEA should provide a recommendation on classification in no more than 30 calendar days, otherwise the need to wait for an opinion will mean this process has no timing advantage over a Type II variation.
- **Timeline for deciding to upgrade from Type IB to Type II:** EFPIA/EBE/EVM considers that the timeline allowed for a MS to upgrade a Type IB to a Type II, and inform the applicant, should be no more than 14 calendar days.
- **Procedural timeline if Type IB upgraded to Type II:** if should be clarified that if a upgrade is considered necessary, the applicant should be notified within 14 days of validation, and thereafter the review clock will continue according to the Type II timeline, with no clock stops or interruptions. EFPIA/EBE/EVM strongly advocates that the clock should not restart, otherwise from a timing perspective the procedure will be longer than for a standard Type II.

C) Documentation

- **Documentation requirements if Type IB is upgraded to Type II:** the content of a Type II variation typically requires an addendum to the Quality Overall Summary, Clinical Overview and or Non-clinical Overview, whereas a Type IB application does not. It should be clarified that if a Type IB is upgraded to Type II, the documentation does not need to be supplemented, reformatted and/or resubmitted.

D) **EMEA recommendation on classification:**

The option for the applicant (at the applicant's discretion) to ask for EMEA opinion on the classification of a new variation is supported. We propose that an applicant wishing to approach the Agency with an unforeseen change would be required to propose a classification for confirmation.

- **Information to be provided to EMEA:** It should be clarified what information EMEA would need to receive in order to provide a recommendation on classification.

- **Transparency of EMEA opinions:** we strongly support the publication of EMEA opinions on classification and for such opinions to feed into the continuous update of the detailed guideline. This is an optimal route for bringing a change initially unforeseen, but likely to recur in the future, into the public domain in a consistent fashion.
  Over time this is expected to decrease the number of changes that are not foreseen by the detailed guidelines and hence the number of Type IB by default applications.

E) Right to Appeal EMEA recommendations: The possibility for the MAH to appeal on the categorisation of the variations

8.1 CLASSIFICATION OF VARIATIONS

The proposal to publish guidelines, as opposed to Annexes to the Regulations, to classify variations is appreciated. Not only will this add flexibility but ensure that the document evolves through the introduction of a mechanism to allow scientific recommendation regarding unclassified variations.
The currently proposed definition of major impact/substantial potential negative impact on Quality, Safety ands Efficacy is not clear and there is a risk of divergent interpretations.

Publication of EMEA recommendations for Type II case definitions should be compiled in a guidance document
There is still a need to down regulate changes to biological products to be handled with greater parity along side Chemical Entities than already proposed

Any variation not listed in the proposed detailed guidelines will be considered as type IB by default. We believe that the current list is not extensive enough.

We propose a new type IA category for administrative changes for module 3 (similar to "NEW.7. Administrative change in the summary of product characteristics, labelling and package leaflet/insert", page 47 of the Annex). There are many administrative changes to be submitted on module 3 (like contract laboratories or supplier address changes, changes to the method coding system, changes to floor plans etc.) Those purely administrative changes, where no supporting scientific data are required, should only require a Type IA (annual report) notification.

We suggest that further listing is included e.g. for Type II for major changes.
In the proposed detailed guideline only a very limited number of type II variations has been defined, there are more opportunities for SmPC changes than those mentioned in the guideline.

8.2 GROUPING VARIATIONS

EFPIA supports the concept of grouping of variations as it may significantly reduce the number of submissions. However, while we are supportive of the proposals to allow for grouping of variations to simplify procedures, the proposals appear to unnecessarily discriminate between the different variation types. They also do not fully address commonplace commercial arrangements in the pharmaceutical sector with respect to the MAH.
The proposed wording of Articles 7 and 24 suggests that, with the exception of Type IA variations, grouping of multiple variations to several MAs requires use of the worksharing procedure, regardless of whether only one or more than one relevant authority is involved. In cases where several variations to several MAs require submission to only a single authority (e.g. all MAs are Centralised), grouping should be possible without recourse to worksharing for **all variation classifications**.

In addition, the provisions on grouping and worksharing appear to be applicable only in cases where all concerned MAs are held by the same MAH. In many cases, different marketing authorisation holders may hold "duplicate" MAs for products where licensing agreements are in place, or national MAs for a product may be held by different affiliate companies in different Member States. In order to fully realise the benefits offered by grouping and worksharing, their use should be permitted where MAHs have licensing agreements in place or are part of the same group of companies. Further clarification on this point is provided in Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03, Section E, point 3, 7th paragraph, p. 11).

Guidance will be required to ensure that it is 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.

The final decision for whether to group variations should be made by the MAH and not required as mandatory by a national competent authority.

