European Medicines Agency

London, 3 January 2008
Doc. Ref. EMEA/INS/550862/2007

EMEA COMMENTS ON

COMMISSION REGULATION (EC) No …/..

of […]

concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Process and general comments

EMEA is pleased to provide comments on the Commission's draft regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. As a general comment, EMEA welcomes the overall streamlining of the handling of variations. However, we are concerned that the flexible and simplified submission requirements are not associated with a simplification of administrative processing and decision-making to the same extent at the level of the regulatory authorities. In general, a more in-depth reflection on how to further reduce the number of post-authorisation changes to a Marketing Authorisation, requiring review by regulatory authorities, would be welcomed.

The challenge for EMEA remains the need to continue to ensure its public health responsibilities in the light of increasing demands on the regulatory network. The EMEA's main concerns are therefore those which have the potential to have a major impact on the capacity of EMEA's Scientific Committees, its Working Parties and experts i.e. the proposal for a scientific recommendation on unclassified variations and the work sharing proposals where scientific involvement from EMEA is foreseen. Given the potential for these proposals to place additional strain on the available resources, we are concerned about how they can be implemented in practice.

The EMEA comments, which were presented and discussed by the relevant Scientific Committees are summarised under the articles of the regulation below. More detailed EMEA comments and wording proposals can be found in the annotated version of the draft Regulation which is provided as a separate document. Contributions from specific Working Parties and HMPC are provided in the Annex to this document.

Please note that work is continuing on the guideline review and further contributions will be provided to the Commission, in the light of the final approach taken by the Regulation on classification. This also applies in the area of Advanced Therapy medicinal products, for which internal discussions are still ongoing. It will also be important to ensure that the proposals are compatible with any new legislative proposals expected to be developed on Pharmacovigilance

The financial implications of the final approach will need to carefully reviewed, and the EMEA Fee Regulation will require significant revision before implementation of the new proposals. EMEA would like to be closely associated with this revision.

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Specific comments

1. Article 2: Scope

In the current variations regulation, 1085/2003, Article 1 states "….This Regulation also applies for the examination of applications of variations to the terms of a plasma master file and of a vaccine antigen master file, as defined in Annex I of Directive 2001/83/EC. "

This paragraph does not appear in the new draft regulation. However, the draft does mention VAMF/ PMF (inclusion in a MA) as part of the "new variation conditions."
EMEA would like to clarify with the Commission if the above paragraph (or similar wording) would be needed in the Regulation to ensure applicability of the relevant provisions of the Regulation to VAMF/PMF changes.

Many of the changes which may be made to VAMFs would ordinarily be covered in the existing regulation by those changes specified as changes to the "active substance." However, the antigen may not be the designated active substance in all cases e.g. the adsorbed antigen may be classed as the active substance, whereas the VAMF applies only to the point of manufacture and storage of the antigen itself. Clarification could perhaps be inserted in the Regulation as follows:

"*For the purposes of this regulation, in case of a VAMF, the term "active substance" could be replaced by "antigen."*

2. Article 3: Definitions

EMEA considers that the use of the reference to "negative impact" in the definitions of minor and major variation should be changed, as it implies that negative consequences of variations are always to be expected.
It is therefore suggested to use the wording "(not) expected to have a significant impact on the quality, safety or efficacy".

3. Article 4: Classification of variations

The proposal to remove the detailed list of Type IA/IB variations from the Regulation is welcomed, as this should allow a more flexible and frequent updating of the list in order to reflect experience and scientific progress.
In order to ensure the greatest amount of predictability and to ensure a harmonised approach across the European regulatory network, it is suggested that as many as possible Type IBs and Type IIs be defined and described in the guideline foreseen under Article 6. EMEA has included preliminary comments on the list, and will provide further detailed comments during the future development of the guideline.

In general, changing the classification of variation after validation (upgrading or downgrading), is not considered good administrative practice. A case-by-case decision on a possible Type II upgrade, will lead to a lot of uncertainty and possible inconsistent decisions within the EU Regulatory system, and may lead to an increase in administrative burden and approval delays as the dossier requirements and procedural handling of a Type II variation are significantly different from Type IB variations.
EMEA therefore considers that the default classification should remain Type II – see our comments under Article 5.
However, as new experience becomes available, based on real cases handled by regulatory authorities, this should be used to rapidly update the guideline. It is suggested that interim new variations be classified by questions and answers to be agreed between the CMDs and the EMEA. These would then be published and could be used to facilitate an annual update of the guideline.

4. Article 5: Scientific recommendation on unforeseen variations

EMEA considers that the proposal to introduce a new procedure for scientific recommendation on unforeseen variations at the request of the MAH, and for any upcoming product-specific variation, creates an additional, significant workload and strain on the EMEA, their scientific committees and working parties who are already over stretched, especially when the outcome of such consultation results in a non-binding scientific recommendation.
However, it is accepted that there is a need to harmonise interpretation of non-listed changes.

EMEA proposes that a more workable solution requiring less resource would be to maintain the Type II Variation as the default, together with an increase in and frequent updating of pre-defined Type IA/IB variations. In the case that a marketing authorisation holder considers that, based on specific justification, a specific unforeseen variation should be included as a Type IA or Type IB, a system to consider this as a possibility for amendment of the guidelines, as referred to in Article 6.1, could be set-up between CMDs and EMEA.

As new experience becomes available, based on real cases handled by regulatory authorities, the outcome should be used to rapidly update the guidance. It is suggested that interim new variations be classified by questions and answers to be agreed between the CMDs and the EMEA. These would then be published and could be used to facilitate an annual update of the guideline.

5. Article 6: Guidelines

In the interest of expectancy and adaptability, and based on the current situation and positive experience, it is suggested that EMEA operational procedures should not be part of the Commission guidelines foreseen.

