Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION

EGA COMMENTS

EGA CONTRIBUTION TO THE EC PUBLIC CONSULTATAION ON THE REVISION OF THE VARIATIONS REGULATION 1234/2008/EC

OCTOBER 2011

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The EGA welcomes the opportunity to take an active part in the consultation process for the revision of the Variations Regulation 1234/2008/EC.

Due to the extensive portfolio of generic medicines manufacturers (up to 20 000 MAs for a large generic medicines producer) each change in the variations system has a significant impact on companies' regulatory activities. Thus, an efficient variations system is of great importance to the EGA member companies.

The general observation related to the proposed consultation is that questions raised in the Consultation Paper are mainly focused on improving the system from the perspective of the European Commission and the products authorised via the Centralised procedure, although those MAs constitute only a small part of all MAs granted in the EU. The consultation shall be extended to all types of procedures, including the MRP/DCP.

The proposed consultation method does not really provide a complete opportunity for the industry to openly express their experience with the revised Variations Regulation. As the initial objective of the Revision of the Variations Regulation defined by the European Commission in 2009 was to *"reduce the administrative burden for industry by streamlining the circumstances obliging industry to file applications for variations of human and veterinary medicinal products"*, we trust that the improvement of the system based on the industry's perspective shall not be neglected.

Thus, the EGA contribution to the consultation process will go beyond the proposed questionnaire and will express the observation of the EGA members related to two years' practical experience of using the new variations rules.

1. **EGA comments related to the purpose of the consultation expressed under point 1.1.**

1.1. The extension of the scope of the Variations Regulation to purely national marketing authorisations.

As already expressed on various occasions, EGA members strongly supported the inclusion of purely national variations in the scope of the variations regulations. Thus, the relevant amendment to the Directive 2001/83 adopted in June 2009 was very much welcome and the follow-on revision of the Variations Regulation was eagerly awaited. We trust that the current process of revision will proceed quickly and all involved parties will be able to fully benefit from a harmonised variation system across all MA procedures in the very near future. The deadline for finalisation of the revision process and for mandatory inclusion of purely national authorisations shall be clearly indicated as a part of the EC proposal. We expect this process to be finalised by no later than 1st July 2012.

1.2. The adjustment of some of the procedures with a view to focusing resources of the authorities on variations with the most impact on public health.

We fully support the intention to optimise the use of existing regulatory resources and for the authorities to be focused on variations with the most impact on public health. However, the adjustment of the procedures shall equally take into consideration the possible reduction of the regulatory burden on industry as well. Otherwise the right balance and the general objective of improving the variations system will not be achieved.

The EC comment on proliferation of variations due to MAHs not submitting the variations in a single annual submission presents only one side of the picture **without analysing why** the MAHs do not use this option extensively.
The main reasons for companies not using annual reporting in practice are related to various organisational and technical reasons such as:

- No significant reduction in workload by "keeping on side" variations for submission within one year
- Necessity to keep track of implementation date/submission date with a higher risk of incompliance
- Document management system within companies
- New variations system (particularly annual reporting/ grouping) not fitting the electronic submission environment
- Last but not least: national variations being out of scope- therefore this imposes two different ways of treating the same variation depending on the MA procedure.

Proposal: Some incentives are clearly needed to encourage companies using "annual reporting" as a preferable route of submission of type IA variations. The existing possibility to submit the variations within 12 months shall not become more restrictive after future revision of the regulation.

1.3. Some workability concerns identified

1.3.1. Type IB

The change in classification of variations "by default" to type IB was highly appreciated by the industry and indeed, the current experience is very positive. Less positive experience is related to the timeline and to the practical possibility of implementing the change if no negative feedback from the authorities has been received within 30 days. As the 30-day period is counted from the "acknowledgment of receipt of valid application", timely validation is critical. In practice, companies experience delays in validation of 1-3 months or if the validation is relatively short, the "day 0" is given to the Applicant in 2-3 months. Thus, the option to implement a change by the MAH after 30 days is practically meaningless.

Proposal: the legislative timelines related to type IB variations need to be more precise in the Regulation and to be better reinforced in practice, as timelines and the procedure defined in the guideline do not constitute a sufficient basis for timely implementation of Type IB variations.