8.3 CLARIFICATION OF DEADLINES

Update of MA after close of procedure

Although the draft Regulation (article 22) stipulates that a MAH may implement the change once a notification is deemed accepted or the relevant authority has accepted the notification or variation, it is not clear how this then works with regard to promotional material, as this must be in line with the officially approved SmPC wording which is only available after the Commission or competent authority has amended the MA. Introducing a six months delay ('sweep' mechanism) for e.g. Type II variations would not be feasible and we recommend to keep the current business practice of 45 or 30 days respectively.

DRAFT REGULATION		
Page, Section title, article	**COMMENT AND RATIONALE**	**PROPOSED CHANGE**
Throughout the text	All occurrences of 'one month' should be amended to '30 days for consistency and clarity. It should be clarified that 'days' refer to 'calendar days'	
Article 3.2 (b)	The definition of minor variation of type IA encompasses also the changes subject to immediate notifications	- a minor variation of Type IA, as defined in paragraph 3 ***and 4***; or
Article 3.3 & Article 3.6	We would recommend to modify the definition of a 'Minor variation of Type IA' laid down in Article 3.3 of the proposed Regulation, as the term "negative" may have a deleterious interpretation. The use of the words negative seems inappropriate as the MAH usually has to demonstrate in the data supporting the variation that there is no negative impact or that the benefit/risk assessment is not adversely affected Related to this comment, the definition of 'Major variation of Type II' as stated in Article 3.6 should also be revised to be in line with the proposed type I definition: As an example, the addition of a new indication which is considered as a Type II variation can not be qualified as having negative impact on the quality, safety or efficacy of a medicinal product. We propose to amend the definitions accordingly.	We propose to re-phrase these points as follows: *Article 3 Definitions* 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 product concerned. 6. Major variation of Type II means a variation, which is not an extension, and which has a substantial potential to have an ~~negative~~ impact on the quality, safety and efficacy of the medicinal product concerned.
Article 3.7	The Public Consultation Paper mentioned that it is proposed to introduce generic definitions of variations, e.g. line extensions. However throughout the whole regulation the word "extension" is used and not "line extension".	
Article 3.8	For MRP/DCP products it is logical to use the existing RMS for the variation procedure and for	8. "Reference Member State" means the Member State as referred to in Article 28 of Directive 2001/83/EC and in Article

	national products when there is no RMS assigned that the holder has the choice. We recommend switching the order. "Approval" should be defined for clarity.	32 of Directive 2001/82/EC, or in absence of such, the Member State chosen by the holder with a view to the application of this Regulation. Additional definition to be considered: "Approval" means notification of acceptance of a minor variation or major variation provided to the holder by the competent authority at closure of a procedure as a result of the examination of a variation submitted by the holder.
Article 4 Classification of variations	The consultation paper highlights the need to support continuous improvement of manufacture, by providing further flexibility to manufacturers who have undertaken the efforts to put in place modern quality tools (e.g. Q8, Q9 and Q10). It proposes that this will be addressed in the Commission guideline on variations, however no text is currently included in the draft Regulation as a basis for this.	Add **3. By way of derogation from paragraphs 1 and 2, where a regulatory agreement has been approved by the relevant Competent Authority, the arrangements defined within this agreement will be applicable. This will be further described in the detailed guidelines referred to in point (a) of Article 6(1).**
Article 4.2	It is **highly** welcomed 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. An upgrade 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. 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 submits it as such.	….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**.
Article 5, Scientific recommendation for unforeseen variations	Further to the comments above, the following changes to the draft Regulation are proposed.	*Article 5 Scientific recommendations on unforeseen variations* 1. ….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 within 30 days following the receipt of the request, taking…… The Agency 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 IB variation, and a statement whether the recommendation is product-specific in nature or is generally applicable to other medicinal products. 2. The Agency shall publish the recommendations delivered in accordance with paragraph 1, subparagraph 2, after deletion of all information of commercial confidential nature. 3. 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.. 4. The Agency shall transfer published recommendations into the detailed guidelines referred to in point (a) of Article 6(1) on a yearly basis.
Article 6 Guidelines	While Article 6(2) refers to the necessity for the proposed guidelines to be updated regularly to take account of "scientific and technical progress", an explicit reference in the Regulation to important new	Amend bullet 2 under Article 6 Guidelines as follows: 2. Guidelines referred to in the point (a) paragraph 1 shall be regularly updated, taking into account the recommendations delivered in accordance with Article 5,