Although some of the changes proposed in the draft Regulation address, to some extent, problems caused by occasional minor non-compliance from the requirements of the marketing authorisation, it is hoped that this topic can be addressed in the guideline to provide a better footing than the current reflection paper.

6. Article 7: Grouping of variations, point b (annual report and immediate notification)

As mentioned in our response to the previous consultation, the concept of “do and tell” is welcomed. However, if this is intended to reduce administrative burden it is essential that there is no expectation of systematic evaluation of the annual report. It would however be important to strengthen “ex-post controls”, for example by reviewing a sample of the annual reports received, through routine inspections and also to strengthen sanction possibilities. In this respect consideration must be given to the resource implications for inspectorates.

With respect to the associated administrative processes it would also be essential that grouping of variations did not require multiple notifications/ opinions/decisions on marketing authorisations (amendments) to be generated. As far as possible a single input should be associated with a single regulatory output. It would also be helpful if annual reports were submitted in an agreed format to ensure consistency and ease of handling for competent authorities. Such format could be agreed as part of the procedural elements to be further developed in a guideline.
It would equally be important to ensure that the proposals for groupings could be supported by electronic workflows e.g. based on the eCTD, as each product file held at Competent Authority/ EMEA level would still have to be updated individually.

With regard to the proposed Type IA and IA(IN) changes, only those changes which do not involve a change to the terms / Annexes of the Commission Decision should be permitted to be included in the Annual report. Type IA changes affecting the Annexes to the Commission Decision should be reported immediately, as they will form the basis for any future variation/extension submission.

However, it is acknowledged that due to differences in content of Marketing Authorisations in the EU, a harmonised classification of Type IA and IA (IN) may be difficult to achieve.
The opportunity to review the annexes to the Commission decision should also be taken.
From EMEA statistics (Human products), the number of Type IA notifications received which affect the Annexes of the Commission Decision is about 30-35%. For Type IB variations (some of which are proposed to be downgraded to Type IA), this is about 15-20%.

To ensure a consist and practical interpretation of "same MAH", a reference to the 1998 Commission Communication could be given.

7. Article 7, Grouping of variations point c)

From the current wording, it is not clear whether variations can be combined both within the list in Annex II and variations that do not come within the scope of this list. It is also unclear if or how variations that fall into more than one category in Annex II can be grouped together, and whether Type IA variations can be included in a group of variations which also includes Type IB and/or Type II variations (which should be possible in our view). Please also refer to our comments in the annotated Regulation, for specific proposed amendments to this Annex.

8. Article 7, Grouping of variations point d)

In general, EMEA also considers that it should be possible to group identical changes to different products held even by different MAHs, within the Centralised Procedure. This would be in particular important for grouped changes to the Pharmacovigilance System.
However, our above-mentioned concerns regarding support of such grouping by electronic workflow and the need for an equally simplified output, also apply in that case.

Pharmacovigilance system
With respect to the suggestion that Pharmacovigilance systems come within the scope of the grouping concepts, it will also be important to ensure that the proposals are compatible with any new legislative proposals expected to be developed on Pharmacovigilance.

Class labelling
In line with the above general comment, since the majority of class labelling will be applicable to similar MAs held by different marketing authorisation holders (rather than the same MAH as foreseen in Annex II) it is suggested that the possibility of grouping should be extended to include different MAHs for class labelling actions. In order again to reduce the administrative burden, it is suggested that a single regulatory outcome with annexes applicable to the various MAHs should be acceptable. It would also be important to consider the handling of class labelling under the new legislative Pharmacovigilance proposals in order to ensure compatibility with the amended Variation Regulation.

9. Article 16, CMD and arbitration

Referral to EMEA should only occur after no agreement could be reached in the CMD procedure (i.e. a sequential approach as set-out in Directive 2001/83/EC and 2001/82/EC). This should also apply to requests from holders (i.e. no direct referral from MAH to EMEA, first via CMD).

10. Article 19, Type II variations

The (existing) Type II provision for a change to or addition of a non-food target species needs to be included in the guideline (as has been done for the provision on the change to or addition of therapeutics indications).

We would also recommend including the addition of 1 further sub-paragraph under point 3:

(c) the period referred to in the first sub-paragraph shall be extended to 90 days in the case of variations concerning the replacement or addition of one or more new master seed viruses resulting in a new antigen or combination of antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

The same change should be made under Article 14.3 (variations to authorisations granted by the MSs) to add the same bullet point (c).

11. Article 20, Human influenza

Paragraph 1: We should ensure that this can be used for pre-pandemic and also seasonal vaccines. Therefore, the "annual" update should be changed to strain update.

Paragraph 2: Recommend not to detail the requirements in Annex III, but rather in the guideline (EMEA Fast Track Procedure for Community human influenza inactivated vaccines Annual strains update according to Article 7 of Commission Regulation EC/1085/2003) and potential respective pre-pandemic guideline.

Paragraph 3-7: Propose to delete these paragraphs and replace with "The Agency shall give an Opinion on the valid application within 60 days from the start of the procedure. This period can be reduced by the Agency as necessary. Within this period, the Agency may send the holder a request for supplementary information within a time limit set by the Committee. The procedure shall be suspended until such time as the supplementary information has been provided. In this case, the periods laid down before may be extended for a further period to be determined by the Committee. "

From the current experience, the legal timelines laid down in Article 7 have been extremely difficult to handle especially if the MAH has manufacturing issues with the seasonal vaccine. Due to the strict timelines defined in the legislation, one such MAH had to withdraw the application and re-submit, paying double fees. Therefore, flexibility for the Agency to define the procedure in the guidance would be needed, taking into account the CHMP meeting dates.

There is no legal basis for charging fees for these changes.

12. Article 21, Closing of procedure

EMEA would prefer to include EMEA-closure steps within the actual Type IA/IB articles (as is the case in the current Regulation). Additional detailed comments on this Article are included in the Annotated Regulation text.

