

Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQTm

WHO Technical Report Series (TRS) 992, Annex 7 (2015) 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 and there may be situations where the scaling of the acceptance criteria for AUC, as described for C_{max} in Section 7.9.3 of TSR 992, Annex 7, in bioequivalence studies conducted with these APIs may be justified without an undue increase in risk regarding therapeutic safety and efficacy of the proposed drug product. On a trial basis, PQTm will consider scientific justifications from applicants to permit the scaling of the AUC acceptance criteria for data from full replicate design bioequivalence studies.

The following requirements apply:

- A request to apply the scaling approach described in Section 7.9.3 to AUC data should be submitted to PQTm along with a final draft of the proposed study protocol prior to undertaking the study.
- The request should report the data available from literature or pilot data demonstrating the magnitude of the variability in the AUC parameter. It should also include a scientific discussion of the possible impact of widened AUC acceptance limits on the therapeutic/clinical effect and safety of the API and drug product under development.

The applicant should receive confirmation that PQTm will accept reference-scaled bioequivalence for AUC for the specific API under consideration, as described in Section 7.9.3, prior to undertaking the bioequivalence study. In cases where reference-scaling for the AUC acceptance limits is accepted, a four period, full replicate design study should be conducted to demonstrate bioequivalence, in order to assess the variability associated with each product.