	ICH Quality concepts (the importance of which is mentioned in the public consultation paper) is deemed important.	as well as scientific and technical progress, **including new ICH quality developments**. And introduce a third bullet as follows: 3. Continuous improvement of pharmaceutical manufacturing should be by supported by providing flexibility to manufacturers that have introduced modern quality tools, described within ICH Q8, Q9 and Q10; for example by introducing the regulatory agreement concept.
	It is important to make sure that no specific local requirements will be added on top of the ones defined in the detailed guideline. by the Member States	Suggested additional paragraph after 6.2: ***"All relevant national competent authorities are deemed to limit their regulatory requirements to what is listed in the detailed guideline on the conditions for classification of variations."***
Article 7.2 (a)	The term "package inserts" is not usually used in the EU, so we suggest removal of the words "or insert". In addition, it should be clear that the grouping in Art.7(2)(a) applies where labelling **or** the package leaflet are revised.	(a) where a variation leads to the revision of the summary of product characteristics, labelling and***/or*** package leaflet ~~or insert~~, this revision shall be considered as part of the same variation
Article 7.2 (b)	In many cases, **different** marketing authorisation holders may hold "duplicate" MAs for products where licensing agreements are in place. These products will usually be affected by the same variations (e.g. SPC or manufacturing changes), and it is reasonable that these variations should require only a single assessment	(b) where several minor variations of Type IA to the terms of one or several marketing authorisations ~~owned by the same holder~~ are notified simultaneously to the same relevant authority, a single notification as referred to in Article 8, 12 or 17 may cover all such variations;
Article 7.2 (d)	In addition, Art 7(2)(d) concerns the worksharing procedure which may be used where the same product has purely national MAs in several MS. In such cases, it is likely that there will be a different MAH in each MS: the MAH may be either local affiliate companies that are part of the same group of companies, or companies may have licensing agreements in place. The full advantage of the proposed new flexibility of	(d) Where a minor variation of Type IB, a major variation of Type II, an extension and/or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing *authorisations that need to be assessed by more than one competent authority* ~~owned by the same holder~~, , such variations may be covered by a single application as referred to in Article 24

	grouping variations would not be realised, therefore, if the wording "owned by the same holder" remains. We suggest that either this wording be deleted, or that the Regulation be amended to include MAs held by different MAH. The worksharing procedure described in point (d) should be reserved for those variations that would normally have to be assessed by **more than one authority** (e.g. affecting national MAs in more than one MS, or affecting products approved via a mixture of national, MRP/DCP and/or centralised procedures).	
Article 7.2	It appears from Article 7 that Type IB and Type II variations that affect several MAs may only be grouped if the worksharing procedure (Art 24) is used. We can see no justification for restricting the grouping of variations affecting several MAs for submission to the **same authority** to Type IA variations (Art 7(2)(b)). For example, where a Type II variation concerns a major change to the quality data for an active substance used in several different products, it should be permissible for the variations to the several MAs to be grouped to allow for a single assessment of the change without recourse to worksharing. We suggest that additional derogations from the first paragraph be added to paragraph 2	Suggest adding a point to paragraph 2: ***"(x) where a minor variation of Type IB, a major variation of Type II or a group of variations falling into one of the categories listed in Annex II relating to changes that concern several marketing authorisations are submitted simultaneously to the same relevant authority, such a variation may be covered by:*** ***– a single application as referred to in Articles 10, 14 and 19 where at least one of the referred variations is a major variation of Type II;*** ***– a single notification as referred to in Articles 9, 13 and 18 where at least one of the referred variations is a minor variation of Type IB."***
CHAPTER II NATIONAL PROCEDURE		
Article 8 "Do and Tell" Procedure for Type IA Variations [Nat.]	The consultation paper clearly states that Type IA variations do not require any prior approval and can be implemented anytime before notifying the competent authorities. Paragraph 2. of Article 8 introduces ambiguity with regard to implementation. The following addition to the text is therefore proposed.	1. Where a minor variation of Type IA is made, the holder shall submit to the relevant authority a notification including the elements listed in paragraph 1 of Annex III. This notification shall be submitted: (a) forthwith in the case of minor variations requiring immediate notification; (b) within twelve months following implementation of the variation in the other cases.

	The timeline for acknowledging receipt and validating the application should be shortened. This timeline reflects current business practice. In general, validation timelines should be included in the legal text. A notification cannot be rejected. It is suggested that article 21(1) be amended to reflect the 'Do and Tell' procedure more accurately and include the impact of the 'Report within 12 months' variant of the Type IA procedure.	**2. Type IA variations do not require any prior approval and can be implemented anytime before notifying the relevant authority.** 3. Within **14 calendar days** following receipt of a notification referred to in paragraph 1, the relevant authority shall **acknowledge the validity of the notification,** close the procedure in accordance with Article 21(1) **and inform the holder accordingly.**
Article 9 "Tell, Wait and Do" Procedure for Type IB (Nat.)	We recommend clarifying the legal text for the evaluation of Type IB variations, regarding the required documents and the possible switch mechanism to Type II. If a Competent Authority determines that the classification of a variation should change, this should be notified to the Marketing Authorisation Holder within the first period of assessment based on detailed grounds with the possibility for the MAH to raise objections. For unclassified variations, a re-submission should not be necessary, if the Type IB is switched to Type II based on an authority request. The timetable would only be amended to reflect the further Type II procedure. A clock-stop which may be necessary to submit extra documentation would be acceptable, but the procedure should *not* be set back to zero and/or resubmission required. This would be particularly unacceptable, if the holder did not initially have the option to submit directly as a Type II.	1. With regards to minor variations of Type IB, the procedure laid down in paragraphs 2 to **7** shall apply. 2. The holder shall submit to the relevant authority a notification including the relevant elements listed in paragraph 2 of Annex III. If the notification fulfils the requirements laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid notification **within 14 calendar days**. 3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in **paragraph 2 subparagraph 2** the relevant authority has not sent the holder its opinion provided for in paragraph 4, the notification shall be deemed accepted. Where the notification is accepted, the relevant authority shall **inform the marketing authorization holder and** close the procedure **within 7 calendar days** in accordance with Article 21(1). 4. **Within 30 days following the acknowledgement of receipt of a valid notification referred to in**