13. Article 24, Worksharing

EMEA is not in favour of the proposed worksharing proposal, which foresees EMEA to be in charge of the evaluation of all types of variations of medicinal products independent from their route of authorisation. The worksharing proposal is based on the experience with worksharing in the area of PMF and the pilot quality project. Such experience is however very limited (and is expected to remain limited) and its number of applications can not at all be compared to the possible 1000's of variations that may be submitted through such a worksharing procedure.

Although the workload implications for the EMEA is acknowledged in the accompanying Commission consultation paper, the expectation that such worksharing will be carried out using the existing Working Parties is not realistic. EMEA Committees and Working Parties have been set-up to provide for a EU-wide forum for high-level experts to discuss innovative and complex scientific issues, prepare guidelines on emerging topics, assist Committees with the evaluation of new medicinal

products etc …. The extensive work programmes and ever increasing meeting agendas of Working Parties do not allow for an extension of their tasks to be involved in assessment of all types of variations, and is contrary to the process improvements and efficiency gains which the EMEA and its Committees are introducing.
Moreover, within the working parties, the actual assessment of the proposed worksharing will have to be allocated to one or more national experts together with a coordinator/Rapporteur.
It should also be noted that the dossier history, access to the dossier, and knowledge of current authorisation status of nationally authorised products is available only at MS level. In addition, consideration should also be given to the need for dossiers to be updated individually at national level. In this regard, please note that Article 35 of Directive 2001/83/EC states that "any application by the MAH to vary a MA which has been granted in accordance with the provisions of this chapter shall be submitted to all the MSs which have previously authorised the medicinal product concerned."

The proposed worksharing also implies a significant and new coordination workload for the EMEA secretariat.

EMEA is also concerned about the non-binding nature of the EMEA opinion. As such a non-binding EMEA opinion is to be followed by a further national procedural step, any divergent views between MSs could subsequently trigger a referral to the EMEA, resulting in a duplication of efforts.

Based on the current difficulties experienced in the area of referrals involving different nationally authorised products (e.g. correct identification of products involved, adoption and subsequent implementation of product information amendments when such PI may not be harmonised between MSs, etc ….), EMEA can foresee even more practical difficulties with the proposed EMEA co-ordinating role for variations of nationally authorised products.

Based on the above EMEA is of the opinion that, for variations affecting only nationally authorised products, a coordinating role could therefore perhaps be better taken on by the CMDs, or a new dedicated sub-group, supported by the necessary electronic tracking tools.

With regard to the scope of worksharing in general, it is considered that this should only apply to significant changes in well defined situations e.g. PAT related or harmonisation of module 3 and not to very minor changes, because this could become administratively very burdensome for competent authorities to manage.

14. Article 25, Pandemic influenza

We would propose to foresee the possibility of having accelerated commission decisions for pandemic variations in the Regulation.

We would propose that this Article should be used for all variations during a pandemic, except those which could be classified as Type Is or considered as USRs in accordance with Article 26. The text should be amended to reflect this.

If Article 25 is used, there is no legal basis for charging fees for these changes.

15. Annex I, Extensions

The current Annex I only refers to "replacement of ….": taking into account the broad spectrum of biologicals, EMEA is of the opinion that for relatively simple biologicals (e.g. insulins) which are fully characterisable by physico-chemical test methods, the option should be provided for a MAH to apply for an alternative manufacturing process. It would be up to the scientific assessment to decide whether such an approach would be acceptable for the molecule concerned.

In line with the comment under Article 19, the exempting text under point 1 (c) of Annex I should be amended to read;

"Replacement of one or more new master seed viruses resulting in a new antigen or combination of antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue"

To be consistent this text, the guideline needs to be updated by deleting "New 3" (Replacement or addition of a new master seed virus for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue (Type II))

and amending "new 4" to read:

"the replacement or addition of one or more new master seed viruses resulting in a new antigen or combination of antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue".

16. Annex II

The proposed grouped variations in Annex II will require further consideration as e.g. implementation of an PSUR assessment or USR, is normally only one variation (and not several variations for which the option of grouping should be created).
Preliminary proposals for amendments to this Annex are included in the separately provided annotated Regulation. EMEA will be happy to further provide input to this Annex once the final approach to grouping and variation classification is known.

17. Annex III

The inclusion of detailed, procedural elements as an Annex to the Regulation does not seem bto be fully necessary, and may create difficulties if amendments would be required when starting to prepare for the practical implemention of the Regulation or to reflect future, practical experience.
It may therefore be better to agree the details of this Annex as a Guideline (e.g. after discussions at the level of NTA, CMD). The Regulation itself could contain a very high-level statement on elements to be included (similar to what is in the current Regulation), and refer to the Guideline to be developed.

18. Draft Guideline

Specific comments on the draft guideline are included in the Annexed contributions from the QWP, BWP, PhVig WP and HMPC. As the guideline will continue to be reviewed, further comments will be provided in due time. Preliminary comments from the EMEA are included in the annotated Regulation document. EMEA would also like to refer to its comments provided in December 2006 which listed in Annex III specific new changes for VAMFs and PMFs, which are not yet included in the current guideline proposal.

As no specific proposals have been made with regard to PV Systems and RMPs, then all such changes are by default Type IB variations. It is generally acknowledged that some changes will involve a "Do and Tell" (Type IA_{IN}) variation, whereas other major changes requiring thorough assessment will necessitate a Type II variation procedure. Specific suggestions for variations to the PV System will be provided by the ad-hoc pharmacovigilance inspectors group.

The applicability of the concept of Design Space to veterinary medicinal products needs to be clarified.

