

Figure 1. The results of two BE studies A & B. Both have the same GMR and the same number of subjects. Drug A: ANOVA-CV 15%, the 90%CI falls easily within the BE limits. The study passes easily. Drug B: ANOVA-CV 35%, the 90%CI violates the lower BE limit. The study fails.

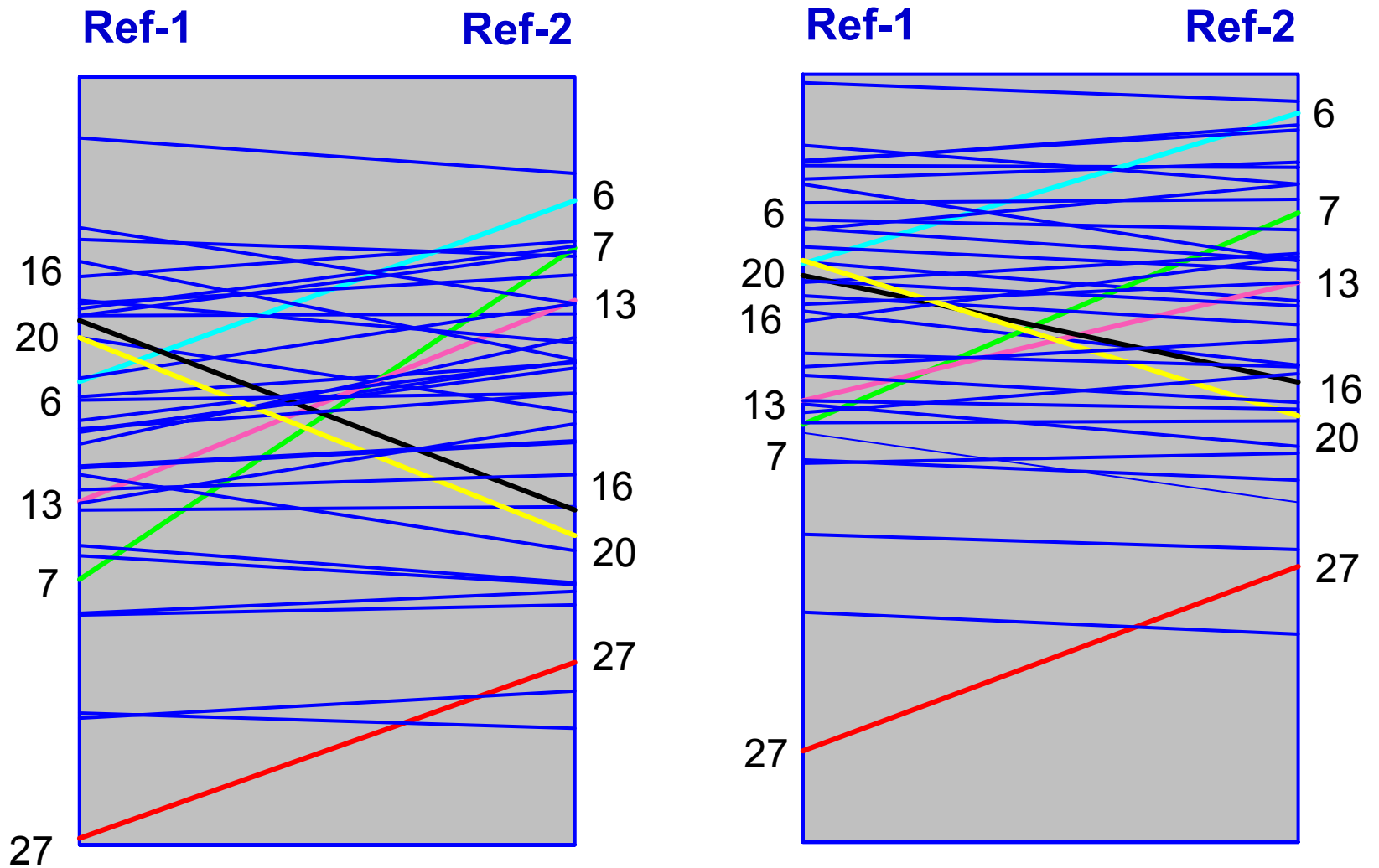


Figure 2a: Stick plots showing parametric values (on the vertical axes) for each of 37 subjects after two doses (from the same lot) of chlorpromazine; left panel In Cmax, right panel In AUClast. The numbers refer to selected subjects.

