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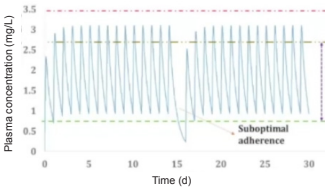
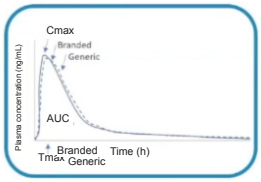
"Managing the PK tail in BE studies"

Bioequivalence

Traditional BE studies were for oral drugs.

- Plasma concentration-time curve.

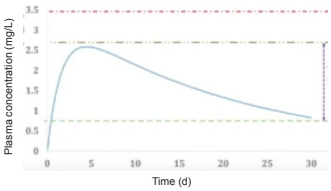




- BE limit: Generic and brand formulations are BE if the 90% CI for GMR of Cmax and AUC (log transformed) is within 80-125%.

BE studies for LAIs.

- Plasma concentration-time curve.



What about the tail?
We also care about the end of the PK curve, not just the beginning

- **Traditional BE does not consider the PK tail phase.**

LAIs behave very differently than oral formulations.

- Release-dependent (flip-flop) PK.
  - ◊ The rate of absorption is slower than the rate of elimination.
  - ◊ The elimination half-life is much longer following extra vascular (Appropriate LAI route) vs IV dosing.
- The PK tail is pharmacologically important and highly variable.
  - ◊ Terminal slope is controlled by BA and absorption rate, not clearance and Vd.
  - ◊ Absorption rate depends on many characteristics, varies widely across different drugs and formulations, and has significant inter-individual variability.
- **Is the traditional 80-125% BE limit appropriate for LAIs?**
  - ◊ When elimination depends on absorption, does it matter whether Cmax is within the BE limit if the decay is similar and concentrations are well-above therapeutic cut-offs?

Challenges around the design of in vivo PK BE studies of LA agents

Single dose (SD) vs multiple dose.

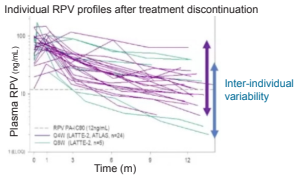
- Is steady state necessary for ARVs?
  - ◊ Some LA ARVs have loading doses, which are known to have significantly more inter-individual variability than later doses (e.g. Differences in males vs females during first 6m).
  - ◊ Time to steady state may not be realistic.
- SD provides no information on intra-individual variability.

Standard two-period crossover design.

- Washout period for controlled-release products is 8.5 half-lives.
  - ◊ SD parallel design avoids long washout period, but high intra- and inter-individual variability is a concern.
  - ◊ **It would take 3y to conduct a cross-over PK BE study of RPV at steady state (RPV half life ~ 29w).**

Recruitment and retention of study participants.

- High inter-individual variability in the PK tail and long PK washout are important to consider when selecting healthy volunteers or PLWH.
  - ◊ Data from P3 trials of RPV+CAB LA.
    - * For some, RPV quickly drops below the minimum effective concentration but is present for many months. **Risk for HIV infection and resistance.**
    - * For others, very high RPV concentrations are maintained for 1y. **RPV will be present for years, not months.**



- Long follow-up period ≥ 1y. To maintain a low drop-out rate, you must consider many circumstances (How much and when you pay and transparency matter).

Healthy volunteers vs patients.

- Choice is driven by safety and ethical considerations.
  - ◊ Fasting vs fed; Biological matrix; Highest dosage or multiple; Parent drug/metabolite.
- Active metabolites are a complicating factor.
  - ◊ PK curve, tail and behavior may be completely different for LAIs vs oral formulations. Concentrations depend on drug release and absorption, and time to steady state is unknown.

Lessons from veterinary medicine.

BE studies of oxytetratcycline IM.

- Test and brand formulations were bioequivalent in pigs.
- Formulations behaved similarly in cows but not bioequivalent.
  - ◊ Tmax and AUC met BE criteria.
  - ◊ Cmax was not within the BE limit (90% CI of test:reference: 65.04–134.97%). High inter-individual variability in drug exposures.
  - ◊ More studies needed: Larger sample size? Lower dose?

80-125% limit complicates the simplification of BE studies.

- Inter-individual variability in LAI exposures requires larger studies.

Potential solutions & areas for research

Role of the in vitro component in studying BE.

- Each LAI is different. Developing a better understanding of the in vitro-in vivo correlation is important (i.e., How to administer? Adequate dosing interval? PK tail duration for safety?).

Partial AUC assessment.

- May be difficult for time- and concentration-dependent drugs (i.e., Many anti-infective drugs). We care what happens at the end of the dosing interval.
- Ctrough is not included in BE criteria. Is it different for LAIs?
- Do we need BE data during the tail? What sampling frequency?
- Injection site/procedure effect. How the drug is formulated impacts absorption, elimination/tail, and inter-individual variability.
- Dropout rate and participant safety. Risk of resistance and developing HIV with exposure to low drug concentrations.

Modeling approaches.

- FDA workshop (2021): Model-integrated evidence to demonstrate BE of LAIs.

Summary

- Understanding the PK tail of different LAI formulations is important. Don't get fixated on traditional BE concepts.
- PK tail depends on absorption (high inter-individual variability).
- Parallel design is more realistic than crossover. Sample size increases due to wide inter-individual variability.
- Ideally assess BE beyond the loading dose. Steady state may be too long.
- Volunteer retention is important. Need to include different populations if there are differences (e.g., age, weight, women, men, etc.).
- PK tail is a challenge for BE/generic development but achievable.
- Increase our knowledge of half-lives and tools to predict the PK tail. No need to sample for years.