GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HORMONE REPLACEMENT THERAPY

(CHMP/EWP/021/97, Rev. 1, Draft, 20 January 2005)

German Region of the International Biometric Society

Comments:

1. Prevention of Osteoporosis

It is stated in the introduction that the guideline focuses on oestrogen deficiency symptoms rather than on prevention of osteoporosis. Nevertheless, the prevention of osteoporosis is mentioned in Section C.1.1, Clinical Efficacy Studies.

2. Page 5, Section 2.1.5, Methodological requirements, c) Sample size; and Page 7, Section 2.1.5. Methodological requirements, e) Results analysis

The criteria to conclude for endometrial safety (which means to be better or comparable to a marketed HRT (first sentence of Section 2.1.5, c)) and the proposed sample size to achieve this criteria are not clear.

Using a binomial model (normal approximation) and assuming that the new HRT has a true incidence rate of 1% (the upper bound of the rate in untreated women), about 1600 women would be needed in order to obtain an upper limit of the two-sided 95% CI lower than 2% with a probability of at least 90%. Therefore, the statement *"This requires approximately 300 patients ..."* is not true in this case.

Therefore, it is not quite clear, what is meant by *..the upper limit of a two-sided 95% confidence interval should not exceed 2%...*
Possibly, it is meant that non-inferiority of the new HRT vs. an old HRT with an incidence of 2%, given a non-inferiority margin of 2% should be demonstrated. This would require fewer patients than the calculation above. If the latter is intended by the guideline, then the last sentence of Section 2.5.1., c, should be revised as follows: For a new HRT, the non-

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inferiority of the new HRT compared to marketed products with an incidence of up to 2% should be shown by using a non-inferiority margin of 2%. Therefore, the upper limit of a one-sided 97.5% confidence interval should not exceed 4%. The last sentence of Section 2.5.1, e, should be revised in the same way.

Of course, we are not aware whether the CHMP is considering 2% as an acceptable non-inferiority margin for the indication discussed, but the current wording produces more confusion than provides it clarity. In any case the intention of the proposed study design, the specific non-inferiority margin, the sample size and the recommended strategy for the analysis should be explained in a more detailed way.

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