	A clarification has been included to prevent changing the classification if it has previously been determined by the EMEA according to Article 5. 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.	**paragraph 2 subparagraph 2** and where the relevant authority is of the opinion that the notification cannot be accepted, it shall inform the holder, stating the grounds on which its opinion is based. **In case of disagreement the MAH has the right to make his position heard.** (2 last sub paragraphs unchanged) 5. **Within the period laid down in paragraph 3, b** ~~**B**~~y By the way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) **and a scientific recommendation on the classification by the Agency has not been given according to Article 5,** and the relevant authority is of the opinion that the referred variation has a substantial potential to have an ~~negative~~ impact on the quality, safety and efficacy of the medicinal product concerned, the relevant authority will inform the applicant within 14 days from the date of acknowledgement of receipt of a valid notification and the variation shall be evaluated in accordance with the procedure laid down in paragraphs **3** to 5 of Article 10. 6. Where an amended notification has been submitted in accordance with paragraph 4, the relevant authority shall assess it within 30 days following its receipt and close the procedure in accordance with Article 21(1). 7.
Article 10 Prior approval procedure for Type II {nat.}	Timelines should be added to reflect that if the application fulfils the requirement laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid application. Evaluation periods for safety related changes and AEs are suggested to be shortened and fixed as 30	1. … 2. …If the application fulfils the requirement laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid application **within 14 calendar days.** 3. The relevant authority shall evaluate the valid application

	days to allow the speedy update of product information for the benefit of patients. A re-structuring of the paragraphs is suggested to provide better clarity on procedural timelines for specific cases. Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information within a time limit set by that competent authority. We recommend fixing the maximum timeline for the assessment of the supplementary information provided by the holder to avoid any delays or unpredictability in timelines. This has been added to paragraph 4. Within the period laid down in paragraph 3, the relevant authority shall, where it reaches a final opinion on the application, close the procedure in accordance with Article 21(1) and inform the holder of the approvable notification.	referred to in paragraph 2 within 60 days following its receipt. By way of derogation from the first subparagraph: (a) the relevant authority may reduce the period referred to in that subparagraph, having regard to the urgency of the matter. (b) **The period referred to in that subparagraph shall be 30 days if the change is related to adverse events , new safety information or as a consequence of Article 9 (5).** **(c) The period referred to in that subparagraph shall be 90 days if the variation is concerning a change or addition of a therapeutic indication or a non-food producing target species.** 4. Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information within **90 days. The holder may request to extend this period with appropriate justification.** The relevant authority shall take the supplementary information into account within 30 days of its receipt. ~~In this case the period laid down in paragraph 3 may be extended for a further period to be determined by the relevant authority.~~ 5. Within the period laid down in paragraph 3, the relevant authority shall, where it reaches a final opinion on the application, **inform the holder that the variation isapproved and provide him with the SmPC, leaflet and labelling, 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.**”
CHAPTER III MUTUAL RECOGNITION/DECENTRALISED PROCEDURE		
Article 12 “Do and Tell” Procedure for Type IA Variations [MRP]	Similar comment as for Article 8 with reference to paragraph 2 of Article 12.	The proposed rewording is the same as for Article 8 with only a few adjustments to take into consideration the differences of procedures under consideration