1.3.2. General increase of company regulatory expenses related to the submission of variations

The pharmaceutical companies report a general increase of company regulatory expenses related to the submission of variations in 2010 in comparison with 2009. Although the introduction of type IB by default instead of type II has contributed to the reduction of costs, the way of calculating the grouped variation caused the increase. The EGA fully understands that variations fees remain a purely national competence of the MS and is out of the scope of the Regulation. However, we trust that on-going public consultation on the revision of the Variations Regulation is an important opportunity to raise this issue publicly.

In the EGA letter addressed to the Heads of Medicines Agencies in February 2011, the EGA gave several examples of very costly grouping of variations having a significant impact on companies' budgets.

Costs of grouping variations:
Each case of improvement e.g. the manufacturing process or quality of the medicinal product, is made up of several changes which need to be submitted to the competent authorities and assessed at the same time by the assessors. Previously all these changes were submitted as a single type II variation (called "consequential variation"). Currently, all these variations need to be submitted as "grouped variations" for which the fees for each change are added up. In some cases, costs of the same change have almost tripled.

Example I:

Grouping of 10 variations (7xIB and 3xIA)
DCP procedure with 13 countries and up to 4 strengths
Variations fee in total: approx 116.000 EUR
If submitted as a one type II variation fee: approx 47.000 EUR

Costs of company's related change(s):
The submission of a **company's related change(s)**, applicable to all Marketing Authorisations (e.g. new category - change of QPPV and DDPS; change of QP, change of MAH address etc.) has become a significant financial burden. Although the amount for a single change does not look very high, due to the implication on all MAs of the same MAH, the total sum is very consequential, particularly for a large company.

Example:
For a large generic medicines company which has around 19 000 MAs (resulting from MRPs/DCPs, CPs and purely national MAs) across the EU, ***the fees for changing the Qualified Person for Pharmacovigilance (QPPV) reached approx 13 Million EUR!***

The implementation of the Pharmacovigilance Master File (PhVMF) concept will contribute in the future to some reductions of the number of variations related to the Pharmacovigilance system. This opportunity shall be maximised (e.g. including the change of the QPPV).

Proposal:
The **concept of consequential changes** as a single variation shall be re-introduced.

The fees system **should better distinguish between individual product related changes and the company's related changes** which apply to several or even all products of the MAH.

Further reflection is also needed on **counting the grouped variations' fees** (e.g. the fees for grouped variations should not be higher than for one Type II). Fees should also reflect whether real **assessment is needed** or not (e.g. particularly for administrative changes), whether **the same change applies to other strengths, pharmaceutical forms** etc.

The elements of the **PhVMF versus the data on the Pharmacovigilance system in each MA Application Form shall be carefully defined** in view of the possible impact on variations (including the name of QPPV which shall be a part of PhVMF).

2. Detailed answers to the questions raised in the consultation process:

Consultation item no. 1:
Do you agree that where dossiers are not harmonised difficulties could arise for worksharing when accepting the assessment carried out by one member state by other member states?

EGA position: Yes, the worksharing procedure where dossiers are not harmonised may be more challenging, but it should not be a barrier for using the worksharing procedure in practice.

Consultation item no. 2:
Therefore, it is necessary to consider whether the worksharing procedure could also be extended to the same variations to several products with purely national marketing authorisations.

Several possibilities could be envisaged:
a) Not to allow worksharing where the same product has several marketing authorisations in different member states which are not harmonised. A precondition to benefit from worksharing would be the harmonisation of dossiers.
b) No additional restrictions to include variations to purely national marketing authorisations as long as the worksharing variations refer to a part of the dossiers that is considered not to need harmonisation.
Which option a) or b) mentioned above do you consider that should be adopted to allow worksharing ?

EGA position: The preferable option is b). The prerequisite that "*worksharing variations refer to a part of the dossiers that is considered not to need harmonisation*" should not be read too restrictively. Some slight disharmony in the relevant part of the dossier should be allowed if there is no direct link between proposed variations and those elements of the dossiers which are not fully harmonised.
It is also confirmed in the **CMDh Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure" which states that "*Harmonisation of the complete initial dossier or SmPC, PL and labelling is not a prerequisite for a worksharing procedure*"**

We strongly believe that the worksharing procedure could be an excellent tool to harmonise some parts of the dossiers when disharmony exists. The CMD(h) **is clearly considering this opportunity as in the separate Q&A document on implementation of Variations published by the CMDh, the possible option of dossier harmonisation via a worksharing procedure is already foreseen.**
QA: *Can harmonisation of Module 3 be done by worksharing? Module 3 harmonisation is surely an option for worksharing as worksharing does not require product harmonisation in advance. The aim is to have a harmonised result.*

The worksharing procedure is an excellent tool for optimising the use of resources. However, in view of the current complexity of the worksharing procedure and unattractive timelines, additional incentives are clearly needed for the applicant to use this procedure. Otherwise the potential benefit of saving resources will not be achieved as companies will not use this option in practice.