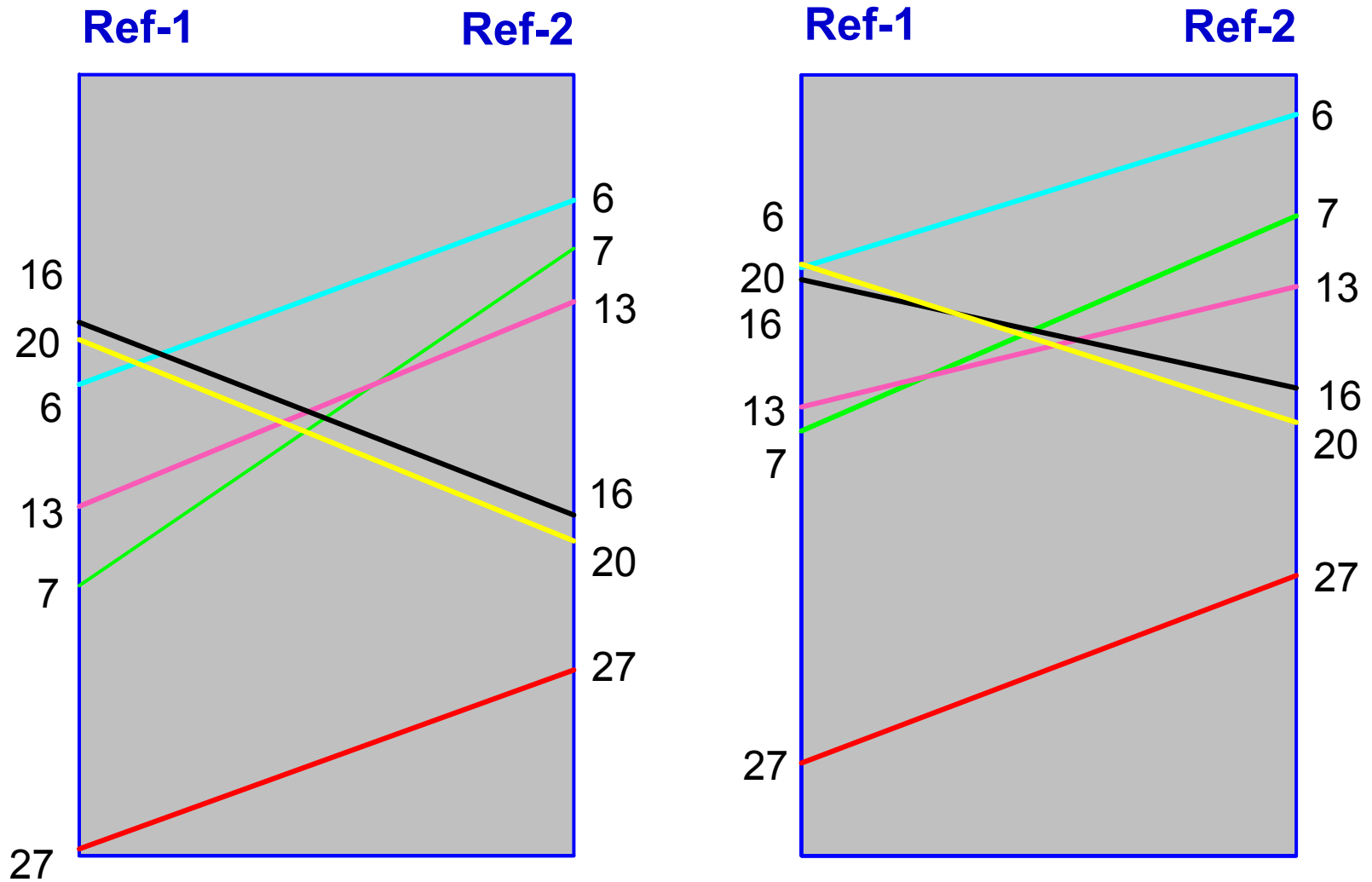


Figure 2b: Stick plots exactly the same as Figure 2a, emphasizing 6 subjects showing large dose to dose variations. Note the similarity of the patterns in the left panel ($\ln C_{max}$) and the right panel ($\ln AUC_{last}$)