Article 13 "Tell, Wait and Do" Procedure for Type IB Variations [MRP]	Similar comment as for Article 9.	1. The proposed rewording is the same as for Article 9 with only a few adjustments to take into consideration the differences of procedures under consideration
Article 14 Prior approval procedure for Type II variations MRP	Timelines should be added to reflect that if the application fulfils the requirement laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid application. Evaluation periods for safety related changes and AEs are suggested to be shortened and fixed as 30 days to allow the speedy update of product information for the benefit of patients. A re-structuring of the paragraphs is suggested to provide better clarity on procedural timelines for specific cases. Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information within a time limit set by that competent authority. We recommend fixing the maximum timeline for the assessment of the supplementary information provided by the holder to avoid any delays or unpredictability in timelines. This has been added to paragraph 4. Within the period laid down in paragraph 3, the relevant authority shall, where it reaches a final opinion on the application, close the procedure in accordance with Article 21(2) and inform the holder of the approvable notification.	2….. If the application fulfils the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid application **within 14 calendar days** and inform the other relevant authorities of the date of the start of the procedure laid down in paragraphs 3 to 6. 3. … By way of derogation from the first subparagraph: (a) the competent authority of the reference Member State may reduce the period referred to in that subparagraph, having regard to the urgency of the matter. (b) The period referred to in that subparagraph shall be 30 days if the change is related to adverse **events**, new safety information or as a consequence of Article 13 (5). (c) The period referred to in that subparagraph shall be 90 days if the variation is concerning a change or addition of a therapeutic indication or a non-food producing target species. 4.Within the period laid down in paragraph 3, the competent authority of the Reference Member State may request the holder to provide supplementary information within **90 days. The holder may request to extend this period with appropriate justification.** …In this case: (a) the competent authority of the reference Member State shall inform the other competent authorities concerned of its request for supplementary information: (b) the procedure shall be suspended until such supplementary information has been provided: (c) the competent authority of the reference Member State shall take the supplementary information into

		account within 30 days of its receipt. ~~The period laid down in paragraph 3 may be extended for a further period to be determined by the competent authority of the reference Member State.~~ 6. Where, pursuant to paragraph 5, the draft decision referred to in paragraph 3 has been recognised by all relevant authorities, the competent authority of the Reference Member State shall inform **the holder within 7 calendar days that the variation is approved and provide him with the SmPC, leaflet and labelling, and** close the procedure in accordance with Article 21(2)
Article 16	We do not understand the proposal of CMD(h) referral for variations under Art. 12 (i.e. Type IA variation) as these are notifications. Referrals should be applicable to Type IB and Type II variations only.	1. Where, during the course of the procedures laid down in Articles **13** to 15, ….
CHAPTER IV CENTRALISED PROCEDURE		
Article 17 "Do and Tell" Procedure for Type 1A Variations [Centr.]	Similar comment as for Article 8 with reference to paragraph 2 of Article 17.	The proposed rewording is the same as for Article 8 with only a few adjustments to take into consideration the differences of procedures under consideration
Article 18 "Tell, Wait and Do" Procedure for Type IB Variations [Centr.]	We recommend clarifying the legal text for the evaluation of Type IB variations, regarding the required documents and the possible switch mechanism to Type II. If a Competent Authority determines that the classification of a variation should change, this should be notified to the Marketing Authorisation Holder within the first period of assessment based on detailed grounds with the possibility for the MAH to raise objections. For unclassified variations, a re-submission should not be necessary, if the Type IB is switched to Type II based on an authority request.	1. With regards to minor variations of Type IB, the procedure laid down in paragraphs 2 to **7** shall apply. 2. The holder shall submit to the Agency a notification including the relevant elements listed in paragraph 2 of Annex III. If the notification fulfils the requirements laid down in the first subparagraph the Agency shall acknowledge receipt of a valid notification **within 14 calendar days**. 3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in **paragraph 2 subparagraph 2** the Agency has not sent the

	The timetable would only be amended to reflect the further Type II procedure. A clock-stop which may be necessary to submit extra documentation would be acceptable, but the procedure should *not* be set back to zero and/or resubmission required. This would be particularly unacceptable, if the holder did not initially have the option to submit directly as a Type II. A clarification has been included to prevent changing the classification if it has previously been determined by the EMEA according to Article 5. 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.	holder its opinion provided for in paragraph 4, the opinion shall be deemed favourable. Where the opinion of the Agency is favourable, the Agency shall **inform the marketing authorization holder and** close the procedure **within 7 calendar days** in accordance with Article 21(3). 4. **Within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 subparagraph 2** and where, the Agency is of the opinion that the notification cannot be accepted, it shall inform the holder and the other relevant authorities, stating the grounds on which its opinion is based. **In case of disagreement the MAH has the right to make his position heard.** (2 last paragraphs unchanged) 5. **Within the period laid down in paragraph 3, b B**~~B~~y the way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) **and a scientific recommendation on the classification by the Agency has not been given according to Article 5,** and the Agency or the **European** Commission is of the opinion that the referred-variation has a substantial potential to have a ~~negative~~ impact on the quality, safety and efficacy of the medicinal product concerned, , the Agency will inform the applicant within 14 days from the date of acknowledgement of receipt of a valid notification and variation shall be evaluated in accordance with the procedure laid down in paragraphs **3** to 6 of Article 19. 2. Where an amended notification has been submitted in accordance with paragraph 4, the relevant authority shall assess it within 30 days following its receipt and close the procedure in accordance with Article 21(3).

