European Medicines Agency

SUBMISSION OF COMMENTS ON GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE CPMP/EWP/QWP/1401/98 Rev.1

Comments from the European Federation of Statisticians in the Pharmaceutical Industry (www.EFPSI.org)
GENERAL COMMENTS
NA

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Line 42 + 1 Introduction MINOR COMMENT	Please change following sentence: "In bioequivalence studies, the plasma concentration time curve…"	Suggested rewording: "In bioequivalence studies, the plasma, serum or blood concentration time curve…"
Line 100 to 115 MINOR COMMENT	ICH E9 "Statistical Principles for Clinical Trials" is missing in the list of reference guidelines	Suggest to add ICH E9 in the list of reference guidelines
Line 148 to 151 + Standard design	Randomisation and avoiding bias is mentioned in different places in the document (line 244 to 246 for bias and line 580 for randomisation) but not specified in the standard design section.	Suggest to add the following sentence at the end of Standard design section: Whenever possible, trials should be randomised.

Public

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int http://www.emea.eu.int

Line 152-175 + Section 4.1.1 Alternative designs	The guidance does not cover other possible designs (e.g multiple test products in a bioequivalence study testing a combination of product or different formulations).	Suggestion: Other alternative design can be considered with rationale for implementation.
Line 152-220 + 4.1.1-4.1.2	If similar product from the same originator is available both in EU and USA, BE comparison with either reference should be enough for both regions to reduce number of BE studies.	We would like to se more harmonisation between FDA and EMEA on guidances for bioequivalence studies.
Line 159	The first 90% confidence interval mentioned is the narrow version for no specific reason here. Indeed; the thresholds are mentioned several times in several paragraphs : 90-111 in section 4.1.1, section 4.1.6…, 75-133 in section 4.1.10 Moreover in the introduction bridge data are mentionned but then no further information appears in the acceptance limit section	Suggest regrouping all different thresholds of interest and reasons for considering them in section "acceptance limit" (line 548).
Line 223 to 229	No rationale is given for the minimum sample size to be considered for cross over designs in the document (i.e. 12 subjects). The proposed figure is not justified. If combined to section "Subject accountability" (line 573) it seems that it should be 12 evaluable (i.e. complete) patients. If the reason for this number is to make sure that a sufficient number of complete – evaluable cases are present, then suggestion is made to clarify the section. Moreover, no miminum sample size is suggested for alternative design (parallel group)	Suggest to give more details on reason for such sample size or to delete it if found out to be not appropriate. Suggest clarifying whether it is 12 included subjects or 12 evaluable subjects for the cross over design.
Line 320 + 4.1.5 MINOR COMMENT	Reference to definitions is wrong (there is no section 6 in this document)	
Line 496-499; 537-547	Confidence intervals (CIs) are the traditional statistical tool for BE studies, but the request for its use implies prohibition of Bayesian highest posterior density intervals (HPDIs). After an experiment, a 90% HPDI (unlike a 90% CI) has a 90% chance of containing the unknown parameter, and as such its use may be preferable to the use of a 90% CI.	Suggest expressing more openness to other statistical techniques as non-frequentist statistical techniques (in a similar way to ICH E9), e.g by adding "Alternative methods, eg Bayesian methods such as the highest posterior density interval (HPDI) may be considered." to Line 499.

Line 504 and 505	The statement that "non-parametric analysis is not acceptable" seems unnecessarily strong, as there may be situations where a non-parametric analysis may be appropriate (in particular if the analysis of T_{max} is performed, although this is not necessary in most cases).	Suggest rewording sentence to "A non-parametric analysis is not usually acceptable unless justified".
Line 509	Suggest not proposing any specific statistical model. Moreover the level of information on the proposed model for 2 by 2 cross over may not be sufficient. The role of the sequence effect (between subject information) should be clarified. The importance given to the sequence effect highlights the need for a randomised trial.	Suggestion to remove details on any specific statistical model
Line 512 4.1.8 Statistical analysis MINOR COMMENT	Sentence should be rephrased: "… number of observations for the observations in the respective …"	Suggestion: "…number of observations ~~for the observations~~ in the respective…"
Line 512-514	The rationale for the request "In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment." is not clear as it raises the following issues: • The reporting of a test for a treatment effect is not relevant for a bioequivalence study as it contradicts the hypotheses tested in a bioequivalence study. • The next sentence states "a test for carry-over should not be performed", which contradicts the request for a sequence effect test. • The confidence interval for a period effect is not relevant or informative.	Suggest amending the sentence "In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment." to "In addition, the test for the period effect and the confidence intervals for the treatment effect should be reported for descriptive assessment."
Line 514-516	This sentence contradicts the previous one. It states that a test for carryover should not be performed, but the previous sentence recommends testing for sequence effect. Sequence and carryover effects are equivalent in a simple 2x2 crossover study.	Please clarify that the test for carry-over and sequence effect are equivalent for 2x2 cross-over studies.

Line 517-519	Generally, the proposed method for dealing with carryover (exclusion of subjects with suspected carryover from the biometrical evaluation) appears problematic from a statistical perspective.	Suggest adding in design section information about how to avoid carry over effect: sufficient enough wash out period should be defined in the protocol e.g 5 times t1/2 depending on the reference/ tested product.
Line 543-547	These lines call on sponsors to compare various bioequivalence studies in terms of their strengths of evidence. Weighing evidence is problematic within frequentism, however. Whereas analysts often try to measure evidence using statistical tests and estimation, the theory behind those methods contains no defined concept of evidence. Without having defined evidence, one cannot determine whether some studies' evidence "outweighs" other studies' evidence.	Please clarify what is meant here as outweighing has no statistical background. Suggest removing any references to the concept of outweighing evidence in the guideline.
Line 558-559 + 4.1.8	Cmin,ss should not always be a critical variable for showing bioequivalence in steady state studies.	Suggest to change in sentence line 558 : For studies to determine bioequivalence at steady state AUCτ, and Cmax,ss, (and Cmin when appropriate) should be analysed using the same acceptance interval as stated above.
Line 641	Suggest to put this sentence in section "alternative design"	
Line 574-576 Line 583-584	The exclusion of subjects who did not complete both the test and reference product period from the analysis does not make the best use of the data collected (as a mixed model analysis is able to suitably incorporate such partial data in the analysis).	Suggest rewording the sentence from lines 574-576 to "All treated subjects should be included in the statistical analysis, with the exception of subjects in a crossover trial who do not complete at least one period (or who fail to complete the single period in a parallel group trial)." Suggest rewording the sentence from line 583-584 to "Ideally all treated subjects should be included in the analysis provided that at least one treatment period has been completed."
Line 631- 641 + Section 4.1.10 Highly variable drugs	As AUC may be highly variable (although usually to lesser extent than Cmax), widening the acceptance range based on reference variability should be considered.	Please reword to allow for more flexibility on the acceptance range especially for bridging studies