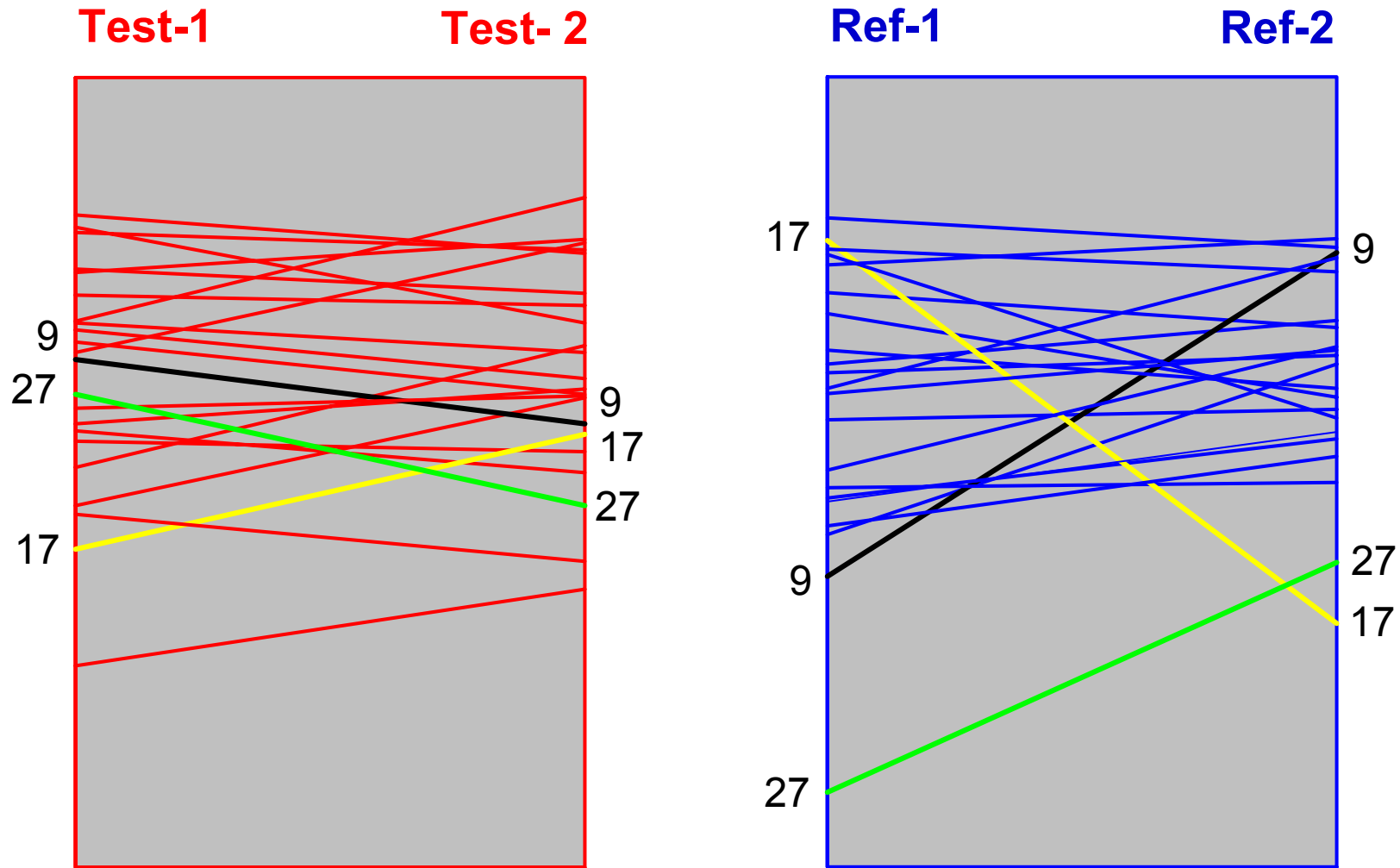


Figure 3a: Stick plots showing parametric values (on the vertical axes) of In Cmax for each of 22 subjects after four doses of nadolol: left panel, test product; right panel, reference product. The numbers refer to selected subjects.