London, 6 December 2007
Doc. Ref. EMEA/INS/GMP/579894/2007

NEW VARIATIONS REGULATION:
FEEDBACK FROM GMP/GDP INSPECTORS WORKING GROUP

1. Reference is made to ICHQ9 and Q10 in the Commission's consultation document to guidelines (referred to in Art 6.1 of the draft Regulation) in which it is foreseen that compliance with Q9 and Q10 may reduce the risk of certain changes and facilitate more flexibility in the classification of variations. At present the practicalities of such an approach are unclear. The group wishes to stress that GMP inspectorates do not foresee certifying compliance with Q9 or Q10. The basis of inspections will remain assessment of GMP compliance as required by legislation (noting that the principles of Quality Risk Management and Quality Systems are part of GMP).

2. While not explicitly stated in the draft, the group reiterates its concern that workload may be shifted from the assessment to the inspection function in terms of following up many "minor" variations. As stated above GMP compliance has to remain the main focus of GMP inspections so any additional workload for inspectors will have resource implications. Furthermore it should be understood that inspectorate overview of variations would in any case be limited because inspections are site specific rather than product specific so in many cases only part of the overall picture will be seen by inspectors. The task in any case would be best tackled on a sampling approach, ideally based on risk.

3. The new proposal appears to have many of the features of the existing Regulation, which are at the root of existing problems i.e. attempting to predefine all possibilities.

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Doc Ref: EMEA/CHMP/BWP/576919/2007

BIOLOGICS WORKING PARTY
MEETING ON 3-5 December 2007
Chairman: J-H Trouvin
Vice-chairman: S. Ruiz

BWP comments on the Revision of the Variations Regulation

BWP Rapporteur: A. Baeckmann (DE) and M. Welin (SE)

Today all unforeseen variations are considered as type II variations. The BWP welcomes the possibility to reclassify these variations based on their impact. We are however of the opinion that the type II by default instead of type IB by default should be kept for the following reasons.

What is to be considered as a type IA, IB and line extension is clearly defined in the legislation whereas type II variations are currently defined as any variation that is not type IA, IB or a line extension. Certain variations not fulfilling the conditions for e.g. a type IB variation will clearly be a type II variation but many more fundamental changes for biological medicinal products are today not mentioned at all but considered by all as type II variations. Examples of these are major changes to the manufacturing process, deletion of tests etc. There is a risk that the system of type IB by default will be misused and e.g. major changes to a manufacturing process will be applied as type IB by default while a minor change according to the legislation will be classified as a type II for a biological medicinal product. Considering the complexity and the importance of the production process of biological medicinal products as well as their diversity, such applications will most likely very frequently be reclassified as type II, but the upgrading may create a lot of debate with companies or member states, create practical difficulties and increase administrative burden. On the contrary, a situation where unforeseen variations will be type II by default but may be downgraded to IB when relevant is expected to lead to less discussions and possible referrals, and, as a consequence, to less administrative burden. This will reach the same goal of flexibility and timely completion of procedures as in the proposed text in the legislation. For instance, some changes to in-process controls as well as changes to the specifications for drug substance and drug product in certain circumstances could be downgraded to type IB on a case-by-case basis.

As a second option, if the less preferred Commission proposal of type IB by default is maintained, the following safeguards would be required:

1. A procedure for the final classification is required. In order to avoid criticism that companies are forced to accept an upgrading to a longer, more expensive procedure and not to lose time if a lengthy referral process is needed before the variation can start, it is important that an easy, understandable and fast procedure is established.

2. The conditions of the different variations currently listed in the directive and guideline should be further elaborated to avoid ambiguous conclusions.

Draft detailed guideline referred to in article 6(1)(a): conditions for classification of variations:

The BWP considered the proposal made to change the classification of some of the variations for biological products and made the following comments.

#8 Change in the batch release arrangements and the quality control testing of the finished product

a) and b)2 Type II to a type IB

We would have concerns over the method transfer and validation and guarantees that this had been completed correctly. It is clear that no systematic approach can be envisaged. Indeed it should be acknowledged that while there are some methods for which a transfer would be easy, there are some other methods which are not that easily transferable.

As a general remark, the guideline shows discrepancies for the following variation 12b/13b, 26b/27b and 37b/38c: thus, for **#12b/13b** Addition of a new test parameter which implies that a new test procedure is added can not be a type IA in 12 b and a type IB in 13b
The same comment can be done for 26b/27b and 37b/38c.

#12 Change in the specification of an active substance or a starting material /intermediate /reagent used in the manuf. of the active substance

(b)1: Type II to Type IA (addition of a new test parameter to the specification of an active substance)

We do not agree that there is no justification for a Type II, where more stringent requirements (i.e. addition of a new test parameter) are introduced.
The introduction of an additional test parameter may also be needed for an insufficiently controlled process or the emergence of previously unknown drug substance characteristics due to availability of new state of the art analytical techniques. As such, setting up a new specification should be reviewed carefully.

#13 Change in test procedure for active substance or starting material/ intermediate / reagent used in the manuf. of the active substance

13(a): Type II to Type IA 13(b): Type II to Type IB
Type II to Type IA and IB. Variability of biological products is higher compared to chemical entities. Amongst others, variability is influenced by starting material and reagents. Therefore, it should be assured that the quality and suitability of these materials is adequately covered. For some starting materials and reagents even viral safety issues have to be considered. In these cases Type IA is inadequate. Test procedures for biological substances may be more demanding that test procedures for chemicals. Thus a difference in requirements is fully justified.
In addition for 13(b) we would also have concerns as according to the conditions the method of analysis does not have to remain the same.

#17 Change in the re-test period of the active substance

17(a): Type II to Type IB
Retest periods are not applicable to biological products, see ICHQ1A. They have been allowed in the past but not in recent times. For all biological/biotech products authorised centrally, a shelf life is declared in the MA, for both the drug substance and the drug product. Any change of in the shelf life should be carefully assessed.

