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Oss, October 21, 2011

Re : EC Consultation Paper Revision of the variations regulations

Dear Madam

Merck & Co., Inc, known as MSD outside the United States and Canada, is a global healthcare leader. Through a combination of the best science and state-of-the-art medicine, Merck has produced many important medicines and vaccines. Today the company is continuing to actively develop a broad portfolio of small molecules, vaccines and biologics products, including biosimilars to significantly improve worldwide patient access to important/life-saving therapies.

Merck has reviewed the above referenced document and is providing the following comments for your consideration. Merck welcomes the initiative to review Commission Regulation (EC) 1234/2008 with the aim to adjust some of the procedures with a view to further focus resources and we appreciate this opportunity to comment on the subject document and hope that you will take our comments into consideration.

We support the extension of the scope of the Variations Regulation to purely national marketing authorizations as we believe this will contribute to an efficient and focused processing of variations. In addition to the responses to the topics identified by the Commission as requiring public feedback, we have also added at the end of our response some further proposals which could be considered to further improve workability.

Should you need additional information or wish to hold further discussions with our company experts, do not hesitate to contact me.

Yours sincerely,

A handwritten signature in blue ink, appearing to read 'L. Vromans', with a long, sweeping underline.

Lisette Vromans
Encl.

Merck Sharp & Dohme (MSD) responses and comments to the specific consultation topics

Consultation item no. 1:

Do you agree that where dossiers are not harmonised difficulties could raise for worksharing when accepting the assessment carried out by one member state by other member states?

MSD Response:

In general, the same data has been submitted to agencies; however, due to divergent opinions from the national Competent Authorities or divergent medical practices, the product information and specifically the indication section may not be fully harmonized. But this should not prevent MAHs from submitting changes through the worksharing procedure and achieve harmonization of marketing authorizations progressively. A case-by-case evaluation may be necessary.

Consultation item no. 2:

Which option a) or b) mentioned above do you consider that should be adopted to allow worksharing?

MSD Response:

Option a) would prevent the use of Worksharing for nationally approved products as the huge efforts to reach harmonization from both the industry and Competent Authorities perspective would not outweigh the benefit of the use of a Worksharing procedure.

Option b) appears the most appropriate. In particular, product information revisions due to new safety information should be allowed even if the safety information in different SPCs is not fully harmonized.

2.2 Focusing public resources on the procedures with most impact on public health

MSD Comments on section 2.2:

We would like to highlight the issues that are preventing MAH from submitting minor variations as single annual submission:

- Many non-EU countries rely on EU CPP to approve variations. For several CMC variations to be filed as IA variations, prompt submission is often favored to the annual reporting to be able to get the updated EU CPP and have those variations approved in non-EU countries in due time.**
- The reporting period of the current system is not fully aligned with the US annual report system. It should be possible to submit the EU annual report within 60 days of the 1-year reporting period to allow the alignment of the annual reports for the EU and the US.**

MSD Comments on section 2.2.i):

The proposals made in section 2.2.i relate only to the products approved through the Centralized Procedure.

For MRP/DCP products, although the Variation Regulation foresees update of the national MA for type II variations within 2 months of the RMS positive opinion and allows implementation 30 days after the RMS positive opinion, this is not yet followed by all Competent Authorities and major delays can sometimes be observed to receive the updated Marketing Authorization. Reinforcement of this deadline by the Commission would be necessary, in particular for changes with most impact on public health, to ensure that updated information can be made available to the patients and practitioners without delay.

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?

MSD Response:

We agree with this principle. For our viewpoints on the system of adoption and implementation of variations, see our response to consultations 4 and 5.

Consultation item no. 4:

Which category of variations do you consider that should be adopted within shorter deadlines?

MSD Response:

Adoption within a shorter timeline should be allowed for all types of variations. The current deadline for adoption of the EC Decision (2 months) for type II variations should be maintained for 'variations with significant public health implications' to ensure that patients and practitioners have access to updated Product Information on the Commission website without delay. For variations with no significant public health implications, adoption of the Commission Decision within 6 months appears sufficient if implementation is allowed anytime after the CHMP Opinion. However for revisions related to change of manufacturing sites, in order not to delay the issue of the CPP needed for non-EU countries, adoption of the EC Decision within 2 months should be maintained.

Consultation item no. 5:

Do you agree to extend 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)?

MSD Response:

We agree to extend the current system and suggest to also include the changes with most impact for public health as those should be communicated as quickly as possible to patients and practitioners. We favor the following system for type II variations:

- for variations involving the product information, implementation is possible 30 days after the CHMP Opinion and once the linguistic review process is completed;**
- for all other variations, implementation is possible at the time of the CHMP Opinion**
- Update of the Commission Decision on a periodic basis (every 6 months) except for variations with significant public health implications, for which related Commission Decision should be updated within 2 months of the CHMP Opinion and except for revisions related to change of manufacturing sites, in order not to delay the issue of the CPP needed for non-EU countries.**

It will be important to clearly define those 'variations with significant public health implications'.

We favor the following system for type IB variations:

Type IB variations can be implemented as of the adoption of a positive CHMP Opinion, even if they are reviewed through a Worksharing procedure

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?

MSD Response:

We would like to highlight that it is in MAHs best interest to implement important public health related changes into their product information as quickly as possible. So a specified deadline is not necessary in our view.

If the Commission sees an urgent need to define a deadline for implementation, a clear definition of 'implementation' must be developed together with stakeholders. MAHs can control the time between regulatory approval of a change and the shipment of the first finished good with the revised product information. However, depending on the supply chain and different operators in various Member States the timeline between the shipment of the finished good from the manufacturer until the time to arrive in a pharmacy or be given to a patient is very variable and beyond MAHs control.

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

MSD Response:

We agree that the number of variations is high, but we observe that CMC and administrative changes represent a large part of these procedures. Many changes to the SPC are related to safety findings or requests from the Competent Authorities to update the information as a result of a review of follow-up measures or PSURs. Some variation procedures could be avoided if more flexibility would be given by the Competent Authorities on the deadline to submit those changes. Furthermore, fewer variations would be submitted if the possibilities of grouping would be extended. We also observe that since the implementation of the New Variation Regulation, the EMA is stricter on this point, while more grouping was allowed in the past.

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?

MSD Response:

We did not experience this issue so far. The current Variation Regulation already offers flexibility for the timing of the review of type II variations: if the group is considered to be too complex, a longer clock-stop may be chosen. We believe that extending the review time limits would not be of additional benefit.

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

MSD Response:

No comment .

MSD additional suggestions to improve the current variation system, which can mainly be addressed in guidance documents:

- The CMD(h) pilot allowing the grouping of IA variations with different RMS is welcome. Transposition into the guideline as standard procedure would be appreciated.
- Administrative burden related to the use of Worksharing procedure should be decreased: an easy and rapid process to get the WS numbers for MRP/DCP products would be welcomed, in particular when this WS procedure applies to original and duplicate applications (same RMS), in which case no Reference Authority appointment is needed.

- **The use of one common EU Application Form and Cover Letter for MRP/DCP products would be welcome. Current national requirements for original signed application form or translation of those documents increase the administrative burden.**
- **The timetable for the review of IB variations processed in Worksharing procedure should be aligned to the timetable of stand-alone IB variations (30-day). The additional review time as per the current Regulation (60-day) discourages the MAH from using this WS procedure.**

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