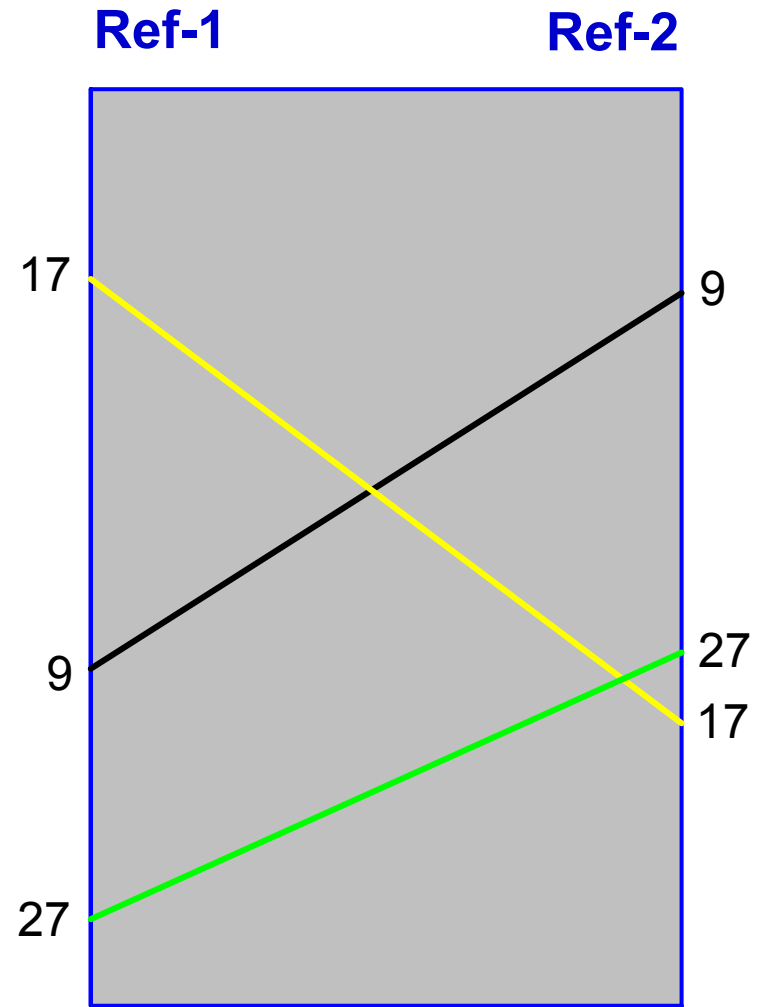
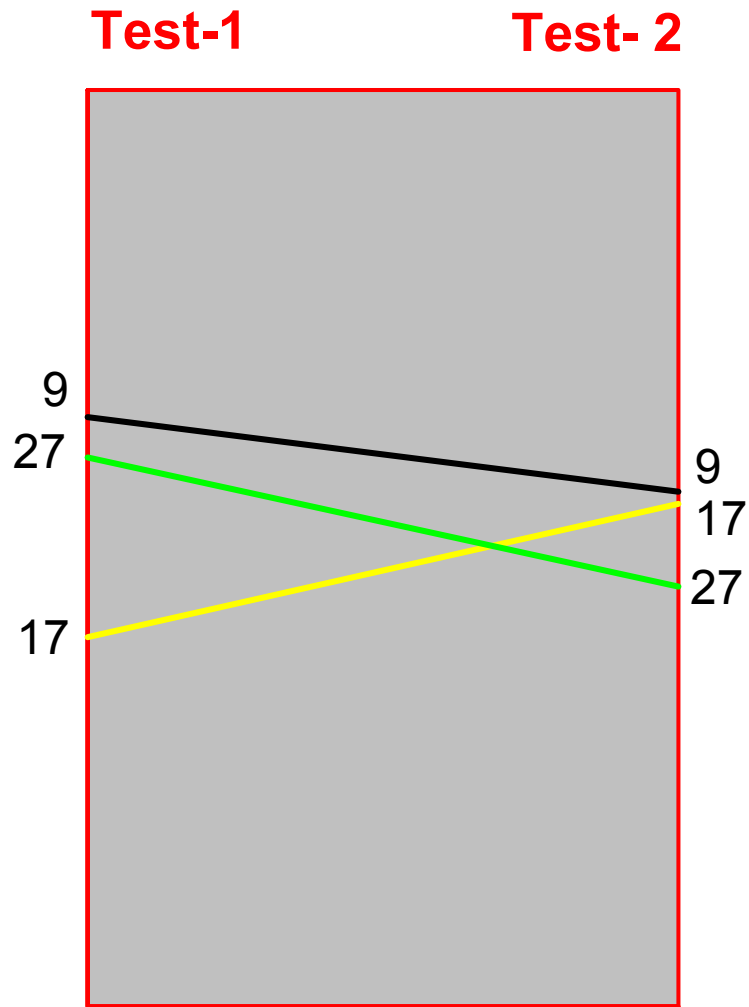


Figure 3b: Stick plots exactly the same as Figure 3a, emphasizing 3 subjects who show markedly greater variability in their response the reference product in comparison with the test product in terms of $\ln C_{max}$