#19 Change in specification of an excipient (addition of a new test parameter to the specification of an active substance)

19(b): Type II to Type IA We do not agree that there is no justification for a Type II where more stringent requirements (i.e. addition of a new test parameter) are introduced.
The introduction of an additional test parameter may also reflect an insufficiently controlled process or the emergence of new previously unknown drug substance characteristics due to availability of new state of the art analytical techniques. See 12

#20 Change in test procedure for an excipient

20(b): Type IB to a Type IA No added value
20(c): Type II to a Type IB

Variability of biological products is higher compared to chemical entities. Amongst others variability is influenced by starting material and reagents. Therefore, it should be assured that the quality and suitability of these materials is adequately covered. For some starting materials and reagents even viral safety issues have to be considered. In these cases Type IA is inadequate. Test procedures for biological substances may be more demanding that test procedures for chemicals. Thus a difference in requirements is fully justified.
In addition, for 20(c) we would also have concerns as according to the conditions the method of analysis does not have to remain the same

#37 Change in the specification of the finished product

37(b): Type II to a Type IA
We do not agree that there is no justification for a Type II where more stringent requirements (i.e. addition of a new test parameter) are introduced.
The introduction of an additional test parameter may also reflect an insufficiently controlled process or the emergence of new previously unknown drug substance characteristics due to availability of new state of the art analytical techniques.

#38 Change in test procedure of the finished product

38(b): Type IB to a Type IA
38(c): Type II to a Type IB
Variability of biological products is higher compared to chemical entities. Amongst others variability is influenced by starting material and reagents. Therefore, it should be assured that the quality and suitability of these materials is adequately covered. For some starting materials and reagents even viral safety issues have to be considered. In these cases Type IA is inadequate. Test procedures for biological substances may be more demanding that test procedures for chemicals. Thus a difference in requirements is fully justified.
For 38(c) we would also have concerns as according to the conditions the method of analysis does not have to remain the same.

#42 Change in storage conditions of the finished product or the diluted/-reconstituted product

42(b): Type II to a Type IB
The procedure for type IB is too short to correctly assess the data given by the applicant. A careful assessment is needed as regards to the use of pilot scale material as a verification of shelf life.
As the manufacturing process is critical the scale of manufacture may cause differences in the finished product.

However, as regards to biological medicinal products, downgrading variations could also be envisaged on a case-by case basis.

New variations numbering system with the wording “new” is to be replaced by implementing the new number according to the existing numbering system.
New 2: as a remark PMF annual update is very difficult to handle. It is too frequent.

Line extension applications:
BWP identified that the definition of a line-extension might be reflected upon, to see whether clarification is possible. The text has been modified.

The new regulation mentions in annex I:
1 c: replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different
1 d: modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different.
If this is interpreted strictly, then a new MCB from the same source would not qualify for a line-extension. However, the word 'including' would suggest that a less strict interpretation might be possible, and that a new MCB from the same source would qualify. Unambiguous wording would be preferable.

CONSULTATION PAPER

BETTER REGULATION OF PHARMACEUTICALS: TOWARDS A SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK ON VARIATIONS INCLUDING DRAFT COMMISSION REGULATION AND DRAFT DETAILED GUIDELINE

Version: 24 October 2007

"QWP COMMENTS"

Date – 28 November 2007

1. GENERAL COMMENTS

It is noted that the new consultation is very much in line with and builds on the original consultation process that was carried out during October 2006. The removal of the classification of the different types of changes and associated conditions from the main legislation is welcomed. This should provide a straightforward mechanism for making changes, including any updates that may be required to reflect experience and possible future developments e.g. ICH. However, although one of the main objectives for change is for simplification there is a danger that the system could become more complex.

It is noted that comments should currently be focused on the draft legal proposal rather than on the draft guideline, because the guideline will be discussed after the end of the consultation process. However, in addition to including comments on the legal proposal, the opportunity has been taken to also include some initial comments on the guideline, recognising that very detailed consideration will need to be given to the content of this key document in terms of the categories, conditions and documentation requirements.

2. SPECIFIC COMMENTS

2.1 KEY ITEM 1: PURELY NATIONAL AUTHORISATIONS

Comment

The group welcomes this initiative.

2.2 KEY ITEM 2: ICH

Comments

The inclusion of reference to design space and the support for continuous improvement in the document is welcomed and acknowledged. In addition, it is noted that changes within a design space will not require any variation and will consequently not need to be presented in the annual report. Discussions regarding ICH Q8, Q9 and Q 10 are still on-going; however, the inclusion of variation requirements in a detailed guideline should offer the flexibility to easily make updates in the light of experience gained and any new developments.

2.3 KEY ITEM 3: "DO AND TELL" PROCEDURE

2.3 Comments

It is noted that under the current proposal, in future, it will be possible for all Type IA variations to be implemented anytime before notifying the competent authorities and that some changes will require immediate notification. However, there needs to be clarity of how competent authorities will be able to apply sanctions when it is discovered that changes may have already been inappropriately introduced.

In addition, clarification is required of what competent authorities are expected to do with these submissions, especially as some submissions could cover multiple Type IA changes that are not required to be immediately notified (Annual report) or a mixture of both immediate and non immediate changes are presented. Is the expectation that they will be checked in any way and what will need to be issued to the applicant. The legal text (Article 21 – closure of procedures) suggests that some sort of formal approval or rejection will need to be issued for all these Type IA, submissions in line with Type IB and II procedures, compared to an acknowledgement letter that is currently issued for Type IAs.

- Immediate notification

It is not clear how long after a change has actually been implemented should these categories of changes be notified. There is reference to forthwith but this needs to be clarified.

- Annual report

It is acknowledged that the annual report will potentially cover a number of different Type IA changes that have been implemented in the previous 12 month period. These will need to be submitted in an agreed format to ensure consistency and ease of handling for competent authorities. In addition, clarification is required of what competent authorities are expected to do with the annual report, because as already highlighted it is understood that there may be a requirement for some sort of review. This would be different to currently where Type IA changes are not reviewed on submission, although some Member States carry out routine audits. A consistent approach should be applied to immediate notifications and annual reports.

