Abstract: Traditional bioavailability studies assess average bioequivalence (ABE) between the test (T) and reference (R) products under the crossover design with TR and RT sequences. With highly variable (HV) drugs whose intra-subject coefficient of variation in pharmacokinetic measures is 30% or greater, assertion of ABE becomes difficult. In 2011, the FDA adopted a more relaxed, yet complex, ABE criterion and supplied an assessment procedure exclusively under TRR-RTR-RRT and TRTR-RTRT designs. However, designs with more than two periods are not always feasible. This present work investigated how to evaluate HV drugs under TR-RT designs. A mixed model with heterogeneous residual variances was used to fit data from TR-RT designs. Under the assumption of zero subject-by-formulation interaction, this basic model is comparable to the FDA-recommended model for TRR-RTR-RRT and TRTR-RTRT designs. Statistical tests were developed via the generalized pivotal quantity (GPQ). Simulation studies showed that in comparison to the FDA's approach, this GPQ-based procedure gave similar performance when the product's inter-subject standard deviation was low (<0.4) and was most useful when practical considerations restrict the crossover design to two periods.