Making Medicines Affordable

POSITION PAPER

ON THE EUROPEAN COMMISSION DRAFT OF REGULATION CONCERNING THE EXAMINATION OF AMENDMENTS TO THE TERMS OF MARKETING AUTHORISATIONS FOR MEDICINAL PRODUCS FOR HUMAN USE AND VETERINARY MEDICINAL PRODUCTS

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1. EXECUTIVE SUMMARY

The EGA welcomes the opportunity to comment on the European Commission's proposal on the revision of the Variations Regulation. We recognise the importance of this initiative, as the current manner of dealing with variations has become inefficient and is no longer satisfactory neither to the authorities or to industry. The increasing number of variations, including the approval process of those which are not related to public health protection, demands the involvement of significant resources from the authorities and the industry which might otherwise be used to better effect (eg, to assess new applications).

The main comments of the European generic medicines industry can be summarised in the following points:

1. The EGA supports the proposal to include the national variations in the scope of the Variations Regulation. The EGA is in favour of common rules, conditions, categorisations and timelines for assessment and approval across Europe regardless of the types of procedures used (MRP, DCP, CP and national) in all Member States.

2. The EGA fully supports the implementation of the ICH Guidelines Q8, Q9 and Q10 as a part of new concept of dealing with variations.

   Although an introduction of a new design space as a Type II variation is accepted, a change to an approved design space classified by default as a Type II Variation is not supported. If the change itself is classified in the guideline as a lower category (eg, as type IB), the change of the already approved design space, should not be Type II by default, but lower.

3. The EGA welcomes the proposals of a Type IA variation as "Do and Tell" which would not require any prior approval, only notification to the Authorities within a 12-month period.

   The EGA further welcomes the proposals of "Do and Tell" variations, especially alongside 'Group Reporting', as this will significantly reduce the administrative burden of Type I A variations, which by definition have no impact on the quality, safety and efficacy of a medicinal product.

4. The EGA very much supports the concept of sharing the workload related to the assessment of variations among Authorities. It will provide a great opportunity — particularly for Authorities — to better use the limited existing resources.

   Some further clarification is needed to fully understand the proposed procedure and the role of the EMEA in the context of work sharing.

   Downgrading of the classification of variations is supported by the EGA in principle. However, after assessment performed on the basis of the work sharing procedure coordinated/performed by the EMEA, the change should be down graded to type IA, not to type IB. Otherwise a variation will have to be submitted and assessed twice.

   The whole concept of work sharing, while well described in the explanatory paper, is not fully transposed into the draft of Regulation.

5. The EGA welcomes the proposals to handle variations that are not explicitly recognised as Type IA, II or line extensions, as Type IB variations by default.

   We fully understand the need to introduce a safeguard clause into the system to allow a reclassification from Type IB to Type II, but use of this situation should be

the exception only. To avoid too many reclassifications and to increase a predictability of the system, an example of Type II Variations should be introduced in the legal text.

The proposal allows the implementation of the change to be done if the competent authority has not sent the holder its opinion within 30 calendar days following acknowledgement of receipt. However a set period of 14 days needs to exist for the acknowledgement of receipt. Otherwise the implementation can be indefinitely delayed.

The draft detailed guideline states that a variation which is classified in the guideline but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type II. The EGA believes this statement should be removed, as it is possible for there to be no substantial potential impact with some variations even though all the conditions have not been met. This also undermines the concept of Type IB variations by default.

6. The EGA strongly supports a separation of the conditions for classification of variations from the text of the Regulation and the elaboration of the further guideline covering the conditions of the changes and the necessary documentations supporting those changes
7. The EGA very much welcomes the proposal to allow the grouping of variations into a single submission.
8. The closure of the procedure needs to be further clarified in several articles of the draft Regulation.
9. Arbitration by the CMD(h) should be allowed only during the course of the procedure laid down in Articles 14 and 15, not in case of IA and IB variations (Art 12 and 13). In the case of Type IA and IB, current experience with the recognition of the RMS decision by the CMSs during the procedure should be used instead of the arbitration to the CMD(h).

The following sections of this document provide a more detailed explanation of the EGA's views regarding this conception of the new variations system.

