



**Comments on**  
**Note for Guidance on Clinical Investigation of Steroid Contraceptives in**  
**Women**  
**(CHMP/EWP/519/98 Rev 1, Draft, 23 June 2004)**

**German Region of the International Biometric Society**

**Page 4, section 3.1, 2<sup>nd</sup> paragraph:**

”The key studies, carried out in a sufficiently representative population, should normally be at least large enough to give the overall Pearl Index (number of pregnancies per 100 women years) with a 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 women years). This may require up to 20,000 cycles.”

**Comments:**

1. The Note for Guidance should state whether the confidence interval for the Pearl Index should be one- or two-sided. It is assumed that a two-sided 95% confidence interval is requested with the consequence that the difference between the one-sided upper 97.5% confidence limit and the point estimate should not exceed 1. The calculations should be based on a pre-specified statistical model and pre-specified distributional assumptions (as, e.g., suggested by Gerlinger et al [1]).
2. Depending on the true Pearl Index, the number of cycles required to obtain a two-sided 95% confidence interval for the Pearl Index of the required precision, i.e. a half-length of less than 1, may be considerably lower than 20,000 cycles (e.g. Benda et al [2]). Since the



number of cycles actually required to fulfill the precision requirement for the estimation of the Pearl Index has to be determined in a sample size planning under the assumptions of the specific situation at hand, no absolute number of required cycles should be given in the Note for Guidance. Therefore, we propose to delete the sentence "This may require up to 20,000 cycles".

**References:**

- [1] Gerlinger C, Endrikat J, van der Meulen EA, Dieben TOM, Düsterberg B.: Recommendation for confidence interval and sample size calculation for the Pearl Index. Eur J Contracept Reprod Health Care. 2003 Jun;8(2):87-92.
- [2] Benda N, Gerlinger C, van der Meulen EA, Endrikat J.: Sample Size Calculation for Clinical Studies on the Efficacy of a New Contraceptive Method. Biometrical Journal. 2004 Feb; 46(1):141-150.