Public consultation paper 'Better regulation of Pharmaceuticals: Towards a simpler, clearer and more flexible framework on variations' - Comments from Medicines Evaluation Board, the Netherlands

Introduction

The Medicines Evaluation Board (MEB) has prepared this reaction on the initiative of the European Commission and welcomes the proposed change in the future variations legislation as to decrease the administrative burden for both the pharmaceutical industry and Competent Authorities. Key -items mentioned in the consultation such as 'purely national authorisations', 'do and tell procedure' and 'type IB by default' are endorsed by the MEB. In general the MEB supports the Commission's proposal, however all details as proposed will not lead in a decline of the administrative burden for the competent authorities. The MEB therefore proposes adjustments which cover the experience of the daily work of the MEB and our cooperation with the other national competent authorities and EMEA. The formalisation by legislation of an important concept of 'work sharing' is supported by the MEB, however mould in a different procedure.
In this document the MEB provides input on the draft Variations Regulation, including Annexes I – III. The MEB supports the proposal to include the classification of variations in a guideline, which will allow a more frequent update of the last of classified variations.

Comments on the consultation

The analysis in this report draws upon an article by article approach. The proposals for a change in the future legal framework are made clear in *italics* sections. Furthermore the MEB was informed by the Commission that the advice of Legal Service on the conversion/implementation of the Annex in a guideline will be given in 2008. Therefore at a later stage the MEB will provide input on the draft Guideline on the Classification of Variations, based on the experience we obtained over the last years (e.g. changes in Risk Management Plans or Description of Pharmacovigilance Systems).

Art. 5 Scientific recommendation on unforeseen variations

Instead of the proposition that the Agency will provide a recommendation for classification of unforeseen variations, the MEB proposes the CMD to provide a scientific recommendation. The CMD is a better forum for such decisions, because all competent authorities (including the Agency) participate monthly in the discussions of the CMD. Therefore the current expertise available at all National Competent Authorities should be used for these for decisions.

Art 7. Grouping of variations

- Choice of procedure

In the consultation it will be up to the MAH to decide which variations will be grouped;

1. a group of variations relating to one marketing authorisation, or
2. a group of variations relating to a number of marketing authorisations held by one marketing authorisation holder.

In the 1st case, the variations will be assessed by the competent authorities who granted the marketing authorisation, whereas in the 2nd case the work sharing procedure should be followed. In the 2nd case the assessment can not be done by the competent authorities who granted the marketing authorisation if the applicant wishes to group the variation in a single application, but the work sharing procedure with the Agency will have to be used.
The MEB proposes to allow in the 2nd case also assessment by the competent authorities. Art. 7(d) should be adapted accordingly so that the applicant can choose whether or not the work sharing procedure will be used or not and the MEB suggests the following text:
"Where a minor variation of type 1B, a major variation of type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations owned by the same holder, ***such variations be covered by a single application as referred to in Article 24 or can be submitted to the respective CA".***

The following example illustrates that most of the grouped submissions will automatically apply for the worksharing procedure. A MAH holds 3 national marketing authorisations (not registered through MRP or DCP) and the MAH submits two variations covering all three national marketing authorisations, then the work sharing procedure will automatically apply if the MAH wishes to group those variations into one single application. Even in the case that this product is registered only in one Member State.

- *Annual updates*

The current proposal for the Commission Regulation allows the submission of several annual updates (i.e. type IA variations not requiring immediate notification) in one application. This means that a different set of variations for each product can be submitted in one application. From a competent authority point of view, this is very difficult to handle because this single application will have to be split into separate applications (one for each marketing authorisation) in order to keep our files up to date. Even in case where eCTDs are used, this will not be easy, since that single eCTD will have to be split by the competent authorities into eCTDs for the single products. Although this might decrease the administrative burden for Industry, it will immediately increase the administrative burden for the competent authorities, resulting in longer time required for handling annual updates which will have a negative impact on the available capacity of competent authorities to handle other applications. However this proposal is not in line with the idea of simplification of the system.
The MEB is in favour of allowing grouping of variations in the following two situations:

1. *identical variations are submitted for several marketing authorisations, or*
2. *a number of different variations is submitted for one marketing authorisation only.*

However, the MEB is not in favour of the submission of different variations for different marketing authorisations in only one submission, which will be the case if all annual updates from one MAH are submitted in one application.