2. EGA General Comments on the EC Draft Proposal of the Revision of the Variation Regulation.

The EGA welcomes the opportunity to comment on the European Commission's draft proposal concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and the veterinary medicinal products.

We recognise the importance of this initiative, as the current manner of dealing with variations has become inefficient and is no longer satisfactory neither to the authorities nor to industry.

The increasing number of variations, including the approval process of those which are not related to public health protection, demands the involvement of significant resources from the authorities and the industry which might otherwise be used to better effect (eg, to assess new applications). Due to the high amount of variations submitted annually by generic medicines companies with very large portfolios, the improvement of the current system will be greatly appreciated.

EGA members very much appreciated the opportunity to be involved in the discussions at the initial stage of the process of revising the variations system. In principle, we support the key points of the proposal and we recognise the effort made to find pragmatic solutions to simplify the whole variations process.

Our detailed comments on the key items of the proposal are presented below.

3. Comments on Key Item 1 - Application to National Authorisations

3.1. Inclusion of the National Authorisations in the Scope of the Variations Regulation

The EGA supports the proposal to include national variations in the scope of the Variations Regulation. The EGA is in favour of common rules, conditions, categorisations and timelines for assessment and approval in all Member States across Europe, regardless of the types of procedures used (MRP, DCP, CP and national). EGA members have highlighted the significant divergence in approval times between various MSs and between various procedures. This lack of synchronised approval in the MSs involved in the procedure produces significant logistical problems for companies involved in implementing changes.

The EGA has already supported the proposed changes to Directive 2001/83/EC as amended allowing this inclusion of purely national MAs into the scope of the Variations Regulation.

3.2. The Scope – Derogation

In accordance with Article 2 of the proposal:

> *By way of derogation from paragraph 1, this Regulation shall not apply to:*
> *(a) transfers of a marketing authorisation to a new marketing authorisation holder (hereinafter "the holder");*

The EGA would welcome an extension of the areas where changes can be made in a single country that is singularly affected by the change in question.

In accordance to the current regulatory practice, this is already possible not only in the case of the transfer of the licence to a new MAH, but also in case of the deletion of any strength or any pharmaceutical form in one country.

Other situations which should also be handled on the same way are:

1. A change in the name of the medicinal product (as type IA immediate reporting);
2. A return to full SmPC for a generic medicine after expiry of any use patent of the reference product in a given country (type IA immediate reporting).

In such cases, only the RMS should be informed so as to allow the record in the MRP/DCP Index to be updated without having to submit this variation in all CMSs.

4. Comments on Key Item 2 - ICH Q8, Q9, Q10

The EGA fully supports the implementation of the ICH Guidelines Q8, Q9 and Q10 as a part of new concept of dealing with variations.

The EGA welcomes the EC clarification that the move within an approved design space would not be considered to require any variations application.

The EGA welcomes the possibility of using the design space concept for the purpose of variations at every stage of the product life cycle once the company is ready to apply it. In the majority of cases, generic medicines companies will obtain sufficient knowledge to create the design space after the combined experience gathered from the developmental and initial production phases.

Although an introduction of a new design space as a Type II variation is accepted, changes to an approved design space classified by default as a Type II Variation is not fully supported by the EGA. If the change itself is classified in the guideline as lower category (eg, as type IB), the change of the already approved design space should not be Type II by default, but lower. If an element of the previously approved design space is changed outside the approved design space (such as, for example, an increase of batch size currently would be a Type IA if within 10 fold or Type IB if outside 10 fold), the change to the approved design space should be classified as type IA/IB, not as type II by default. This will encourage the implementation of the design space concept and will foster improvement during the entire life cycle of the product by the Marketing Authorisation Holders.

The EGA has already expressed the position that the Variations Regulation should be sufficiently flexible to include all future developments coming from ICH processes and to reflect scientific and technical progress. The separation of the detailed guideline on the conditions for classification of variations from the Variations Regulation is strongly supported by EGA members as a more flexible option.

5. Comments on Key Item 3 - “Do and Tell” Procedure

The EGA welcomes the proposals of a Type IA variation as “Do and Tell” which would not require any prior approval, but only notification to the Authorities within a 12-month period.

Our understanding is that there will be no fixed date for reporting of Type IA variations that do not require immediate notification as long as this notification is made within a 12 month period.