Article 19 Prior approval procedure for Type II variations CP	Timelines should be added to reflect that if the application fulfils the requirement laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid application. Evaluation periods for safety related changes and AEs are suggested to be shortened and fixed as 30 days to allow the speedy update of product information for the benefit of patients. A re-structuring of the paragraphs is suggested to provide better clarity on procedural timelines for specific cases. Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information within a time limit set by that competent authority. We recommend fixing the maximum timeline for the assessment of the supplementary information provided by the holder to avoid any delays or unpredictability in timelines. This has been added to paragraph 4. Within the period laid down in paragraph 3, the relevant authority shall, where it reaches a final opinion on the application, close the procedure in accordance with Article 21(3) and inform the holder of the approvable notification.	1 . … 2. … If the application fulfils the requirement laid down in the first subparagraph, Agency shall acknowledge receipt of a valid application **within 14 calendar days.** 3. The competent Committee of the Agency shall issue and opinion on the valid application referred to in paragraph 2 within 60 days following its receipt. By way of derogation from the first subparagraph: (a) the competent Committee of the Agency may reduce the period referred to in that subparagraph, having regard to the urgency of the matter. **(b) The period referred to in that subparagraph shall be 30 days if the change is related to adverse events, new safety information or as a consequence of Article 18 (5).** (c) The period referred to in that subparagraph shall be 90 days if the variation is concerning a change or addition of a therapeutic indication or a non-food producing target species. 4. Within the period laid down in paragraph 3, the competent Committee of the Agency may send the holder a request for supplementary information within **90 days. The holder may request to extend this period with appropriate justification.**. The procedure shall be suspended until such supplementary information has been provided. The competent Committee of the Agency shall take the supplementary information into account within 30 days of its receipt. ~~In this case the period laid down in paragraph 3 may be extended for a further period to be determined by the Agency.~~

		5. Within the period laid down in paragraph 3, the Agency shall, where competent Committee of the Agency reaches a final opinion on the application, inform the holder within 7 calendar days and close the procedure in accordance with Article 21(3).
CHAPTER V SECTION 1 CLOSURE OF PROCEDURES AND IMPLEMENTATION		
Article 21 Closure of Procedures	We fully support the principle set forth in the Article 22 that minor (Type I) and major (Type II) changes can be implemented prior to amending the marketing authorisation and welcome the legal provisions in this respect. It should be clarified in the legal text that variations can be implemented in accordance with Article 22 and that Article 21 purely refers to the process for closing procedures and updating marketing authorisations where necessary. This should also be clearly stated in the guidelines referred to in point (a) of Article 6(1). In principle rejections of Type IA variations are not possible. This may only be justified because important documentation is missing. We agree that an amendment to the Marketing authorisation can be done via a "sweep" mechanism every 6 months. However for major type II variations which involve changes to the product information, we suggest that MA decisions are updated within 30 calendar days for national authorisations and 45 calendar days for Commission decisions, to allow the timely availability of amended product information in EudraPharm as well as officially approved text for creation of promotional materials. The EMEA should make provisions to publish revised product information prior to revision of the Commission Decision, to ensure that patients have access to the	**1. Without prejudice to Article 22, w**here reference is made to this paragraph, the following provisions shall apply (a) The relevant authority shall forthwith provide the holder within 7 calendar days with the following information: - whether the variation or notification is accepted or rejected; **in case of Type IA variations, rejection may only occur if any of the elements listed in paragraph 1 of Annex III is missing;** - where the variation or notification is rejected, the grounds on which that rejection is based; – whether the variation or notification requires any amendment to the terms of the marketing authorisation. (b) Where necessary, the relevant authority shall amend the marketing authorisation in accordance with the accepted variation or notification **- within 30 calendar days following receipt of the notification referred to in paragraph 1 of Article 8 for type IA variations;** - within **30 calendar days** after sending the information referred to in point (a) in the case **of major variations**;- within **180 calendar days** after sending the information referred to in point (a) in the other cases

	most up to date texts. In addition, for Type II variations, the proposed 6-month period for sending the revised marketing authorisation seems incompatible with some other related regulatory activities such as activities in third countries mentioned above as well as the initiation of reimbursement/price processes. The Committee of the Agency is taking part in the opinion process.	**2. Without prejudice to Article 22, w**here reference is made to this paragraph, the following provisions shall apply: (a) The competent authority of the reference Member State shall forthwith provide the holder and the other relevant authorities with the following information: - whether the variation or notification is accepted or rejected; **in case of Type IA variations, rejection may only occur if any of the elements listed in paragraph 1 of Annex III is missing;**… (b) Without prejudice to Article 16, each relevant authority shall, were necessary, amend the marketing authorisation in accordance with the accepted variation or notification **- within 30 calendar days following receipt of the notification referred to in paragraph 1 of Article 8 for type IA variations;** - within **30 calendar days** after sending the information referred to in point (a) in the case **of major variations**; - within **180 calendar days** after sending the information referred to in point (a) in the other cases. 3. **Without prejudice to Article 22, w**here reference is made to this paragraph, the following provisions shall apply: (b) the Commission shall, where necessary and based on **an opinion by the competent Committee of** the Agency, amend the marketing authorisation **pursuant to Articles 10 and 32 of Regulation 726/2004 and** update the Community Register of Medicinal Products provided for in Articles 13(1) and 38 (1) of Regulation 726/2004 accordingly. (c) The amendment to the marketing authorisation referred to in point (b) shall be made: - **within 30 calendar days following receipt of the notification referred to in paragraph 1 of Article 8 for type IA variations;** - within **45 days** following receipt of the information referred to

