Aspectos técnicos y legales de la Bioequivalencia en Colombia

Diseño de estudios de Bioequivalencia

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Design to achieve the objective

- BE studies are designed to compare the in vivo performance of a multisource product with that of a comparator product
- Two purposes:
  - Provide in vivo measure of pharmaceutical quality
  - Surrogate of clinical evidence of safety and efficacy
- It is necessary: Maximize sensitivity to detect differences
  - To minimize variability (within and between subjects)
  - Eliminate bias (unequal carry-over effect in 2x2 designs)

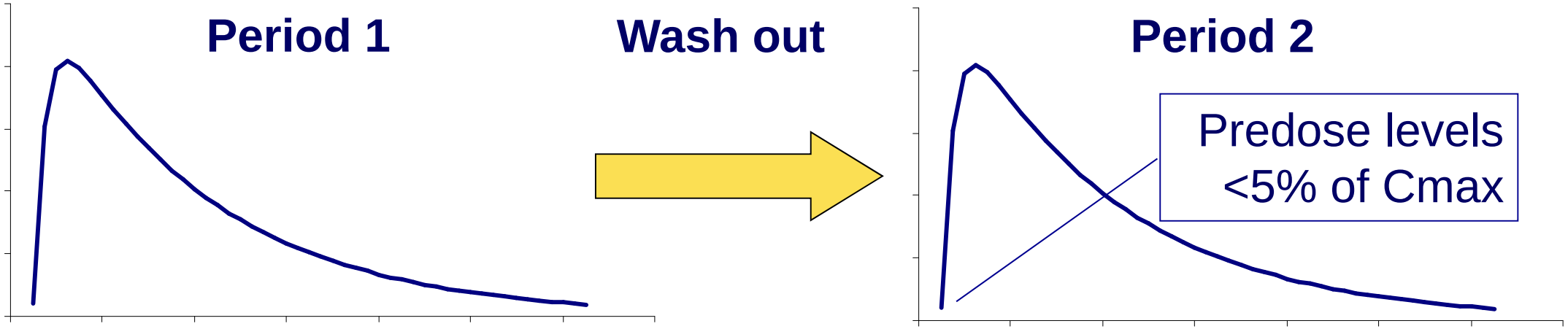
Conventional Design: 2x2

Randomization to sequences of treatment

	Period 1	Washout (passive)	Period 2
Sequence 1 (AB) (n subjects)	Comparator product	 >5 half-lives	Multisource product
Sequence 2 (BA) (n subjects)	Multisource product		Comparator product

- A two-period, two sequence, single dose, cross-over, randomized design in healthy volunteers

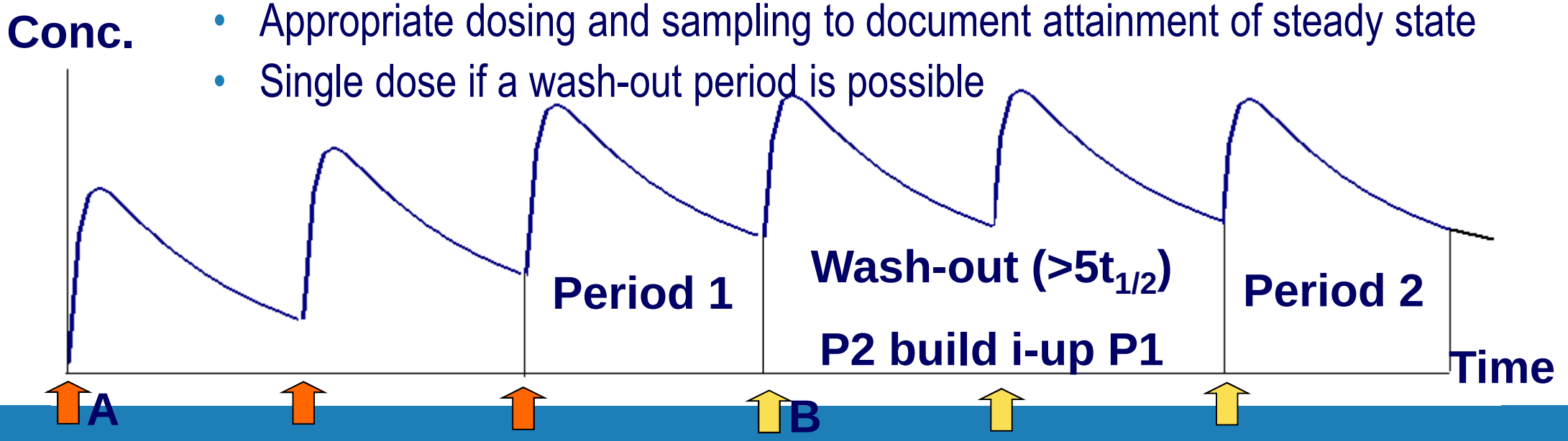
Wash-out to avoid carry-over



- Blood samples are collected and assayed
  - Before and several times after drug administration. No need after 72 h
- Prior to period 2, pre-dose levels must be <5% of Cmax of 2nd period
- Wash-out period must take into account the slow metabolizers
- Minimum wash-out: 7 days (1 week)