This would appear to be a pragmatic solution as fixed date reporting for each licence would not be possible alongside other proposals such as group reporting, grouping of variations or work sharing.

The draft text of the Regulation seems to be sufficiently flexible also to allow e-CTD on-line submission for type IA variations for a given product more than once within a 12-month period.

The clarification that reporting of variations is only required where a change is implemented and not for every licence is also welcomed, as otherwise this would have caused the unnecessary use of administrative resources.

The EGA welcomes the proposals of 'Do and Tell' variations — especially alongside 'Group Reporting' — as this will significantly reduce the administrative burden of Type IA variations, which by definition have no impact on the quality, safety and efficacy of a medicinal product.

The EGA welcomes the clarification that only changes that have not been reported via other routes are notified. This again appears pragmatic as it is possible that Type IA variations will have been reported when grouped with Type II or Type IB variations.

The term "immediate reporting" for type IA is not of itself very precise. In practice, companies may inform authorities about a change within different timelines. This point may cause some discussion amongst the authorities, although it does not seem to be a crucial point for the revision of the draft proposal.

The current sequential numbering system for variations has to be revised to be in line with the new proposal.

6. Comments on Key Item 4 - Work Sharing

The EGA very much supports the concept of sharing the workload related to the assessment of variations among Authorities. It will be a great opportunity particularly for Authorities to better use the existing limited resources.

The concept paper states that the Work Sharing Procedure is proposed in the following circumstances:

- national authorisations in several MS's
- a change common to several, distinct medicinal products.

Our understanding is that in the first case national authorisations in several MSs and not only purely national MAs are covered, but also MAs from MRPs/DCPs. For generic medicines a mix of some purely national MAs plus some MRP MAs must be considered for a single work sharing procedure.

Regarding the work sharing procedure itself, some further clarification is needed to fully understand the proposed procedure. The role of the EMEA needs to be clarified. Will the EMEA appoint a rapporteur/Member State to carry out the evaluation or will the EMEA itself do the evaluation? Can the applicant propose a rapporteur? There are more questions to be answered.

Downgrading the classification of variations after the assessment is performed or co-ordinated by the EMEA is supported by the EGA in principle. However, if the change is downgraded from a Type II to Type IB, a variation will have to be submitted twice (once to the EMEA to obtain an opinion and then again to the relevant authorities for the formal variation procedure including the assessment). It would not seem to be necessary to reassess this change again. There is also a risk that the total timeline for approval will be increased, rather than reduced. The EGA would suggest that once the assessment is performed on the basis of the work sharing procedure coordinated/performed by the EMEA, the change should then be downgraded to type IA.

While the entire work sharing concept is well described in the explanatory paper, it has not been fully transposed into the draft of Regulation. Although the operational details of the procedure may be explained in the further guideline, the downgrading of the changes should be a part of the Regulation itself.

7. Comments on Key Item 5 - Use of Type IB Procedure by Default

The EGA welcomes the proposals to handle variations that are not explicitly recognised as Type IA, Type II, or line extensions, as Type IB variations by default.

The proposal to allow the notification to be deemed accepted by all relevant authorities if the competent authority has not sent the holder its opinion within 30 calendar days following acknowledgement of receipt is also welcomed, as this will improve the efficiency of the process. However, we believe there also needs to be a clear timetable for the acknowledgement of receipt, and we suggest a period of 14 days. Otherwise the implementation can be indefinitely delayed.

We fully understand the need to introduce a safeguard clause into the system. However, reclassifying a variation from Type IB to Type II should be the exception rather than the rule. The way the safeguard clause is currently drafted in the proposal does not make the new variations system predictable for the applicant. At day 29, the Applicant may be notified that the variation is classified not as Type IB, but as a Type II. To avoid the significant increase time required for approval in such cases, the time already spent for the assessment of the change as Type IB should be deducted from the total time of assessment as a Type II.

The draft detailed guidelines currently only contain a few examples of Type II variations. The EGA believes that further examples will be required, to avoid the possibility of too many Type IB variations being upgraded to the Type II procedure. To increase the predictability of the system and especially to limit the use of the safeguard clause, a list of Type II Variations be introduced in the legal text should be considered.