		in point (a) in the case **of major variations;** - within six months following receipt of the information referred to in point (a) in the other cases. **Add:** **Where a variation affects the summary of product characteristics, labelling and/or package leaflet, the Agency shall make the amended product information available to the public without delay.**
Article 22 Implementation by economic operators	Change the title for better clarity	Implementation ~~by economic operators~~ **of variations** –
CHAPTER V SECTION 2 SPECIAL PROCEDURES		
Article 23 Extensions of Marketing Authorisations – timeframes	The assessment time needed for the new clinical data presented for a new therapeutic indication seems to be equivalent to any new quality data provided for a new strength. New indications, e.g. paediatric indications, are often related to lower tablet strengths or new formulations and we strongly recommend that these can be assessed within the variation timelines to allow a speedy access for patients.	*Article 23 Extensions* An application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as laid down in Articles 10 (3), 14(3) or 19 (3) ~~as for granting of the marketing authorisation to which it relates.~~
	We are concerned that the regulation could be interpreted as preventing a company from filing an application for a new marketing authorisation, instead of applying for a variation or an extension of an existing authorisation, in particular for the purpose of the addition of a new therapeutic indication. In order to clarify that a new marketing authorisation application can be filed in such a case we suggest the relevant Recital of the current Regulations on variations remains included in the revised Variations Regulation.	Recital 6 of the Variations Regulation 1085/2003, and Recital 8 of the Variations Regulations 1084/2003 which read as follows: "It is necessary to clarify the definition of an 'extension' to a marketing authorization, although it should still be possible to submit a separate, full application for marketing authorization for a medicinal product which has already been authorized but under a different name and with summary of product characteristics."
Article 24 Worksharing procedure	The consultation paper (Key Item 4: "Worksharing") indicates that the EMEA opinion, if positive, triggers	The addition of the following text may clarify:

	a 'downgrading' of the classification of the change. This downgrading however is not reflected in the draft Regulation. The downgrading provision should be included into the Regulation. In addition, the closure of the procedure and implementation of the change(s) at national level should be clarified.	**8. Where the Agency assessment results in a positive opinion, this results in a downgrading of the classification of the change to a Type IA 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 8(2), Article 12 (2) or Article 17(2).**
	Special provisions should be added to address the case of a negative opinion issued by the Agency with the possibility for the MAH to request a re-examination of the opinion.	
	The development of detailed guidelines on the practical implementation of the worksharing procedure will be welcome for better defining each step of the procedure. Direct reference to the guidelines in the Regulation is necessary to secure harmonised implementation.	The addition of the following text may clarify: **In consultation with Member States, the Commission shall draw up and publish detailed guidance on the worksharing procedure.**
Article 24.1	The first paragraph should make clear that the worksharing procedure can be used 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: -- one product authorised in several Member States and -- several, distinct medicinal products. In addition, it should be clearly stated that the use of the worksharing procedure remains optional for the MAH. For grouped variations submitted across several marketing authorisations, there may be situation where in which a variation could affect products approved via different routes. (e.g. some old	We suggest revising the text as follows: *1.* Where a minor variation of Type IB, a major variation of Type II, an extension and/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**(s)** 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 the following two cases:*** ***(a) where the change concerns one given medicinal product that is authorised in several Member States,*** *but regardless of the route of granting of each of the Marketing Authorisation* ***(b) where the change is common to several, distinct medicinal products,*** *but regardless of the route of granting of each of the Marketing Authorisations.* The holder**(s)** shall submit to the Agency an application