From the explanation provided by the Commission at the Notice to Applicants Meeting on 23 November 2007, it was understood that for grouped variations, the outcome is that all variations are approved or not, i.e. partial approval is not possible. It is welcomed if this information will be added to article 7 of the Commission Regulation to prevent any misunderstanding on this issue.

An explanation of 'the same holder' as used in 7(b) and 7(d) is welcomed in order to prevent misunderstandings. The MEB proposes not to use the broad definitions as used in module 1.2: 'applicants belonging to the same mother company or group of companies or which are "licensees".'

Art 9.5 and 13.5 Upgrading of unclassified variations to type II

In the current proposal, all variations which are not defined as an extension and whose classification is not laid down in the draft detailed guideline (see page 27 of the consultation) shall be considered a type IB variation. If the competent authority is of the opinion that an unclassified variation that is submitted as a type IB variation has a substantial potential to have a negative impact on the quality, safety or efficacy, this variation shall be evaluated as a type II variation. *The MEB endorses this safeguard clause, however proposes some additional changes:*

- *Not during the process of evaluation, however immediately during the validation of the variation application the competent authority should decide whether the variation should be handled as a type II variation;*
- *In that case the variation submitted will be considered invalid and a new variation (as type II) will have to be submitted.*

This change of classification during evaluation of a variation will result in a high level of unpredictability in the procedure both for applicants and authorities. To illustrate; if at day 15 of a type IB variation procedure it becomes clear that the application should be evaluated as a type II variation, the consequences are not clear. Thus will the effect be that it is then day 15 of the type II variation or should the clock start again at day 0? Besides the applicant has to submit additional data to comply with the requirements of a type II variation, and no clock stop early in a type II procedure is foreseen. After receipt of a variation, the application is processed according to the corresponding timelines and internal routine. If the classification of a submitted variation is changed, the timelines and internal routing have to be adapted in line. *Thus, the MEB foresees many practical problems which will result*

in an increase of administrative burden for the NCAs and therefore proposes that in cases of use of the safeguard clause a new variation application will have to be submitted.

Art 15 Human influenza vaccines in MRP

Article 15 paragraph 5 mentions that 'relevant authorities shall recognise the draft decision and inform the competent authority of the RMS to this effect'. It is understood that the CMS should inform the RMS whether or not they recognise the draft decision. In paragraph 6 it is mentioned 'other relevant authorities shall recognise that final decision and .... adopt a final decision accordingly.'. And this paragraph is interpreted that in the 2nd round of the annual update a CMS has no possibility of sending comments to the RMS. *For MEB paragraph 6 is not performable since a CMS should always have an opportunity to provide comments until agreement is reached.*

Art 16 Coordination group and arbitration

The procedure foreseen for CMD in case a CMS is not in agreement with the RMS is not clear. In the current proposal, type IA variations, type IB variations and type II variations should be discussed at CMD. *The MEB proposes the following amendments.*

- For type IA variations no draft decision is issued by the RMS and no involvement by the CMS is foreseen and therefore the CMD is in this case not applicable. *The MEB therefore proposes to remove the reference to article 12 (i.e. type IA variations).*
- For type IB variations, type II variations and line extensions, *the MEB proposes that a 60 days CMD referral procedure will be initiated when Member States involved are not in agreement. A reference to article 29 of Directive 2001/83 and article 33 of Directive 2001/82 should be included, and both Directives should be in the long run (taking into account the co-decision procedur) adapted accordingly.*