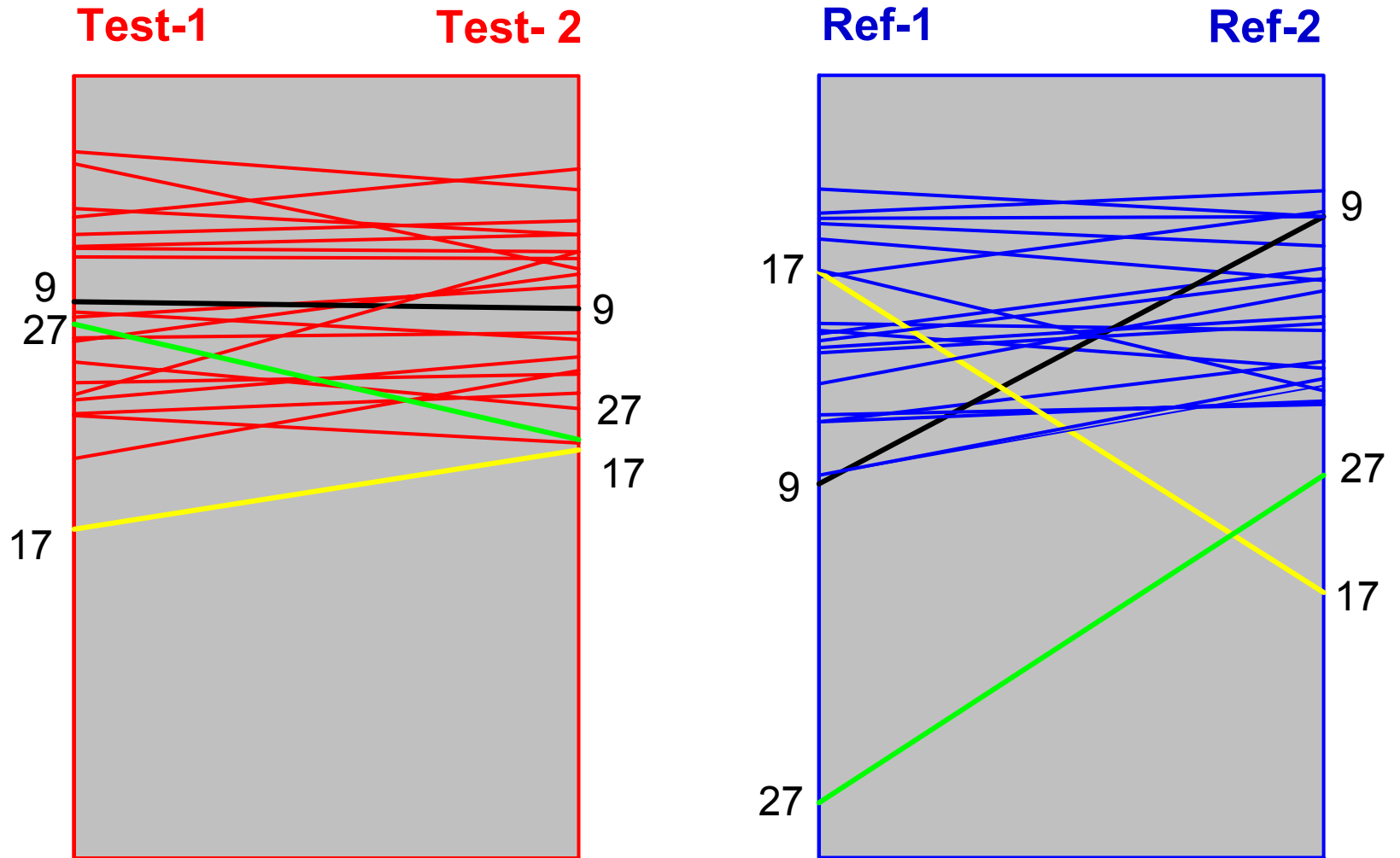


Figure 3c: Stick plots showing parametric values (on the vertical axes) of In AUClast for each of 22 subjects after four doses of nadolol: left panel, test product; right panel, reference product. The numbers refer to selected subjects.

