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Danish comments on Public Consultation Paper dated 24 October 2007 – Better Regulation of Pharmaceuticals: Towards a Simpler, Clearer and more Flexible Framework on Variations

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Danish comments on Draft Commission Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (version: 24 October 2007), including Draft Guideline

The Danish Medicines Agency welcomes the Commission initiative on revising the Variations Regulations and we thank you for this opportunity to comment on the proposals. We fully subscribe to the need of improving and simplifying the legislative framework, and we agree that this should be reached through a reduction of the administrative burden for both the pharmaceutical industry and the competent authorities and without compromising human health.

We are in general positive towards the preliminary proposal. We do however have some concerns which are described more in detail below, and we look forward to discussing them further with the European Commission.

As for the key items listed in the consultation paper the Danish Medicines Agency would like to make the following comments:

Line extension – Article 3 (2) and (7)
The Danish Medicines Agency does not agree with the proposed inclusion of line extensions into the definition of variations.

According to the existing Regulations on variations there is a clear distinction between variations and extensions of a marketing authorisation. The nature of an extension is significantly different from that of a variation, and hence applications for extensions are examined by the national competent authority or the Community in accordance with the procedure for granting a new marketing authorisation.

The legal basis for the Commission Regulation according to Article 35 in Directive 83/2001 (as amended) only concerns variations. We would

question the Commission's legal basis to change significantly the concepts on extensions and variation in a Commission Regulation and thereby include the examination of extensions into the legal scope of the proposed regulation to an extent beyond the already existing regulations.

The distinction between variations and extensions are also found in the wording of Article 6(1) in Directive 83/2003 (as amended), where changes in the form of any additional strengths, pharmaceutical forms, administration routes, presentation or extensions are notions which are separate from the notion of variations.

Definition of "Reference Member State" – Article 3(8)
The Danish Medicines Agency would like to see a more detailed explanation on this new definition. Does the definition entail that a Reference Member State within the meaning of Article 28 of Directive 2001/83/EC and Article 32 of Directive 2001/82/EC can act as a Concerned Member State and vice versa?

"Do and Tell" procedure for Type IA variations – Articles 8, 12 and 17

The Danish Medicines Agency is in principle in favour of a "do and tell" procedure for all Type IA variations, including the idea of grouped reports.

However, if the proposal on a "do and tell" procedure is adopted in its present form, this would present a significant problem to the Danish Medicines Agency.

Every second week the Danish Medicines Agency publishes a complete list of range and prices of all medicinal products marketed in Denmark (the Price List) with only a few exemptions.

For each medicinal product the list contains information on ATC Code, name of the product, name of the holder of the marketing authorisation, name of the active substance, pack size and consumer prices.

The information in the list is updated every second Monday on the basis of pharmaceutical companies' information to the Danish Medicines Agency. The information consists partly of data stemming from approved variations and partly of in advance-notifications concerning changes to range and prices on the marked.

The information, which is published only electronically, is intended to ensure identical prices of medicinal products at all Danish pharmacies, and to contribute to correct handling and dispensing of medicinal products at Danish pharmacies. Thus, the electronic data is used in IT-systems at the pharmacies to form the basis of the pharmacy's dispensing of the product.

The Price List and the electronic data also form the basic information concerning reimbursement on the medicines to be used in connection with the dispensing of a prescription. The electronic data is also used in IT-systems used by all general practitioners when issuing electronic prescriptions, and by medicine modules in hospitals' electronic patient records.

Since the operation of this system is based purely on prior notification and that the proposal entails notification after implementation for some of the key information in the list, the list as such would no longer present an up to date image of the market.

For these reasons the Danish Medicines Agency can only support this part of the proposal if changes to the basic administrative information as described above are notified to the national competent authorities prior to implementation. We would however be happy to participate in discussions with the Commission in order to find possible solutions.

Notification – format
We would strongly prefer if the possibility for grouping Type IA variations was limited so that each notification document covered only one dosage form. This to prevent a report from becoming too comprehensive and thus a considerable administrative burden for the competent authorities to process.