Art 19 Type II variations for Centralised Procedure

In art. 6 of Regulation 1085/2003 reference is made that the Competent Committee (i.e. CHMP) will issue an opinion on type II variations for Centralised Products. However, the Competent Committee is forgotten in art 19 and only a reference is made to the Agency. *The MEB is of the opinion that not the EMEA, but the CHMP should issue an opinion on a type II variation, because the CHMP is the competent scientific committee.*

Art. 22.2 Implementation of variations

For MRP variations, the applicant can implement the variation once the RMS has informed the applicant that the variation is approved. However, for a number of variations (e.g. revision of SPC, package leaflet and labelling) implementation in the national marketing authorisations should follow. According to art 22.2, the applicant will be allowed to implement the variation prior to approval of the national revised SPC, PL and labelling. This will either result in applicants implementing changes in a national SPC, PL and labelling that have not yet been approved or CMS will be forced to provide their input on the national translation during the MRP variation procedure.
The current situation is that the national translations are assessed and approved once the English MRP texts are finalised. This two-step procedure is followed for efficiency reasons, otherwise the national translations will have to be assessed and discussed while still changes in the English text might occur.
The proposed situation will stagnate in a lot of communication on the national translations during the MRP variation procedure, which should all go through the RMS and which will result in an increase of administrative burden both for the NCAs and for applicants.

Art. 22 paragraph 4 states that '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'. Nevertheless this will lead to difficulties in situations where the competent authority and the holder can not come to an agreement. In these situations, the competent authorities should be able to impose a variation. The following wording is therefore proposed: '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, or the competent authority may update the summary of product characteristics and package leaflet.'. *The latter wording is also used in article 46 paragraph 3 of the Paediatric Regulation (1901/2006), and it gives the competent authority the possibility to implement information resulting from safety issues or urgent safety restrictions without the submission of a variation application by the holder.*

Art 24. Work sharing procedure

The concept of work sharing is welcomed; however *the MEB is of the opinion that the work sharing should be performed by the authority that granted the marketing authorisation.* In practice this *means that for products approved through the Centralised Procedure the CHMP should be responsible for assessing the work sharing. For products approved by the national competent authorities (either through MRP/DCP or purely national marketing authorisations), the concept of work sharing as currently used for the assessment of paediatric data and Periodic Safety Update Reports should be followed.* Another example for work sharing is the 'change in the qualitative and quantitative composition of rubber stoppers from West Pharma'. In these work sharing procedures, the draft assessment report is prepared by one of the competent authority and all other competent authorities can provide their input. The work sharing procedure currently followed for the assessment of paediatric data is done under the auspices of the HMA, and the HMA gave CMD(h) a mandate. *The MEB proposes that for work sharing of variations the same procedure is followed.*

In the above mentioned work sharing procedures, the national competent authorities are not obliged to implement the outcome of the work sharing in their national authorisations, however experience learns that a consensus is reached and that all competent authorities do implement the outcome of the work sharing procedure. This is not different from the Commission's proposal for work sharing in which there is also no legal requirement for the national competent authorities to implement the result of the work sharing procedure.

The proposed procedure for work sharing for products approved nationally or through MRP/DCP in which the documentation is submitted to the Agency only, is not acceptable for the MEB, for the following reasons.

1. The competent authority that granted the marketing authorisation has the expertise and knowledge for that particular product.
2. The EMEA won't have direct access to the registration dossier, since that was submitted to the national competent authorities.
3. The EMEA won't have direct access to the assessment reports from the initial marketing authorisation application and possible earlier variation applications.

In the proposed Variations Regulation it is foreseen that the EMEA requests the national competent authorities to provide the documents mentioned under (2) and (3), however this will not lead to less administrative burden and therefore not in line with the objective of a more efficient process.