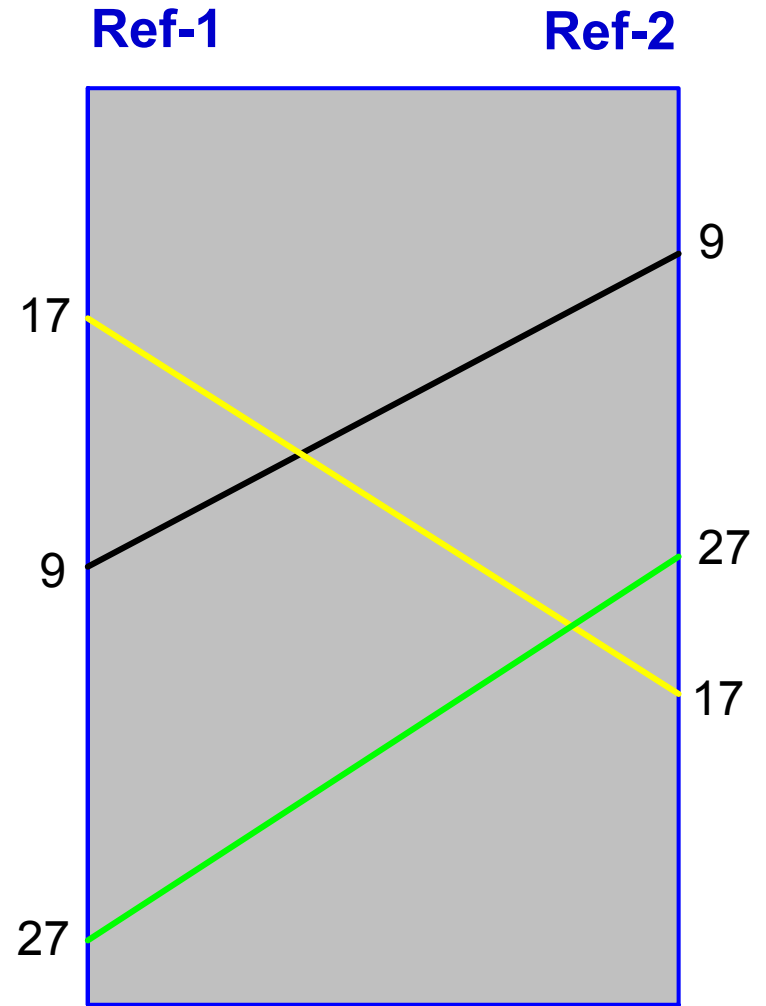
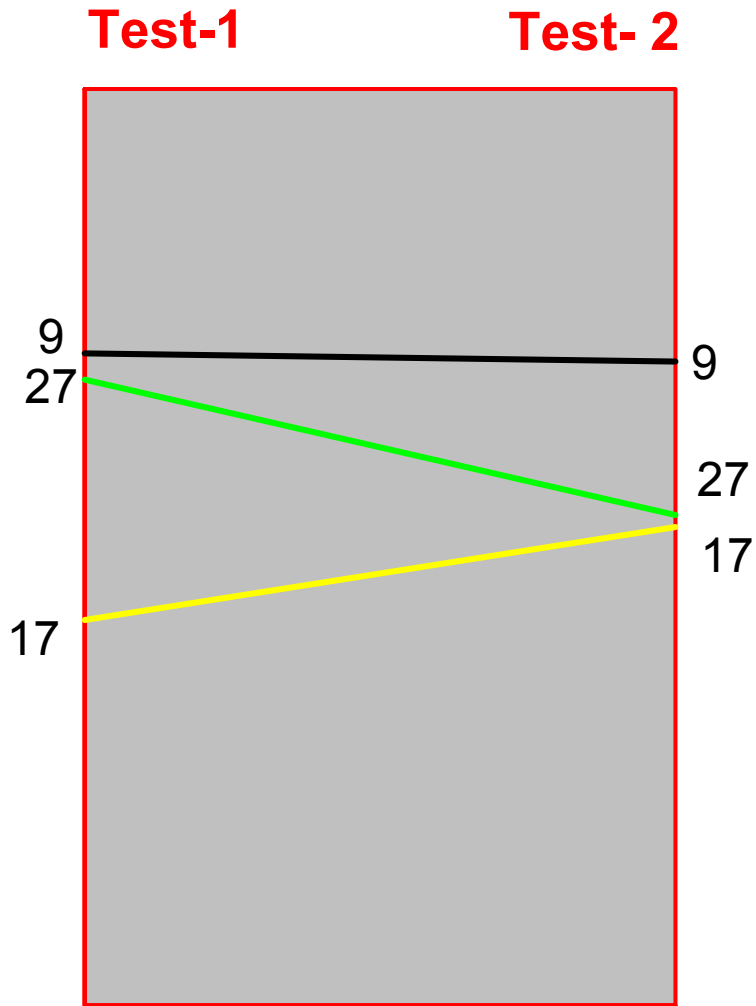