Availability of necessary information at the time of inspection and control
The Danish Medicines Agency would like to add that a delay in notifications with up to twelve months, and the consequential delay in updating internal databases, could have an impact on the planning and execution of regulatory inspections could be compromised.

Mandatory guideline Art 4
Finally we would like to question the possibility for the Commission to draw up a mandatory guideline on the conditions for classification of variations. A guideline is per definition only of a guiding nature. We would prefer to see the classification of variations in an annex to the regulation rather than in a guideline. Alternatively, the regulation should specify the criteria for classifying variations as either type IA, IB and II, in order for the Commission to make use of when adopting and changing the guideline.

Worksharing – Article 24
The Danish Medicines Agency welcomes the principle of worksharing, which could be an important element in the work towards improving and simplifying the legislative framework. As the coordinating factor in such worksharing the Danish Medicines Agency would like to suggest using CMD and the current network in the area of national variations.

Variations to purely national authorisations that were eligible to worksharing could thus benefit from the expertise and procedures which are all ready gathered in CMD. Such a solution should the necessary mechanisms to ensure that the workload is shared fairly between the national competent authorities.

We have also noted that the proposal does not specify the procedures in Member States following a opinion from EMEA, the possible binding character of such opinion or how to solve disagreements etc. in the worksharing concept. In order for worksharing to work in reality all of these elements should be dealt with and this is the case whether CMD or EMEA is chosen to be the coordinating factor. In the opinion of the Danish Medicines Agency the proposal would need further elaboration, especially on the possible binding nature of an opinion delivered by the Agency, before we would be able to support it.

In the light of this it might be considered to allow variations on nationally approved products in the MRP/DCP-procedure (on initiative from the company choosing RMS and Member States involved) instead of creating a new procedure alongside the already existing procedures for cooperation. This alternative solution would of course require further changes to the legal basis and therefore it could considered if the necessary changes could be incorporated in the co-decision procedure concerning the amendment of Directive 2001/82 and Directive 2001/83.

Finally and for reasons mentioned above we are of the opinion that line extensions should not be eligible for worksharing.

Type IB as Default – Articles 4(2), 5 and 6
The Danish Medicines supports this part of the proposal. It should however be noted that its use in practice is closely linked to Articles 5 and 6, why we would like to suggest that a more in depth description of the criteria's for classifying a variation within the different categories is incorporated in the regulation. Concerns regarding biological products have to be taking into consideration.

Grouping of variations – Article 7
The Danish Medicines Agency supports the notion of grouping. However it should be considered if the rejection of one variation in a group necessarily should cause the rejection of the group as such. The Danish Medicines Agency would prefer that the whole package of variations is not rejected. It should also be considered if one printed form pr. group is preferable to one printed form pr. variation in a group.

Furthermore and for reasons mentioned above we are of the opinion that line extensions should not be eligible for grouping.

Design Space
With the precondition that "design space" only concerns changes related to quality, the Danish Medicines Agency agrees that a formal introduction of the notion in the Variations Regulations could enhance the flexibility in the regulatory approach to changes and we can support this approach.

Furthermore it should be considered that there is a very limited amount of experience with design spaces, why such an introduction should be accompanied by detailed definitions and guidance in order to obtain a common understanding of the concept.

Guideline on the Conditions for Classification of Variations
Although the focus of the public hearing is on the draft legal proposal, the Danish Medicines Agency would like to make a few preliminary remarks on the draft guideline.

Concerns are expressed for the nos. 25, 29 and 37:

- The proposed amendment of nos. 25a1 and 25a2 from IB to IA are not supported as these changes quite often will need assessment.
- The proposed amendment of no. 29b from IB to IA is not supported as assessment could be necessary.
- The proposed amendment of no. 37b from IB to IA could be a problem for old products where specifications are insufficiently updated according to current guidelines, e.g. addition of limits for degradation products (without any assessment).

Concerns raised by the BWP regarding a number of variations for biological products (nos. 8, 12, 13, 17, 19, 20, 37, 38 and 42) should also be taken into consideration.

Kind regards,

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