Alternative designs: Multiple dose

- Very potent or toxic drugs: Healthy volunteers in a lower strength
  - Patients (stable) if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons
  - Multiple dose study in patients is acceptable, when a single dose study is not feasible in patients
    - Multiple dose if patients cannot have passive wash-out. Usual dosing.
    - Appropriate dosing and sampling to document attainment of steady state
    - Single dose if a wash-out period is possible



Alternative designs: Multiple dose

- Other situations in which multiple-dose studies may be appropriate are as follows:
  - cases where the analytical sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
  - for extended-release dosage forms with a tendency to accumulate (in addition to single-dose studies).

Limitation of the multiple dose study

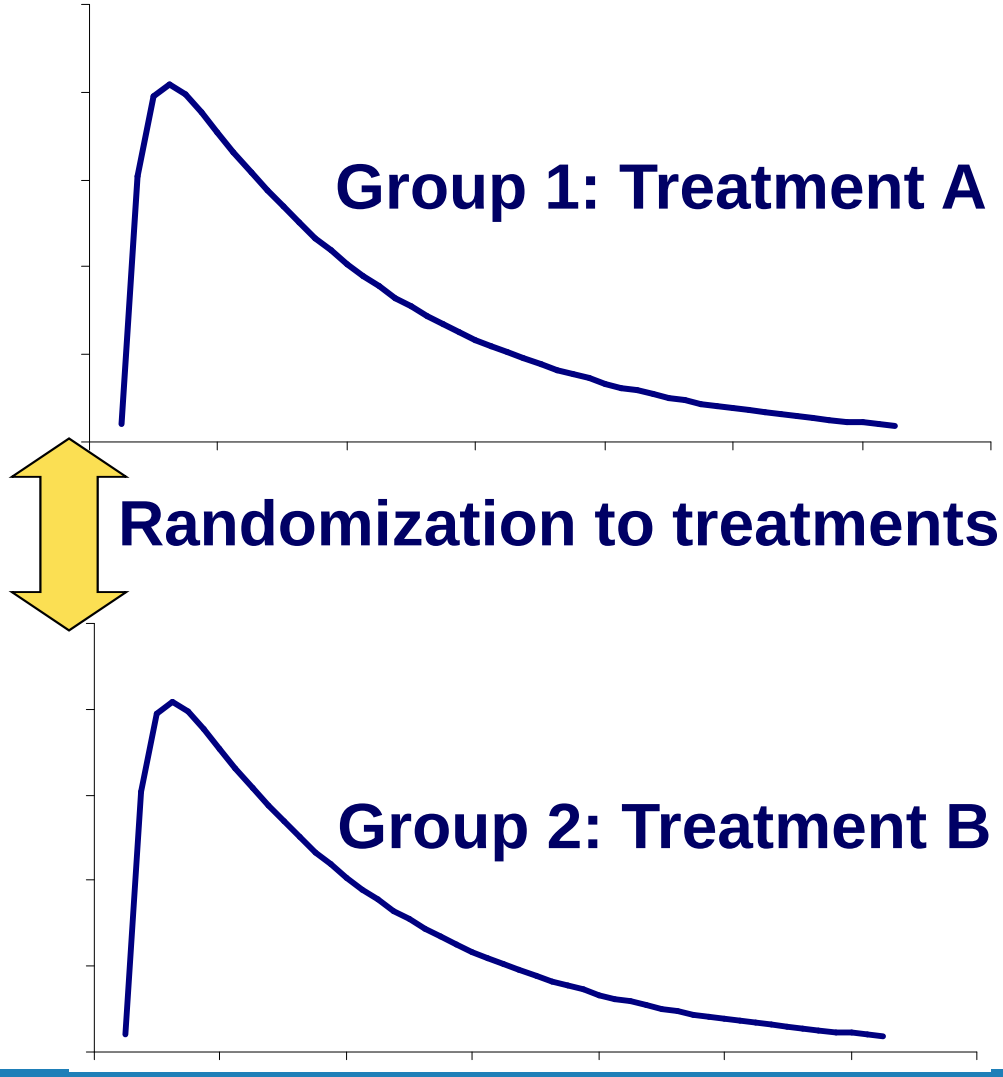
- A multiple dose study is less sensitive in detecting differences in Cmax
- A multiple dose study will only be acceptable if the applicant adequately can justify that the sensitivity of the analytical method cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a supra-therapeutic dose in the BE study (no solubility or tolerability limitations)

