Dear Madam, Sir,

With regard to the above mentioned draft guidance, I would like to make the following comment:

3. Drug Interactions

(page 9) **Ascorbic acid** and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol.

**Comment:** Since ascorbic acid is occasionally used in high doses, and since it, like ethinyl estradiol, is extensively metabolized to sulfate conjugates, it was hypothesized that gram quantity doses of ascorbic acid might interfere with the sulfation of ethinyl estradiol resulting in an increased oral bioavailability of the drug. Two studies carried out in small numbers of women seemed to confirm this interaction: ethinyl estradiol availability appeared to be increased by 50-60% when 1 g ascorbic acid was given half-hour before estrogen administration [1,2]. However, in a more recent study this finding has been re-investigated in 37 women and there was clear evidence for the absence of a significant interaction of ascorbic acid with the metabolism of ethinyl estradiol [3]. Based on the outcome of this study it was suggested to remove ascorbic acid from the list of drug interactions with oral contraceptive steroids.

I hope that you will find these comments helpful for finalizing the guidance document.

Yours sincerely,

W. Kuhnz

Dr. W. Kuhnz

cc: Dr. G. Rohls, Dr. B. Müller
References