The draft detailed guideline states that a variation which is classified in the guideline, but which does not fulfil all the necessary conditions laid down in the relevant subcategory, shall be considered to be of Type II. The EGA believes that this statement should be removed as it is possible for there to be no substantial potential impact with some variations even though all the conditions have not been met. This also undermines the concept of Type IB variations by default.

8. Other Comments

8.1. Guideline on the conditions for classification of variations

The EGA strongly supports separating the conditions for classification of variations from the text of the Regulation and elaborating a further guideline to cover the conditions of the changes and the necessary documentation to support those changes.

The EGA has already provided the EC with some proposals of changes to the conditions and the documentation required along with suggestions of the new categories of changes not covered by the existing Annex to the Regulation.

We trust that this contribution will be helpful during the initial preparatory work on the Guideline. As industry, we also very much welcome the further opportunity to contribute to the discussions on the details of the guideline once the general framework of the revision of the variations and the final classification are agreed.

To fully benefit from the revised variations system, the guideline must be finalised at the same time as the other legislative processes (comitology and co-decision parts). Taking into consideration the complexity of the guideline, discussions on the revised draft must also be initiated very quickly.

8.2. Grouping of Variations

The EGA welcomes the proposal to allow the grouping of variations into a single submission.

Regarding Annex II on grouping variations, in several points listed in the annex the variations can be grouped under the condition of being “consequential”. This is also possible in the current system, although the understanding of the term “consequential” differs amongst authorities, which makes discussions with the authorities long and can discourage a company form applying for grouped variations. Less emphasis on the consequentiality of variations may help to group all changes in a single submission that are not necessarily related, but which occur simultaneously. This would result in a single update to the file, a single update of the MAs instead of the multiple updates that would otherwise required. This will be of particular benefit in cases where all the changes (not just consequential changes) are made to one medicinal product.

Point 6 in the Annex II allows a certain flexibility to combine several changes under a single submission, although the wording may not be sufficiently flexible to cover all possible scenarios.

The usefulness of combining grouping of variations with the work sharing procedure can not be established for licenses granted via MRP/DCP until the role of the EMEA with regard to licenses granted via these routes is clarified (with reference to our comments raised under point 6).

8.3. Clarification of Deadline

In general, the EGA is very much in favour of the legal reinforcement of the timelines associated with the entire variations process in all MSs. We are also in favour of fixed deadlines for national competent authorities to update and/or amend the MA following the approval of a variation. However, six months for the competent authorities to update the MA appears excessive, especially following, for example, an extension when the change can be implemented only after updating the MA. This should not exceed 30 days as is the case of the MA process when the national phase should be finalised within that period.

In accordance with current practice, not all MSs amend the final MAs. We welcome the flexibility of the proposal allowing those MSs to continue their practice without unnecessarily increasing the workload.

8.4. Timelines of the Procedure

One of the biggest issues of the current variations system is related to the lack of respecting the legislated timelines.

The time-scales for assessment and closure of the procedure need to be further clarified in several articles of the draft Regulation.

- **Acknowledge receipt of a valid notification**

  For Type IB variations, the authorities will have 30 days from the day of submission to review the change. The change is considered automatically approved and may be implemented by MAH if no feedback is received from the authorities during 30 days.

  In Articles 9 (for nationals), 13 (MRP/DCP) and 18 (CP), the 30 days to implement a type IB change are calculated based on the moment of acknowledgement of the receipt of a valid notification from the Authorities. However, there is no clear timeline in the legislation for sending this acknowledgement to the applicant after receiving its application for variations.

  We suggest a maximum 14 days for sending this acknowledgement after it has been delivered to the Authorities as a specific timeline for validating a new application.

8.5. Arbitration to the Coordination Group (CMD(h)

In accordance with Article 16, a relevant authority can bring the matter to the coordination group if it is in disagreement with the decision of the RMS during the course of the procedure laid down in Articles 12 to 15. This means that the Coordination Group will be involved in arbitration related to all types of variations, including minor variation types IA and IB. This is an unnecessary burden for the CMD(h) as even in accordance to the current system the decision of the RMS is final. Current experience with the recognition of the RMS decision by the CMSs during the procedure should be used instead of the arbitration to the CMD(h). Otherwise the CMD(h) will be blocked by variation arbitrations.

We suggest that the arbitration to the CMD(h) be used only during the course of the procedure laid down only in Articles 14 and 15.