- Grouping

It is recognised that the grouping of several Type IA variations to one or more marketing authorisations simultaneously within one single notification will be advantageous to MA holders. However, in view of the fact that competent authorities need to maintain and consequently update their own records for each individual product, the information will need to be presented in a suitable format for competent authorities. In addition, consideration needs to be given to CTD updates and also possibly e-CTD submissions. Consequently, clarification is required of what a "single notification" (Article 7.2. (b)) will entail because competent authorities will need the information to be presented in

the most appropriate way. This should really be on an individual product basis, unless identical changes are applied to a series of products. Consideration also needs to be given to the best way of phasing these submissions throughout the year to spread out the work.

It was considered that the opportunity should be taken to critically review the "Type IA" category of changes and conditions to ensure that Type IA, non immediate notifications are maximised and that current problem areas are addressed.

2.4 KEY ITEM 4: "WORKSHARING"

2.4 Comments

The current text suggests that the EMEA will take on the responsibility for the assessment of any application as part of worksharing. It is acknowledged it would be appropriate for the EMEA to co-ordinate a worksharing change that involves a centralised procedure. Careful consideration needs to be given to possible downgrading of the classification and the binding nature of any positive decision to other procedures. However, it is considered inappropriate for the EMEA to be directly involved in the assessment of worksharing procedures involving MR/decentralised or purely national products, because they will not have access to the required registered and approved information.

The principle of worksharing is fully supported, including for purely National authorisations. However, as far as the scope of worksharing is concerned, it is considered that this should only apply to significant changes in well defined situations e.g. PAT related or harmonisation of module 3 and not to very minor changes, because this could become administratively very burdensome for competent authorities to manage.

2.5 KEY ITEM 5: TYPE IB PROCEDURE BY DEFAULT

2.5 Comments

The proposed introduction of a Type IB procedure by default along with the compilation of a list of Type II changes and the possibility to convert Type IB to Type II variations when required is noted. However, this could potentially lead to significant dialogue with applications both before and during procedures and there is a danger that the need for a Type II variation will not be picked up until late in the procedure. Consequently, it is recommended that consideration should be given to retaining the current Type II default. This would require the development of comprehensive lists of Type IA and IB changes to limit those simple changes being processed as Type II variations. In addition, it should be easy to update the list as appropriate in the future if new examples are presented. Consideration should be given to the regular review and update of the detailed guideline e.g. annually.

3. OTHER PROPOSALS

- 8.1 Classification of variations

Please see earlier comment regarding potentially using Type II as default instead of Type IB. It is noted that the draft guideline is only preliminary and will require considerable discussion before it is finalised.

As far as the definitions in the legal text are concerned (Article 3), it is considered that the wording could be improved by replacing negative with significant in the definitions of Type IA and II. In addition, the current Variations Regulations include text concerning updates to Pharmacopoeial monographs and Marketing Authorisation holders are exempted from notifying competent authorities if the registered dossiers refer to the current edition of the monograph and that compliance with updated monograph is actually implemented within six months of its publication. How is it intended to handle equivalent changes under the proposed system, will they be similarly exempted as part of the detailed guideline. Certainly any consequent updates could be captured as part of the annual report.

- 8.2 Grouping variations

A list of potentially grouped variations is presented in Annex II. It is considered that point 6 is already covered under point 2 and could be elaborated on if necessary in separate guidance e.g. Q & A.

- 8.3 Clarification of deadlines

It is acknowledged that something is required to ensure consistency and help Industry to introduce changes. However, some countries highlighted a potential issue which was linked to what local documents needed to be issued on final approval of a variation.

4. DRAFT DETAILED GUIDLEINE

It is noted that the draft is preliminary and that an attempt has been made to downgrade some changes, including those relating to biological products and veterinary products and to identify Type IA changes that need immediate notification.

General comment – As a matter of principle it is considered that any Type IA changes that potentially affect the SmPC, manufacturer of the active and finished product should where relevant be immediately notified. Consequently a number of comments specifically relate to these. In addition, further consideration needs to be given to some of the other categories of changes (specifically specifications of the active or finished product) regarding whether they should be Type IA or IA $_{IN}$ changes.

Some initial comments have been included to capture the initial review and aid future discussions. However, in view of the fact that it is recognised that detailed discussions will need to take place before anything is finalised, including those with all relevant stakeholders, this is not intended to be exhaustive at this stage. This will be the critical document in future and it is acknowledged that the lists, conditions and documentation requirements will need to be fully developed to maximise the success of the revised system. Consideration should also be given for including a Type IA change that covers administrative updates that result purely from the level of information in dossiers.

Specific comments

- Category 2 – Product name changes should be retained as Type IB
- Category 7 – manufacturer of finished product (partial/total)
  7b2 – should be retained as Type IB
  7c – the conditions should be amended to include appropriately supported changes to the manufacture of sterile finished products as Type IB applications.
- Category 8a – QC site - IA $_{IN}$