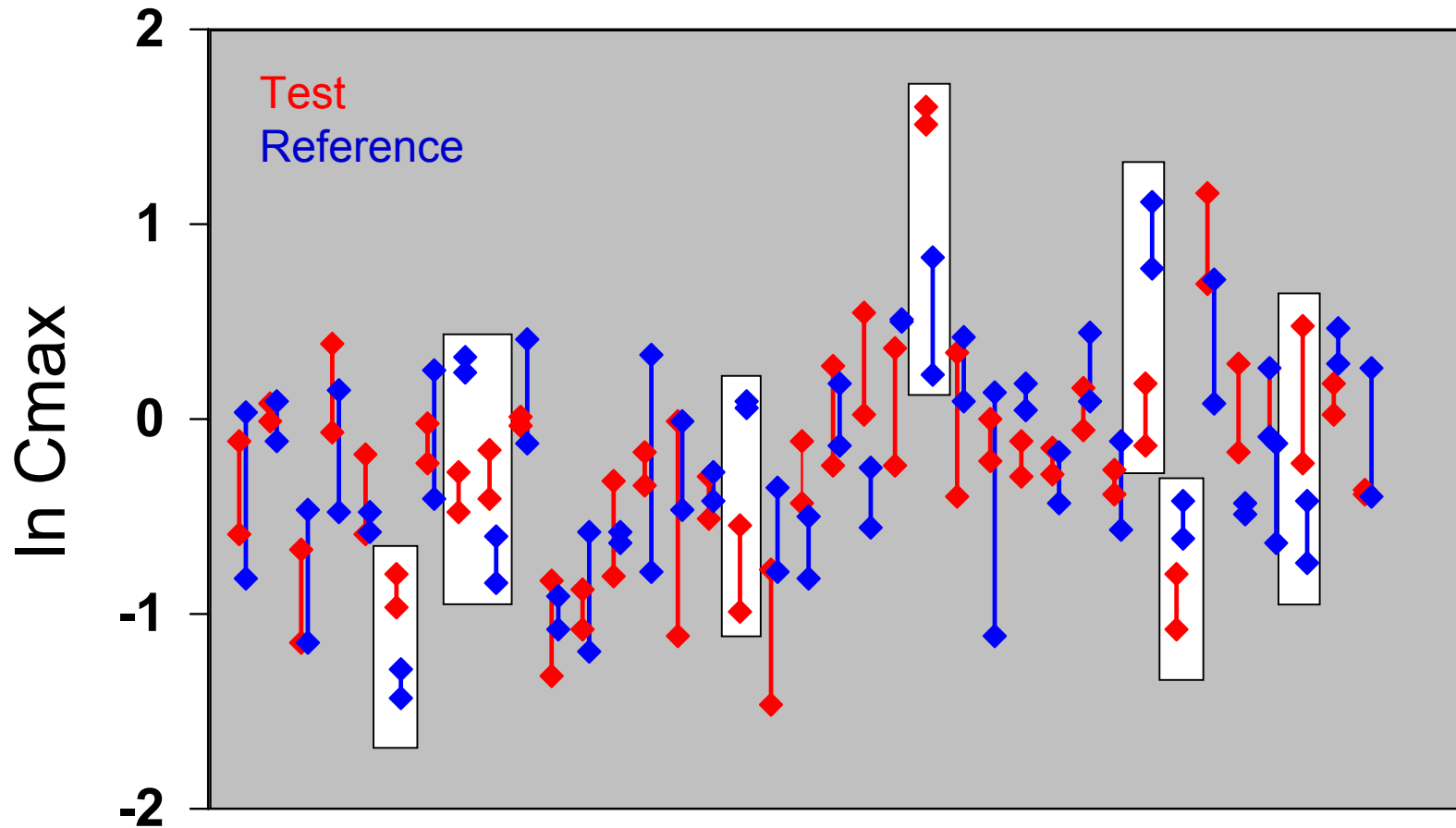
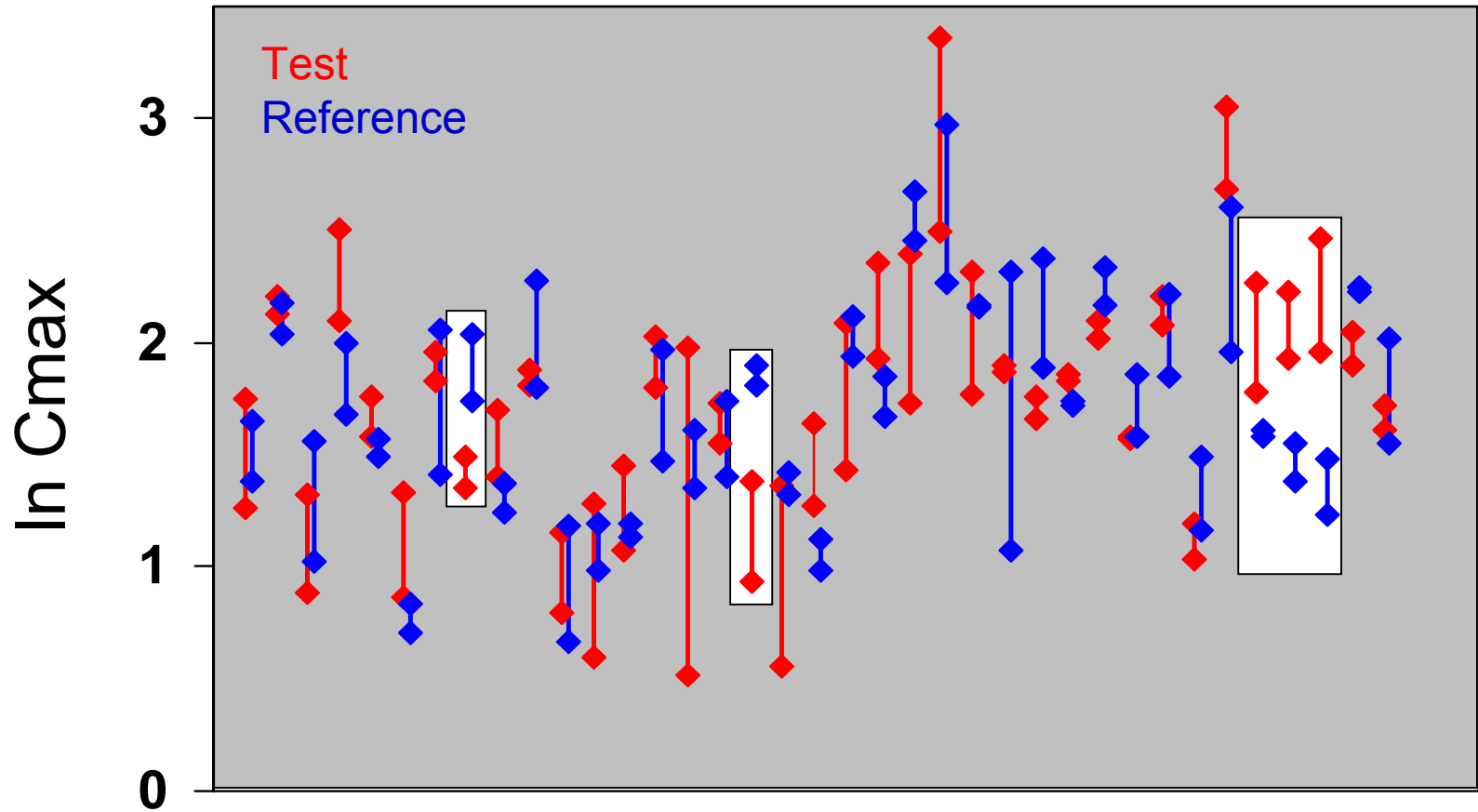


