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Optimal Way to Handle the Variations - Industry's Perspective

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Importance of revision of Variations Regulation

- Current system inefficient and no longer satisfactory for the authorities nor for industry
- Systematic increase of number of variations
 - very time and resources consuming process
 - administrative approval process of changes not related to the public health protection
- The initiative to revise the VR and the general concept of simplification strongly supported by the generic medicines industry



Examples of workloads

- Medium-size Generics Company

Total Number of Variations (2003-2006)

- 2003 - 900 MRP plus 2000 nationals – total 2,900
- 2004 – 1,200 MRP plus 2100 nationals - total 3,300
- 2005 - 1,800 MRP plus 2500 nationals - total 4,300
- 2006 -1600 MRP plus 2400 nationals – **total 4,000**

- Large-size Generics Company

Total Number of Variations (2005-2006)

- 2005 - 12,000 MRP plus 1,500 national – total 13,500
- 2006 - 15,000 MRP plus 4,000 nationals -**total 19,000**



Optimal Way to Handle the Variations

- **Key points for industry**
 - Predictability of the system
 - Harmonised requirements and harmonised assessment
 - Respected timeline
 - Implementation of changes at the same time in all MS
 - Administrative burden reduced to minimum
 - The authorities' resources used more efficiently



Key Item 1: National Authorisation

- The EGA supports the inclusion of purely national MAs into the scope of VR
 - Currently significant divergence in approval times between various MSs and between various procedures
 - This lack of synchronised approval in the MSs causes significant logistic problems for companies in implementing changes.
- The EGA in favour of:
 - common rules, conditions, categorisations and timelines for assessment and approval across Europe independently from the types of procedures used (MRP/DCP, CP, national) in all Member States.



Key Item 1: National Authorisations (2)

- Companies would welcome extension of areas where changes can be made in a single country
 - Currently
 - Transfer of licence to new MAH
 - Deletion of strength or form
 - Propose
 - Change in name of medicinal product
 - Return to full SmPC after expiry of usage patent



Key Item 2: ICH

- EGA fully supports the implementation of the ICH guidelines Q8, Q9 and Q10.
 - Move from a “tick box” system to a quality risk management and design space concept
 - The draft VR is sufficiently flexible to include all future developments coming from ICH
 - The possibility of using the design space concept at every stage of the product life cycle.
 - Should remain optional to the applicant
 - No variation application if a change within the pre-defined design space is welcomed
- Changes to an approved design space (DS) should not be Type II by default
 - e.g., if the change being part of DS is classified as IB, the change of DS should remain IB



Key Item 3: “Do and Tell” Procedure

- EGA in favour of:
 - *Do and tell* procedure with reporting within 12 months
 - No fixed date; moment of submission chosen by MAH
 - Gives flexibility for reporting including e-CTD submission
 - Link to MA birth date/ HB for PSUR too limiting
 - » MRP/DCP- different dates of MA for the same product in MSs
 - No variations- no reporting
 - Reporting
 - MS position- Reporting per MA („family” MAs) or the same changes to several MAs can be supported by the industry
 - Harmonised EU template must be agreed



Key Item 3: “Do and Tell” Procedure

- Immediate notification
 - MSs proposal- to report immediately all changes affecting MA document and SmPC/PIL/package
 - No harmony across the EU
 - EGA proposal: to identify the key changes for IA_{IN}
 - Clear timeline for update of MA (if needed)
 - Term: “immediate notification” not very precise but not critical point
- Possibility to group the variations
 - Including IA_{IN}



Key Item 4: Work sharing

- EGA in favour of work sharing procedure
 - Single evaluation helps to better allocate the existing resources
 - More detailed procedure needed
 - EMEA role as a coordinator- choice of “RMS” if several national MAs plus MRP MAs?
 - Globalisation of the industry should be taken into consideration (e.g. mother/daughter companies)
 - Otherwise a missed opportunity to avoid an unnecessary repetition of the assessment
- EGA in favour of downgrading procedure
 - Downgrading to Type IB still triggers additional national assessments
 - no rational use of resources; should be a Type IA
 - Downgrading procedure from the EC Concept Paper not fully reflected yet in the text of the Regulation



Key Item 4: Work sharing

- After the consultation process:
 - Leading role of the EMEA not supported for national MAs
 - CMD seen as a coordinator
- EGA supports the CMD role in work sharing if
 - CMD as „one entrance point” for industry
 - Nomination of „RMS”/Rapporteur by CMD (suggestion from applicant possible)
 - Distribution of workload among MSs
 - All MSs accept the worksharing system
 - Full harmonisation of the dossier not required
- Downgrading procedure
 - If the current MRP/DCP rules for variations apply- is the downgrading procedure still needed?



Key Item 5: Type IB by Default

- EGA in favour of Type IB by default
 - The safeguard clause to upgrade to Type II should be used exceptionally
 - Clear list of type II or clear conditions for upgrade to Type II needed to allow the predictability
 - eg, only if potential serious risk to public health
 - An upgrade to Type II shouldn't restart the clock on the procedure
 - Stop-clock for industry is needed to provide the missing documentation for Type II



Key Item 5: Type IB by Default (2)

- The 30 day limit on CAs opinion following receipt welcomed
- Recommendation to introduce 14 days for notification of receipt- otherwise no clear timeline to start the procedure
- Concept of Type IB by default is undermined by the guideline statement on variations not meeting the necessary conditions and therefore being automatically Type II



Grouping Variations

- EGA in favour of Grouping of Variations
 - Very important part of the proposal to reduce the workload
 - Efficient way to communicate all changes (including unrelated) at the same time and to update the documentation/MA once
 - Understanding for the MS' position regarding grouping (especially three- dimensions grouping)
 - Compromise must be found
 - eg, how the documentation should be prepared to avoid an extra burden on authorities



Grouping Variations

- Many of the examples listed in Annex II mention grouping of variations that are consequential
 - This is possible under the current system
 - The understanding of ‘consequential’ differs among authorities. This could result in rejection of some groupings
 - Should be possible to group variations which occur simultaneously but which may not obviously be consequential
- Approval/Rejection: “all or nothing”
 - No rejection of a whole package- positive changes approved; Otherwise unnecessary submission/assessment again
 - Exception: consequential changes



Other comments:

- Art.16 - Possibility of referrals to CMD(h) for IA and IB seems too excessive
 - Another mechanism for comments from MSs should be explored (current experience?)
- Timelines must be a part of the procedure in VR
 - e.g. time for acknowledgment of receipt, validation (14 days as for a new application?) are missing



Other comments: Guideline

- Support for separation of the detailed Guidelines on classification and conditions from the Regulation itself
 - In the Guideline on classification: *If not all conditions are not fulfilled- Type II*
 - This undermines the principle of type IB by default and the meaning of the guideline (*deviation allowed if justified*)
- The discussion on the revision of this guideline must start very soon due to the complexity of the guideline
- The EGA has already proposed several changes to the current classification of variations (revised conditions, new categories etc)



Conclusion:

- In general, the EGA strongly supports the proposal as a significant step forward to improve the current system
- The opportunity to contribute to the discussion from the beginning highly appreciated
- Full declaration on behalf of the generic medicines industry to cooperate with all stakeholders in the further discussion

