London, 27th January 2009
Doc. Ref.: CMDh/013/2009

THE FOLLOWING LETTER IS INTENDED FOR
ALL MARKETING AUTHORISATION HOLDERS
FOR CURRENTLY AUTHORISED MEDICINAL PRODUCTS
PRESENTED AS PRESSURISED METERED DOSE INHALERS

REQUEST TO REVIEW DOSSIERS TO ENSURE THAT STUDIES HAVE BEEN PERFORMED TO ESTABLISH WHETHER A STORAGE ORIENTATION EFFECT EXISTS AND IF SO TO ENSURE THAT AN APPROPRIATE RECOMMENDATION FOR STORAGE ORIENTATION AND OR RE-PRIMING IS INCLUDED IN THE PRODUCT INFORMATION

Dear Sir/Madam,

The Quality Working Party (QWP) has recently agreed that it is scientifically justified to include instructions regarding the storage orientation in the product information for formulations administered via pressurised metered dose inhalers (pMDIs) if there is a possibility for dose decrease/increase after storage in certain positions (e.g. after upright storage).

The QWP has indicated that storage orientation studies and harmonisation of product information by including recommendations regarding storage orientation should be carried out for both marketed products and new applications for marketing authorisations.

The following Q&A, which has been recently agreed by QWP and has been published on the EMEA website, is intended to give guidance on the requirements for new marketing authorisation applications for such products:

Q: What are the requirements for storage orientation recommendations in the product information for pressurised metered dose inhalers?

A: During product development the effect of orientation should be investigated in the priming and re-priming studies according to *Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005).*If storage orientation has a significant effect on the delivered dose during these studies (i.e. different re-priming periods / number of actuations are required for re-priming when stored in different orientations) a storage orientation recommendation should be added to the

product information (SPC, package leaflet and label). The preferred storage orientation should be detailed. As it cannot be guaranteed that the product will always be stored in the preferred orientation, the re-priming instructions in the product information should be based on the worst case scenario (i.e. the orientation which requires the shortest re-priming period and / or the highest number of re-priming actuations).

The CMD(h) has recently discussed the QWP's recommendations on this topic and has agreed that marketing authorisation holders for currently authorised medicinal products presented as pMDIs should be requested to review their dossiers to ensure that:

a) storage orientation studies have been performed and that the results of these studies are included in the registered dossier

b) if the results of the storage orientation studies show that there is a possibility for dose decrease/increase after storage in certain positions, an appropriate recommendation for storage orientation and/or re-priming of the product should be included in the product information. Regarding storage orientation the following wording is suggested: 'This inhaler should be stored in a <valve up><valve down><horizontal> orientation'. The storage statement should be included on both the immediate and outer packaging.
Re-priming requirements in the product information should be established on a case by case basis, however they should give a clear indication of the specific length of time the inhaler can be stored before re-priming is required.

If having reviewed their dossiers, marketing authorisation holders establish that their dossiers need to be updated with respect to either of the above points, an appropriate variation application should be submitted using the standard procedures. For marketing authorisations that are part of a mutual recognition or decentralised procedure, the assessment of the variation will be led by the RMS in the normal manner. For purely national marketing authorisations, the variation application should be submitted to each national competent authority and will be assessed on a national basis.

Marketing authorisation holders are requested to carry out the review of their dossiers and submit any necessary variation applications as soon as possible and not later than 30th June 2010.

Yours faithfully,

Truus Janse-de Hoog
Chair of CMD(h)