- Category 9 – deletions of manufacturing sites
  9a – it is considered that deletion of some key manufacturing sites should be IA $_{IN}$. In addition, in order to help MA holders maintain their products multiple deletions should be permitted on a single application.
- Categories 12, and 13 (API etc spec and analytical methods) – consideration should be given to splitting these categories to help differentiate Type IA and IA $_{IN}$ changes.
- Category 14 (API etc manufacturer – No CEP) – consideration should be given to splitting this category to capture possible changes that could be processed as Type IA or IA $_{IN.}$
- Category 15 (API manufacturer - CEP - new manufacturer should be IA $_{IN}$ and the conditions regarding sterile substances should be strengthened e.g. that the sterilisation method is the same and that the manufacturing site has been satisfactorily inspected.
- Category 18 Replacement of excipients – clarification is required of what circumstances it is envisaged that the new sub category (18B) will relate to.
- Category 21 Excipient – CEP – conditions regarding sterile substances should be strengthened e.g. that the sterilisation method is the same and that the manufacturing site has been satisfactorily inspected. [Are there actually any sterile excipients that fit this category?]
- Category 24 Excipient synthesis – should be retained as Type IB. No examples currently but could be critical for novel excipients that are described in dossiers.
- Category 33 Minor change to the method of manufacture of the finished product – should be retained as Type IB
- Category 34 Change to colour or flavouring - a1 & a2 – should be IA $_{IN}$ if the SmPC is affected.
- Category 35a coating weight/capsule weight – ? should be IA $_{IN}$ (Fps).
- Category 37 – finished product specification - 37a1 & 37b – ? should be IA $_{IN}$ (Fps)
- Category 38a – finished product specification – minor changes to test methods - ? should be IA $_{IN}$ (Fps). Need for clarification of minor and some types of changes e.g. dissolution medium and stirrer speeds.
- Category 39 – Imprints – should be IA $_{IN.}$ New condition required regarding communication to market regarding changed description.
- Category 40b – Dimensions - should be IA $_{IN}$
- Category 41 – finished product pack size - category should be clarified to also cover fill volumes and deletions (possibly covered under category 48)
  Category 41a1 – should be IA $_{IN}$
  Category 412a – should be retained as IB
  Category 412b – should be retained as IB
- Category 43a1 – measuring or administration device - should be IA $_{IN}$

London, 12 December 2007
Final Doc. Ref. EMEA/CHMP/PhVWP/593467/2007

Comments from the CHMP Pharmacovigilance Working Party (PhVWP) on the European Commission's proposal for a new Variation Regulation agreed by the PhVWP through written procedure following their meeting in December 2007

The comments are as follows:

Definitions
Use of the term 'negative impact' in Article 3(3), Type IA variation and Article 3(6) is queried.

Implementation:
Article 22 (4*):"Urgent safety restrictions and variations which are related to safety issues shall be implemented within a timeframe agreed by the holder and the relevant authority."*
This timeframe should specifically include the dissemination dates of batches in accordance with the varied terms of marketing authorisation.

New roles and responsibilities of the EMEA
Throughout the draft Regulations, it is proposed that the EMEA assumes responsibility for providing a scientific recommendation with regard to the potential impact of variations on the safety, quality and efficacy of medicinal products. From a scientific point of view, it is considered appropriate that the regulatory authorities who have access to the product dossier, relevant scientific expertise and also have responsibility for maintaining marketing authorisations should, similarly, retain responsibility for this scientific recommendation i.e. that the Rapporteur and CHMP should provide the scientific recommendation in the case of centrally authorised products, Reference Member State in the case of mutually recognised or decentralised products and national regulatory authorities in the case of nationally authorised products (with a possible coordinating role for the CMD in these latter two cases). From a procedural point of view, it would also seem appropriate that any decision to grant such responsibility to the EMEA as involves a policy decision, should, by definition, require a co-decision rather than comitology process.

Urgent Safety Restrictions
Article 22(4) suggests that the MAH may determine the timetable. The Competent Authorities should be empowered to impose a timetable. The following alternative wording is proposed (as per the Paediatric Regulation (1901/2006), Article 46(3) :
"Urgent safety restrictions and variations which are related to safety issues shall be implemented within a timeframe agreed by the marketing authorisation holder and the competent authority, or the competent authority may update the summary of product characteristics and package leaflet."

Article 26(2) states that *"The holder shall take urgent safety restrictions where requested by a relevant authority"*. More directive wording to capture the fact that a USR is being instituted at the behest of the Competent Authority is considered necessary; the wording in the current Variation Regulation is preferred*: "Where the competent authorities impose urgent safety restrictions …….."*

Newly defined variations
NEW.8. "Change in the summary of product characteristics, labelling and package leaflet/insert following an urgent safety restriction, class labelling, or a periodic safety update report" is classified as Type IA_{IN}.

Urgent Safety Restriction:
While in some cases the subsequent variation requires no further changes to the wording as agreed at the time of the USR, given the short timeframe of a USR, further time (in the shape of a Type II variation procedure) should always be allowed to permit a more indepth assessment and /or refining of the wording agreed at the time of the USR. In this case therefore, such changes should always involve a Type II variation.

Class labelling
A Type IA_{IN} variation is only considered acceptable where changes to the SPC, labelling, and package leaflet/ insert are made following the conclusion of a regulatory class review and agreement of the exact wording within a final assessment report.

PSUR
A Type IA_{IN} variation is only considered acceptable where changes to the Summary Of Product Characteristics are made following assessment of a PSUR as part of the PSUR work sharing initiative and where the exact wording to be included in the SPC is agreed as part of the final PSUR assessment report. (It must be noted however that as package leaflets are not part of the PSUR work sharing initiative, no harmonised texts for package leaflets are agreed at EU (supra national) level; as such, assessment of proposed changes to package leaflets is still required and Type II variations should be submitted accordingly.)

NEW.9. "Addition, modification or deletion of a therapeutic indication"
Where the deletion of a therapeutic indication is proposed, a type II variation is more appropriate, given the potential impact of such a deletion on the overall therapeutic alternatives for a disease state/ condition.

<u>Changes to pharmacovigilance systems and risk management plans:</u>
As no specific proposals have been made with regard to PV Systems and RMPs, then all such changes are by default, Type IB variations. It is generally acknowledged that some changes will involve a "Do and Tell" (Type IA_{IN}) variation, whereas other major changes requiring thorough assessment will necessitate a Type II variation procedure. This should be further discussed with input from relevant EMEA experts.