Figure 3d: Stick plots exactly the same as Figure 3c, emphasizing 3 subjects who show markedly greater variability in their response the reference product in comparison with the test product in terms of In AUClast



37 Subjects in Numerical Order

Figure 4a: Illustration of a subject by formulation interaction in ln Cmax after two doses of the test and two doses of the reference percutaneous patch formulations of nitroglycerin. Eight contributing subjects are highlighted



37 Subjects in Numerical Order

Figure 4b: Illustration of a subject by formulation interaction in In AUClast after two doses of the test and two doses of the reference percutaneous patch formulations of nitroglycerin. Five contributing subjects are highlighted

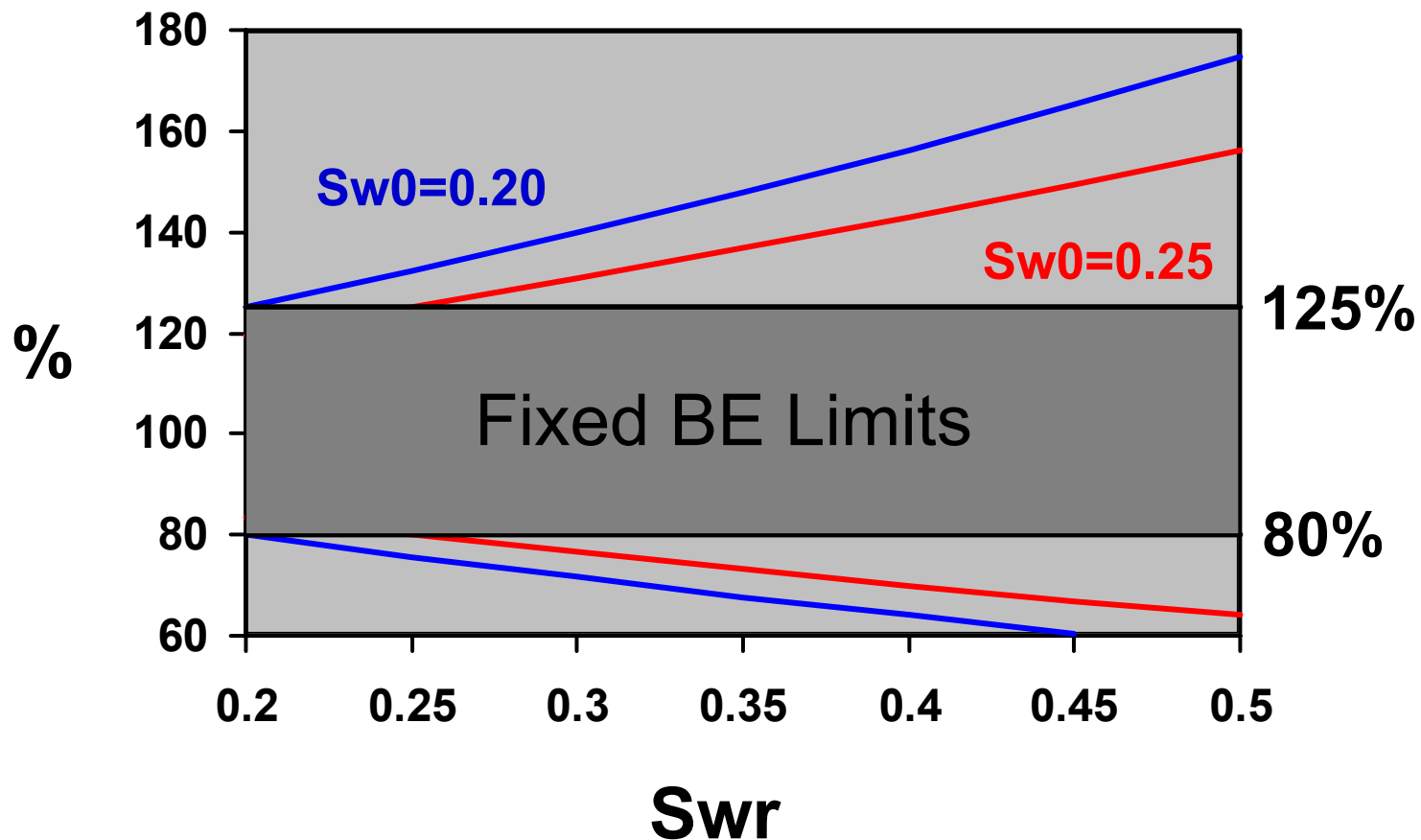


Figure 5: Fixed bioequivalence (BE) limits of 80 -125% compared with BE limits scaled to the within-subject standard deviation of the reference formulation (horizontal axis) with $\sigma_{w0} = 0.2$ (blue) or 0.25 (red)