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RSABE vs ABEL: planning BE studies for highly variable drugs

How the FDA and EMA scale bioequivalence limits to reference variability, and what that means for design and sample size.

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THE PROBLEM

Highly variable drugs make standard bioequivalence impractical

- **Highly variable drug (HVD):** within-subject CV of the reference product (CV_{wR}) of 30% or more for Cmax and/or AUC
- With fixed 80.00–125.00% limits, a 2×2 crossover may need very large samples, and the reference product may fail to be bioequivalent to itself
- **Solution:** scale the acceptance limits to the reference product's own variability, estimated from a replicate design

REPLICATE DESIGNS

Design	Sequences	Estimates
3-period partial	TRR / RTR / RRT	σ_{wR} only
3-period full	TRT / RTR	σ_{wR} and σ_{wT}
4-period full	TRTR / RTRT	σ_{wR} and σ_{wT}

T = test, R = reference. Full replicates also allow comparison of test and reference variability.

SIDE BY SIDE

FDA reference-scaled ABE versus EMA ABEL

Feature	FDA RSABE	EMA ABEL
When scaling applies	$s_{wR} \geq 0.294$ ($CV_{wR} \approx 30\%$); otherwise standard ABE	$CV_{wR} > 30\%$, with clinical justification that the wider difference is not relevant
PK metrics	Cmax and AUC	Cmax only (AUC not widened); Cmin/Cτ for some modified-release products
Criterion	95% upper bound of $(\mu_T - \mu_R)^2 - \theta \cdot s^2_{wR} \leq 0$, with $\theta = (\ln 1.25)^2 / 0.25^2$	90% CI within $\exp(\pm 0.760 \cdot s_{wR})$
Upper cap	No cap; implied limits keep widening	Capped at CV_{wR} 50%: 69.84–143.19%
Point estimate	Geometric mean ratio within 80.00–125.00%	Geometric mean ratio within 80.00–125.00%
Analysis	Linearised criterion (Howe's method) on R–R differences	ANOVA (Method A) with fixed effects; CV_{wR} from R data; check that outliers do not drive CV_{wR}

Health Canada uses a third approach: widening for AUC, capped at 66.7–150.0%, with only a point-estimate criterion for Cmax.

BY THE NUMBERS

How acceptance limits widen with reference variability

CV_{wR}	s_{wR}	EMA ABEL limits	FDA implied limits*
30%	0.294	80.00–125.00%	80.00–125.00% (ABE)
35%	0.340	77.23–129.48%	73.83–135.45%
40%	0.385	74.62–134.02%	70.90–141.04%
45%	0.429	72.15–138.59%	68.16–146.71%
50%	0.472	69.84–143.19%	65.60–152.45%
60%	0.555	69.84–143.19% (cap)	60.96–164.04%

$s_{wR} = \sqrt{\ln(1 + CV_{wR}^2)}$. *FDA limits implied by θ; the actual test is the linearised criterion plus the point-estimate constraint.

Worked example: Cmax with CV_{wR} = 45%. Observed GMR 0.92 with 90% CI 77.0–110.0%. It fails standard ABE (lower bound below 80%) but passes EMA ABEL (72.15–138.59%), and would be assessed under RSABE by FDA.

Note: EMA scaling never applies to AUC, so AUC must still meet 80.00–125.00%, and often drives the sample size.

PLANNING

A planning checklist for global HVD programmes

1. **Estimate CV_{wR}** from pilot data, the literature or public assessment reports; plan with a conservative value.
2. **Choose the design:** a partial replicate is efficient for FDA; a full replicate supports EMA outlier checks and comparison of test and reference variability.
3. **Size by simulation** for each agency's method, assuming a GMR of 0.90–0.95 (e.g. PowerTOST: sampleN.RSABE, sampleN.scABEL).
4. **Allow for dropouts**, which are higher in 3- and 4-period studies with long washouts.
5. **Pre-specify everything**: method, software, CV_{wR} estimation, outlier handling and the AUC criterion.

Pitfalls to avoid

- Type I error inflation near CV_{wR} 30%; consider an adjusted alpha
- One outlying reference subject inflating CV_{wR}
- Planning only for Cmax when AUC also needs to pass
- Narrow therapeutic index drugs, which follow different, tightened rules

REFERENCES

Key guidance and literature

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