	product are registered via MRP in EU 15 and via NP in new MSs, for class label changes for products approved by any route) Also, it should also be possible for different MAHs (either affiliate companies that are part of the same group, or companies with licensing agreements in place) with related products affected by the same variations to use the worksharing procedure.	accompanied by the elements listed in points (a) to (g) of paragraph 2 of Annex II.
Article 24. 2	The validation period should be defined. We propose 14 calendar days.	We suggest revising the text as follows: *If the application fulfils the requirements laid down in the first and second subparagraphs, the Agency shall acknowledge receipt of a valid application* **within 14 calendar days**.
Article 24.3(a)	The worksharing procedure should operate for Type IB in accordance with the usual assessment time: 60 days should be shortened to 30 days.	We propose the following changes: *3. The Agency shall issue an opinion on the valid application referred to in paragraph 2 within:* *(a)* **30** ~~60~~ *days following receipt of the valid application in the case of minor variations of Type IB* ~~*or major variations of Type II*~~ (*b) 60 days following receipt of the valid application in the case of* ~~*minor variations of Type IB or*~~ *major variations of Type II* *7. Upon request from the Agency, concerned Member States shall provide any information related to the marketing authorisations affected by the variations, which is deemed relevant for the Agency for the purpose of:* *- verifying the validity of the application referred to in paragraph 2;* *- issuing the* **final** *opinion referred to in paragraph* **3** ~~*6*~~.
Article 26 Urgent Safety Restriction	Please amend Article 26 to reflect the current business practice. A timeline for implementation of an urgent safety	*Article 26 Urgent Safety Restriction* 1. … 2. The holder shall take urgent safety restrictions where

	restriction should be agreed between the holder and the relevant authorities. It is not clear why an urgent safety restriction (USR)requires a formal variation procedure following the closure of the USR procedure. All relevant information should have been submitted in the USR, and all relevant competent authorities will have had an opportunity to assess the changes in the USR. The new proposal to require a Type IA variation (instead of a Type II) already indicates that this is a purely administrative requirement. Proposal for revised legal text which deletes the requirement for a variation following an USR	requested by a relevant authority. 3. <u>The urgent safety restriction referred to in paragraphs 1 or 2 shall be implemented within a timeframe, as agreed with the relevant authorities.</u> 4. ~~Where an urgent safety restriction is taken, the holder shall submit the corresponding variation within 15 days following the initiation of that restriction.~~

ANNEXES		
Annex I Extension of Marketing Authorisation		
1(c), first indent	In order to allow for an efficient preparedness for a potential influenza pandemic situation, It is important to foresee a legal basis allowing the use of a variation procedure (rather than a lengthy line extension) for the strain update of influenza vaccines prepared from viruses with pandemic potential and intended for use outside of the core dossier context (i.e. so-called “pre-pandemic” vaccines). An efficient preparedness relies on a rapid procedure in order to take into account the continuous strain evolution.	Changes to the following indent: *(c) “replacement of a biological active substance [….], with the exception of:* – pre-pandemic and pandemic vaccines
Annex II		
	The addition of a title may make the purpose of this Annex clearer.	Annex II: **Cases for grouping of variations**
	The legal possibility to group variations in one application for one MA or for several MAs (for example many changes to an SmPC or a number of IA/IB variations, or class labelling) is welcomed. However, it seems that in most cases the variations still have to be consequential. Consideration should be given to expanding the cases in which variations can be grouped e.g. update for compliance/new regulatory requirement/site transfer/update for renewal.	
	The grouping of changes should be facilitated in order to reduce the workload. This applies especially to Point 4 which should include a general update and harmonisation of a range of similar products independently of PSURs or class-labelling.	No. 4: All changes relate solely to the changes to the SPC, labelling and/or package insert, e.g. harmonisation of a range of similar products.
	For changes to chemistry, manufacturing and controls, grouping opportunities are restricted to consequential variations or to changes within a process/quality improvement project. It should be clear that other changes made 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. Other projects, for example site changes, should also be within scope . We suggest that point 6 should also include general dossier-updates (e.g. re-formatting) without any change of procedures. We also recommend that point 6 is broader to include drug substance	No. 6: All variations in the group relate to one of the following: • a project intended to improve or update the manufacturing process and the quality of the medicinal product or the drug substance or the dossier (e.g. re-formatting without procedural changes). • a project to transfer manufacture or controls to a new or additional site, where no negative change in quality or performance is demonstrated

	and finished product.	
	We recommend further consideration of the maintenance of Point 7 in Annex 2 in light of the current discussion on the revision of the European Pharmacovigilance in particular with respect to the Pharmacovigilance System and the concept of Master File.	
	In the context of simplification and enhancement of flexibility, we suggest additional possibilities for grouping in certain cases: - combination of points 10 and 11.	The following points should be added: 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.
	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 Annex II	
Annex III		
	The addition of a title as for Annex I may make the purpose of this Annex clearer.	Annex III: **Documentation for the variation applications (Type IA, IB, II and Extension)**
1 (c)	Please clarify that replacement pages for regulatory dossiers are required.	1. … (c) …That description shall include all necessary documents demonstrating that the conditions laid down in the detailed guidelines referred to in point (a) of Article 6(1) for the referred variation(s) are met, including amendments to the regulatory documents.
1(d)	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;
1	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	**Add a new bullet (h)** all documents amended as a result of the variation(s);

	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'.	