PLENARY 3

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"Patients vs healthy volunteers"

Regulators prefer healthy volunteers (HVs) for BE studies

Use of patients is driven by safety considerations.

- FDA (2021). Perform a BE study with patients if it cannot be safely conducted in HVs.
- EMA (2010). Explicit preference for HVs to eliminate differences unrelated to the product, unless the drug has safety concerns that make this unethical.

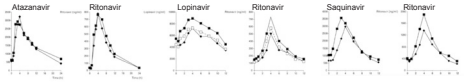
Important assumptions for the ANDA pathway.

- BE is a valid proxy for therapeutic equivalence (TE). If two products are found to be BE, it is reasonable to assume a similar therapeutic effect.
- It is reasonable to extrapolate from HVs to patients.

Differences among HVs and patients

PK differences documented in the HIV and TB fields.

- Protease inhibitors (Current opinion in HIV and AIDS, 2008; 3:296-305).



- Rifampicin (Systematic review and meta-analysis).
  - ◊ PK differences found between: HVs and adults with TB; HIV-positive and -negative status; Studies; Analytical labs; and Different generic products.

Patients are a heterogeneous group.

- The variability is not necessarily normally distributed.
- Effects of aging (Stader et al, BJCP 2021) and obesity (Bettonte et al, CID 2024) on ARV PK.
  - ◊ Modeling predicts high PK variability among HIV patients.
  - ◊ Higher RAL and DTG exposures in older (55-85y) vs younger (25-55y) patients.
  - ◊ Lower CAB and RPV exposures in patients with higher (30-50) vs lower (18.5-30) BMI.

PKPD differences point to a gap between BE and TE

Pharmacokinetics (PK).

- Lower exposures in patients (boosted PIs and many TB drugs).
- Greater inter-individual variability in patients, particularly gut-based mechanisms (DTG and RAL).
- HIV patients have relative achlorhydria and blunted DDI (SQVr+OMP and RPV+ARAs).
- **Injections remove gut-based variability but add injection-to-injection variability**.
- Disease characteristics (HCV DAAs and liver impairment).

Pharmacodynamics (PD).

- Receptor sensitivity and compensatory mechanisms (Amlodipine)
- Other: Intrinsic antagonism (anti-drug antibodies) and Concomitant disease and inflammation (QTc) are not relevant to this discussion.

Exploring the gap between BE and TE

Regulators precisely define BE around "rate and extent" based on the fundamental BE assumption (BE~TE).

- FDA (2021).
  - ◊ Being equal in rate and extent to which the API becomes available at the site of drug action.
- EMEA (2010).
  - ◊ Pharmaceutical equivalents and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.

The BE assumption may not hold when extrapolating from HVs to patients (i.e., From least variability to most variability).

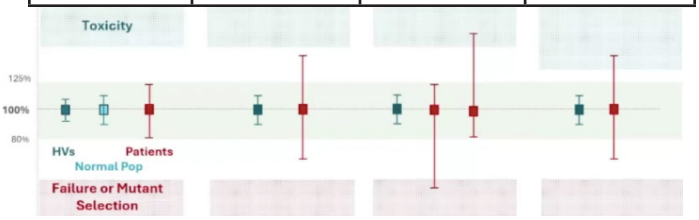
- Four potential scenarios.

	BE	TE	BE Assumption
Scenario 1	Similar DAP	TE	Holds
Scenario 2	**Dissimilar DAP**	**TE**	**Gap**
Scenario 3	**Similar DAP**	**Not TE**	**Gap**
Scenario 4	Dissimilar DAP	Not TE	Holds

DAP, Drug absorption profile.

- BE assumption vs real life.

Scenario 1	Real Life		
HVs are a good proxy for patients	Much more patient variability	Population coverage issues	Altered PD
• Patients have more variability. • BE assumption holds.	• Due to patient or disease characteristics. • Gastric PH, BMI, injection-to-injection variability, etc.	• Variability is not normally distributed. • Subgroups more susceptible to failure or toxicity.	• Patients are more sensitive to toxicity. • The target group and use case is important

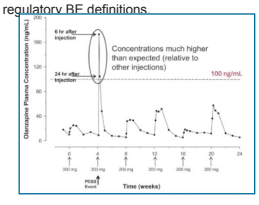


What modulates the gap between patients and HVs?

- There are only questions.
  - ◊ Highly variable drugs (Inter-subject variability>30%). Do they widen the gap? Is this the case with LAIs?
  - ◊ **Multiple dosing. Does it accentuate the difference between patients and HVs?**
  - ◊ Formulations containing combinations. Are they expected to behave the same way in HVs and patients? (Probably a reasonable assumption).
  - ◊ Eliminating first pass metabolism and gut-based interactions (i.e., Injections). Does it make a difference given the addition of other factors, such as injection-to-injection variability?
  - ◊ Indication. Treatment vs prophylaxis vs chemoprophylaxis?
  - ◊ Study design. Long BE study?

The multi-dose issue is interesting.

- Use pAUCs to examine drug coverage over total treatment duration.
  - ◊ Then, need to know what happens in patients, patients with liver disease, etc. Evaluations of TE are dependent on a comparator and outside the scope of regulatory BE definitions.
- Injection-to-injection variability.
  - ◊ Injection events will be a reality of life (e.g., Hit a blood vessel, blood extravasates, and seals the release).
  - ◊ What is the impact on treatment?
  - ◊ How will this be managed?
  - ◊ **Olanzapine example.** Burst release after an injection event changed Cmax and the shape of the curve relative to other injections.



Summary

- BE is only one aspect of therapeutic equivalence.
  - ◊ The problem is that many of the factors we are worried about have been "designed out" through the use of HVs.
- Use of patients is primarily driven by safety considerations.
  - ◊ A number of FDA PSGs for recent LAIs recommend BE studies with patients.
    - * These are primarily related to hormones, opiates, anti-psychotics and chemotherapy.
    - * Leuprolide 2021; Buprenorphine SC 2020; Paliperidone 2021.
  - ◊ Ethical considerations of long BE studies.
    - * Need to cover the tail if you are going to use patients.