Previously the Commission explained that not the Agency itself, but the network of competent authorities will assess the variations submitted under the work sharing procedure. This intention could be reflected in the consultation. For example, in the current proposal, the documentation of the work sharing procedure is submitted to the Agency only (and not to the competent authorities). From the current text in the Commission Regulation, it is not clear whether or not the competent authorities will be involved in the work sharing procedure.

The work sharing procedure is now open for type IB variations, type II variations, extensions and a group of variations falling within one of the categories listed in Annex II. *The MEB is of the opinion that work sharing might give a reduction of the workload from an assessment point of view, but it will not result in a reduction of the workload from an administrative point of view since the variations still have to be submitted at national level.* For type IB variations, the workload for assessing is very small in relation to the workload for the administrative handling, work sharing will not provide a benefit for the competent authorities. *The MEB therefore proposes not to open the work sharing procedure for type IB variations, but to limit it to type II variations and extension applications only. It is therefore proposed to delete 'type IB' variations from art. 24(1), and to remove bullet point (3) from Annex II.*

Implementation of the work sharing opinion in the marketing authorisations granted by Competent Authorities is not described in the proposal for the Commission Regulation. The subsequent national submission of the variations assessed in a work sharing procedure is now only described in the Public consultation paper and not in the proposed Regulation. *The MEB is of the opinion that the national step should also be included in the Regulation.*

The proposed procedure of downgrading the variations is not supported by the MEB. The variations should be submitted at the same level (type II in work sharing remains also a type II variation in the

national process, and line-extension in the work sharing remain line-extensions in the national process),but the competent authorities should process these submissions in a shorter time period. Reason is that national implementation of work sharing might not always be a simple administrative procedure, which is illustrated in the following example. Product A is registered through independent national procedures in a number of member states with different SPCs. Product Ax is a line-extension that is submitted and assessed through a work sharing procedure. The SPC of product Ax is also established in the work sharing procedure. However since the SPCs of product A do differ in the member states, the national implementation of product Ax will require assessment and adaptation of the SPC. Because the level of assessment required for the national implementation of a work sharing procedure might differ, it is proposed that the variations submitted for the national implementation will be submitted as the same level and won't be downgraded.

Art 26.2 Urgent Safety Restrictions

Article 26, paragraph 2 states that 'The holder shall take urgent safety restrictions where requested by a relevant authority'. However, in the current Regulation, article 9, paragraph 2 the more comprehensible wording is used 'Where competent authorities impose urgent safety restrictions ....'. *The MEB wish to maintain the current wording namely 'imposed' instead of 'requested by' so that the text expresses that there is no room for discussion on this point.*

Issues not covered in the current proposal for the Regulation

The following issues are not covered in the current proposal for the Regulation, but would be at place in new variations legislation.

- Change in name and/or address of MAH and change in the name of the medicinal product

It is a missed opportunity if the modification in the name of the medicinal product and the modification in the name and/or address of the MAH for MRP/DCP products can not be handled at national level. *The MEB proposes that such changes are handled at national level and that the RMS is informed once the change is approved in the relevant CMS. Such a change will result in a hugh decrease of the administrative burden, both the competent authorities and for applicants, since in the current situation such changes relating only to one MS have to be submitted in all MSs. Therefore an extra article in Chapter III should be put in place.*

- Change in manufacturing sites, packaging sites and batch release sites

Type IA/IB variations no. 7 and 8 are the vast majority of all variations received by the MEB. In the current proposal, the type IA variations (i.e. change in packaging sites and batch release sites) are all listed as 'immediate notification'. *The MEB proposes to allow the type IA variations 7a, 7b1, 7b2, 8a, 8b1 and 8b2 all for notification after 12 months maximum, so that it will enable the applicant to group these variations. If these variations can be grouped, it will really result in a decrease of the number of submissions.*

Aginus Kalis
Director of the Medicines Evaluation Board
the Netherlands

Hubert Leufkens
Chair of the Medicines Evaluation Board
the Netherlands