Alternative designs: Multiple dose

- In the past a multiple dose study was required in EU for drugs that exhibit non-linear kinetics at steady state (e.g. saturable metabolism, active secretion)
  - No longer required in EU
  - No longer recommended by WHO

Drugs with long elimination $t_{1/2}$: Parallel

- *Normally wash-out period should not exceed 3-4 weeks*
- If a larger wash-out period is necessary a parallel design may be more appropriate
- Variability will be larger, needs higher sample size
  - Parallel design: Total variability (intra+inter)
  - Cross-over: Intra-subject variability
- Sampling: Up to 72 h for IR



Phenotyping!

Replicate design

- In case of highly variable drugs (CV>30%)
  - Two distinguish intra-subject variability from other sources of variability: random error, analytical method, …
  - More information:
    - Intra-subject variability of Test product / Multisource (generic)
    - Intra-subject variability of Reference / Comparator
    - Subject by formulation interaction
  - If scaling / widening limits based on variability
  - Fewer subjects
  - More administrations
  - Similar number of profiles

	PERIOD									
SEQUENCE	1	2	1	2	3	1	2	3	4	
1	T	T	T	R	R	T	T	R	R	
2	R	R	R	T	T	R	R	T	T	
3	T	R				T	R	R	T	
4	R	T				R	T	T	R	

Two-stage designs

- Add-on design
  - Sample size of both groups have a lower limit
- Group sequential design
  - Sample size of both groups are pre-specified
- Adaptative two-stage sequential design
  - Groups sizes are not limited (unless a futility criterion is used)
  - The sample size of the second group is re-estimated from the data of the first group

Add-on designs (not recommended)

- If bioequivalence cannot be demonstrated because:
  - Larger variability than expected
  - Larger difference than expected but still within 20%
- An add-on design can be performed using not less than half the number of subjects in the initial study
- Provided this was anticipated in the protocol
- Combining data only if:
  - Same protocol
  - Same batches

Add-on designs (not recommended)

- Add-on designs must be given appropriate statistical treatment
- Canadian add-on design requires:
  - No interaction formulation effect x study phase
  - No statistical difference in variability of both phases
  - But the consumer's risk is increased
  - Statistically inadequate
  - It must be a sequential design with control of the alpha expenditure (EMA)

Two-stage design (EMA)

- An initial group of subjects can be treated and their data analysed.
- If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis.
- If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study.
- The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%)

Two-stage design (EMA)

- For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion.

Unfortunately, it is not self-evident that this alpha is correct only if the sample size is pre-specified and equal in both stages (Pocock).

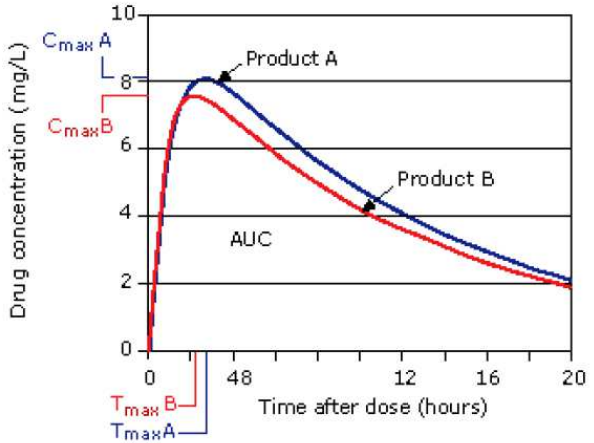
- The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

- When analysing the combined data from the two stages, a term for stage should be included in the ANOVA model.

Sampling times

- Blood samples with frequency sufficient frequency for assessing Cmax, AUC and other parameters

- Sampling points should include:
  - a pre-dose sample,
  - at least 1–2 points before Cmax,
  - 2 points around Cmax and
  - 3–4 points during the elimination phase.
  - Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters.



Sampling times

- For most APIs the number of samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API in the blood (Cmax) and terminal elimination rate constant in all subjects
- Generally, sampling should continue for long enough to ensure that 80% of the AUC (0→ infinity) can be accrued, but it is not necessary to sample for more than 72 hours
- The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form

Thank you very much for your attention!