Consultation item no. 3:
Do you agree with the principle that the deadline for adoption of Commission Decisions amending marketing authorisations must be driven by public health considerations?

Yes, a faster response and faster adoption of Commission Decisions should be envisaged where there are **public health considerations but the used terminology is not very clear. Thus, it is difficult to definitely answer YES/NO** if the term "public health considerations" is not well defined.

Consultation item no. 4:
Which category of variations do you consider that should be adopted within shorter deadlines?
New indications, outcome of Art 30 harmonisation referrals, warnings, new contra-indication, adverse events and contact addresses are items which need to be implemented within shorter deadlines (basically the variations under point C1 of The Classification Guideline).

Consultation item no. 5:

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

In principle yes but as mentioned above (comment on consultation item 3), the clarity on terminology is needed to fully understand the practical implications.

The synchronised update of product information is needed in all places where the same information is supposed to be available. Otherwise there is a risk of confusion among patients and health professionals.

Consultation item no. 6:
Do you consider appropriate to introduce a deadline for the implementation of changes to product information significant from a public health standpoint?

For some changes (e.g. safety related changes) there is already a clear recommendation in the guideline that "*Variations related to safety issues must be implemented within a time-frame agreed between the Commission/ Reference Member State and the holder*."
Also in case of the implementation of art 30 referrals, there is always a clear recommendation when the change should be implemented.

Does question n° 6 mean that the intention is to introduce a fixed deadline in the Regulation itself as the recommendation based on the guideline is not sufficient?

We would rather support the current more flexible system based on the agreement between "*the Commission/ Reference Member State and the holder*."

ii) More stable "Summary of Product Characteristics".
The current proliferation of variation procedures has led to frequent changes to the summary of products characteristics in some cases. The Commission services aim at ensuring that changes that are required to address a significant public health concern are reflected promptly. However, the proliferation of small changes in a short period of time is considered to be detrimental as it makes more difficult to practitioners to keep up with latest information and, more fundamentally, it makes more difficult to distinguish changes with serious implications for public health from other changes.

Consultation item no. 7:
Do you agree with the above analysis?

We support the more rational way of updating the SmPC and PIL, not only for the CP products but for all types of procedures. The generic medicines industry experiences several changes to the labelling and SmPC within weeks or a few months of each other. Competent authorities vary widely in their approach, some not allowing a more sensible consolidated approach. MA renewals are a major problem with authorities often not allowing changes until after the renewal is complete and some renewals are taking more than a year to conclude. With core safety profiles, referrals, keeping labelling in line with the reference product, the product information is changing far too frequently.
Proposal: A special category of grouping variations coming from different regulatory processes and allowing the update of the SmPC and PIL once a while shall be considered.

Consultation item no. 8:
Do you consider appropriate to extend the time limits for assessment of complex grouped applications to enable a larger amount of cases where grouping under one single application could be agreed by the competent authority?

We partially share the opinion that for some very complex groups of variations more time is needed for the assessment. However, the term "complex grouped applications" is not very precise and can cause the extension of the deadline for all grouped applications in practice. There is no further indication what extension of time is being considered. Thus, the simple answer Yes/No is rather difficult.
We may support the extension of the time limit for the assessment of complex grouped applications (once better defined) if other aspects of the grouping is revised at the same time (e.g. simplification of the grouping procedure, increased possibility to group variations, re-introduction of so called "consequential variations" counted and charged as one type IB or II, not being a sum of all individually counted changes as under the current practice).

We would particularly call for rationalisation of several changes to the DMF or updates of the complete module 3 as type II changes without having to submit all the type IA/type IB variations as grouped and charged separately.

Consultation item no. 9:
Do you think that changes to the procedure in Article 21 of the Variations Regulation are necessary?

EGA: No comment since the EGA members do not manufacture these types of medicinal products