

Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED

WHO Technical Report Series (TRS) No. 1003, Annex 6 (2017) reports the following in Section 7.9.3:

- A “highly variable API” has been defined as an API with an intrasubject variability of > 30% in terms of the ANOVA-CV (14). Proving the bioequivalence of FPPs containing highly variable APIs can be problematic because the higher the ANOVA-CV, the wider the 90% confidence interval. Thus, large numbers of subjects must be enrolled in studies involving highly variable APIs to achieve adequate statistical power.
- Although there is variability in how regulatory authorities deal with the issue of highly variable APIs, the most rigorous of the current approaches involve the scaling of bioequivalence acceptance criteria based on the intrasubject standard deviation observed in the relevant parameters for the comparator product (15–17). Of the two most common assessment parameters C_{max} is subject to the highest variability and hence is the parameter for which a modified approach is most needed.

There is evidence to suggest that very high variability may be observed with the AUC parameter for a limited number of APIs in certain comparator products and there may be situations where the scaling / widening of the acceptance criteria for AUC, as described for C_{max} in Section 7.9.3 of TRS No. 1003, Annex 6, in bioequivalence studies conducted with these comparator products may be justified without an undue increase in risk regarding the therapeutic safety and efficacy of the proposed drug product.

For the past five years, on a trial basis, PQT/MED has considered a priori scientific justifications from applicants to permit the scaling / widening of the AUC acceptance criteria for data from full replicate design bioequivalence studies. This trial period has allowed PQT/MED to better understand the risks associated with extending the possibility for scaling / widening to the AUC parameter.

Going forward, PQT/MED will accept the widening of the acceptance range not only of the C_{max} , but also for the AUC for data from four-period, full replicate design bioequivalence studies, if this approach is pre-defined in the protocol and it is justified in the protocol that the potential larger differences between the proposed product and the comparator that might be accepted due to the widened acceptance range lack clinical relevance. A priori approval for this approach is no longer required, however, as a general rule, it is strongly recommended that protocols for bioequivalence studies planned for submission to PQT/MED be submitted to PQT/MED for comment prior to undertaking the study.