European Medicines Agency

HMPC COMMENTS ON
EUROPEAN COMMISSION CONSULTATION PAPER

BETTER REGULATION OF PHARMACEUTICALS:
TOWARDS A SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK ON VARIATIONS
EC Consultation paper dated 24 October 2007

London, 13 December 2007
Ref: EMEA/HMPC/540113/2007

GENERAL COMMENTS

Apart from the preliminary comments made below, It will be necessary for the HMPC Quality Drafting Group to review in detail the conditions for classification of variations listed in the draft guideline referred to in article 6(1)(a) which is enclosed at the end of the draft regulation. Those specific comments will be discussed at the next HMPC meeting on 9-10 January 2008, therefore they will be sent to the European Commission with a minimum delay from the public consultation deadline.

Herbal medicinal products are not specifically addressed in new consultation paper and the draft Regulation presented by the European Commission.

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SPECIFIC COMMENTS ON TEXT		
KEY ITEM 2: ICH		
Page no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
General comment	**Reference to 'old medicinal products' has been removed in the new version of the consultation paper. The HMPC considers that the concepts of 'design space' and 'continuous improvement of manufacture' are applicable also to herbal medicinal products, which have a marketing authorisation or a registration in different Member States.**	

KEY ITEM 3: "DO AND TELL" PROCEDURE		
Page no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
General comment	**In the new consultation paper the MAH has the possibility to notify all the Type IA variations by a "Do and Tell" procedure with the submission of an annual report. The concerns below raised by the HMPC in October 2006 are not addressed in the new consultation paper.** 'Although there is agreement in principle, there are some concerns regarding the feasibility of the "Do and Tell" procedure, since once changes are made it is very difficult to reverse them if at the time of assessment of the proposed annual report the changes are considered inappropriate. Changes in SPC need to be immediately reflected in databases etc.'	Any change that affects the SPC needs to be transmitted to the Competent Authority immediately.

KEY ITEM 3: "DO AND TELL" PROCEDURE		
Page no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
General comment	**The comment raised below by the HMPC in October 2006 is not addressed in the new consultation paper. There is no provision for a specific variation to comply with Community monographs/entries to the Community list according to article 16h(3) of Directive 2001/83/EC as amended by Directive 2004/24/EC.** 'The herbal medicinal products MA/registration holder has to comply with Community monographs/entries to the Community list according to article 16h(3) of Directive 2001/83/EC as amended by Directive 2004/24/EC, this should be taken into account by applicants when using the "Do and Tell" procedure.'	The HMPC would like to emphasize that the Community monographs/entries to the Community list should be taken into account by applicants when using the "Do and Tell" procedure.

DRAFT DETAILED GUIDELINE REFERRED TO IN ARTICLE 6(1)(a): CONDITIONS FOR CLASSIFICATION OF VARIATIONS		
Variation number	**Comment and Rationale**	**Proposed change (if applicable)**
7.b.2	Classification as IA_{IN} not agreed. The same criteria for assessment should apply to semi-solid and liquid pharmaceutical forms as their primary packaging is equally critical for these forms.	Classify as variation type IB
8.a	Classification as IA should be changed in IA_{IN} as the competent Authority should receive immediate notification of replacement or addition of a site where batch/control testing takes place.	Classification as IA should be changed in IA_{IN}
18.b	Clarifications should be provided as when the replacement of an excipient with a comparable excipient does not lead to a change in the SmPC. Please provide examples.	
25(a)	The HMPC does not endorse the change of classification of variation 25(a) from type IB to type IA as this is regarded as a potentially significant variation for herbal preparations (e.g. extracts). The change of classification from Type IB to Type IA for this specific variation represents a concern if applied to herbal medicinal products. Practical examples are provided as follows. Specifications of herbal extracts in the European Pharmacopoeia or a national pharmacopoeia are in general rather broad. For example, it may be allowed to use different types of extraction solvents (e.g. ethanol, methanol or acetone) or different ranges of solvents (e.g. 40-90% ethanol) for production of different extracts within the same herbal extract monograph. A change of approved specification to comply with the European Pharmacopoeia or with the national pharmacopoeia of a MS (e.g. change of extraction solvent from 20% ethanol to 90% ethanol or acetone) may trigger additional changes in e.g. posology, undesirable	Suggestions: -classify as IA, only on condition that an additional condition is included in the list, namely that the synthetic (for chemicals) or manufacturing route, physical form, extraction solvent, drug extract ratio (DER) (for herbal medicinal products) remains the same. With this additional condition listed, variation 25a would exclude the cases where changes in extraction solvent, DER are introduced (/ needed) to comply with the Ph. Eur. monograph. If the manufacturing remains identical, variation 25a would "simply" bring the specifications in line with the Ph. Eur. (which could be considered Ia) (but we would not be opposed to IB either) It should be noted that changes in DER, extraction solvent are line-extensions OR -classify as II, if such additional condition cannot be included in the list of conditions. In this case, such major change in manufacture introduced to comply with Ph.. Eur. monograph or other Ph. monograph needs to be fully assessed. OR -classify as IA, on condition that the herbal medicinal products are excluded..

	effects or interactions of the SPC. This must be assessed by the competent authority. **Such variations are not considered suitable as "do and tell" variations.**	
33	The HMPC expressed concern that, by changing the status of variation 33 to type IA, the competent authority will loose the possibility to assess the concept of 'minor' change in manufacture of the finished product. The concept of "minor changes" needs either to be clarified in detail (which is virtually impossible) or -preferably- be assessed by the authority, certainly in the case of herbal medicinal products.	<u>Suggestions</u> Classify variation 33 as type: -IB (see also similar variation 10: also 1B classification) OR -IA, with exclusion of herbal medicinal products.
34.a.1/.2	Classification as IA should be changed in IA_{IN} as the competent Authority should receive immediate notification of reduction or deletion of one or more components of the colouring/flavouring system used in the finished product.	Classification as IA should be changed in IA_{IN}
35.a	Classification as IA should be changed in IA_{IN} as the competent Authority should receive immediate notification of change in coating weight of tablets or change in weight of capsule shells for immediate release oral pharmaceutical forms.	Classification as IA should be changed in IA_{IN}