Population Pharmacokinetics in Assessing Drug-Drug Interactions: Considerations During Regulatory Review

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FDA Guidance

- FDA Guidance for Industry: in vivo drug metabolism/drug interaction studies – study design, data analysis and recommendations for dosing and labeling; November 1999.

- FDA Guidance for Industry: Population Pharmacokinetics. February 1999.

When can sponsors successfully use PPK to claim labeling statements?

- Systematic evaluation of the various factors affecting the interpretation of PPK analyses assessing drug-drug interactions, although intuitive, is necessary

- We attempt to summarize these factors in the current report

PPK vs. Definitive Study

Characteristic	*PPK*	*Definitive*
Population	Target	Usually Healthy
PD Effect	Effectiveness Toxicity	Very limited
Dosing	Usually Uncertain	Certain
Sampling	Sparse, might be suboptimal	Rich
Sample size	Large	Small
Cost	Cost effective	?

PPK could lead to false negatives

- Known interaction confirmed.
  - Digoxin-quinidine. Bauer et al. Ther. Drug Monit 1996;18:46-52
- Not detected.
  - Tacrolimus-CYP3A inducer (inhibitor). Staatz et. al. Clin Pharmcol Ther 2003;72:660-9

PPK Approach

- Code COMED as a binary variable
  - 1: presence of concomitant medication
  - 0: absence of concomitant medication
- Estimate parameters (such as CL) using COMED as a covariate
  - CL(DI) and fCL(COMED)=fractional change
- Assess interaction
  - Two approaches

Assessment of Interaction

- Change in objective function values
  - Significance of difference

- Irrespective of the significance of difference, the 90% CI for the fractional change is determined using
  - Asymptotic SE
  - Bootstrap

Differences between COMED and Other Covariates

- Constant variables
  - Gender
  - Age
  - Weight
- COMED
  - Time dependent
  - Comprises of several components

Underlying Assumptions

- Dosing and sampling time relative to the dosing of drug of interest
- Dosing frequency of COMED
- Compliance of COMED intakes
  - Less well documented when a COMED is given on a need-to basis
- Others
  - e.g.: randomization; pooling of drugs within each class assumes similar potency for each drug

The usage of PPK is dependent on the goal

- Labeling
  - Reasonable mechanistic expectations
  - Robust design
- Hypothesis generation
  - Reasonable mechanistic expectations
  - Less robust design (e.g.: dosing information missing)
  - Positive or negative results
    - Signal for further investigation
    - May not lead to labeling statements

Mechanistic Expectation

- Potential for the drugs to interact, given the metabolic pathways
- *In vitro* results
- Known interactions in the same class

Robust Design

- Dosing history of comedications should be accurately recorded
- Sampling scheme should be reasonable
- Sample size and samples per subject should be adequate

Prospective vs. Need-to Studies

- Prospective
  - A study in which the comedications (COMEDs) are planned to be administered along with the drug of interest
    - e.g.: oxcarbazepine with valproate
- Need-to
  - A study in which the COMEDs are administered as needed along with the drug of interest
    - e.g.: pain killers

Prospective vs. Need-to PPK

Characteristic	Prospective	Need-to
Dosing	Usually Certain	Usually Uncertain
Sampling	Could be Optimized	Might be suboptimal
Prevalence	Controllable	Uncontrollable

Robust Design

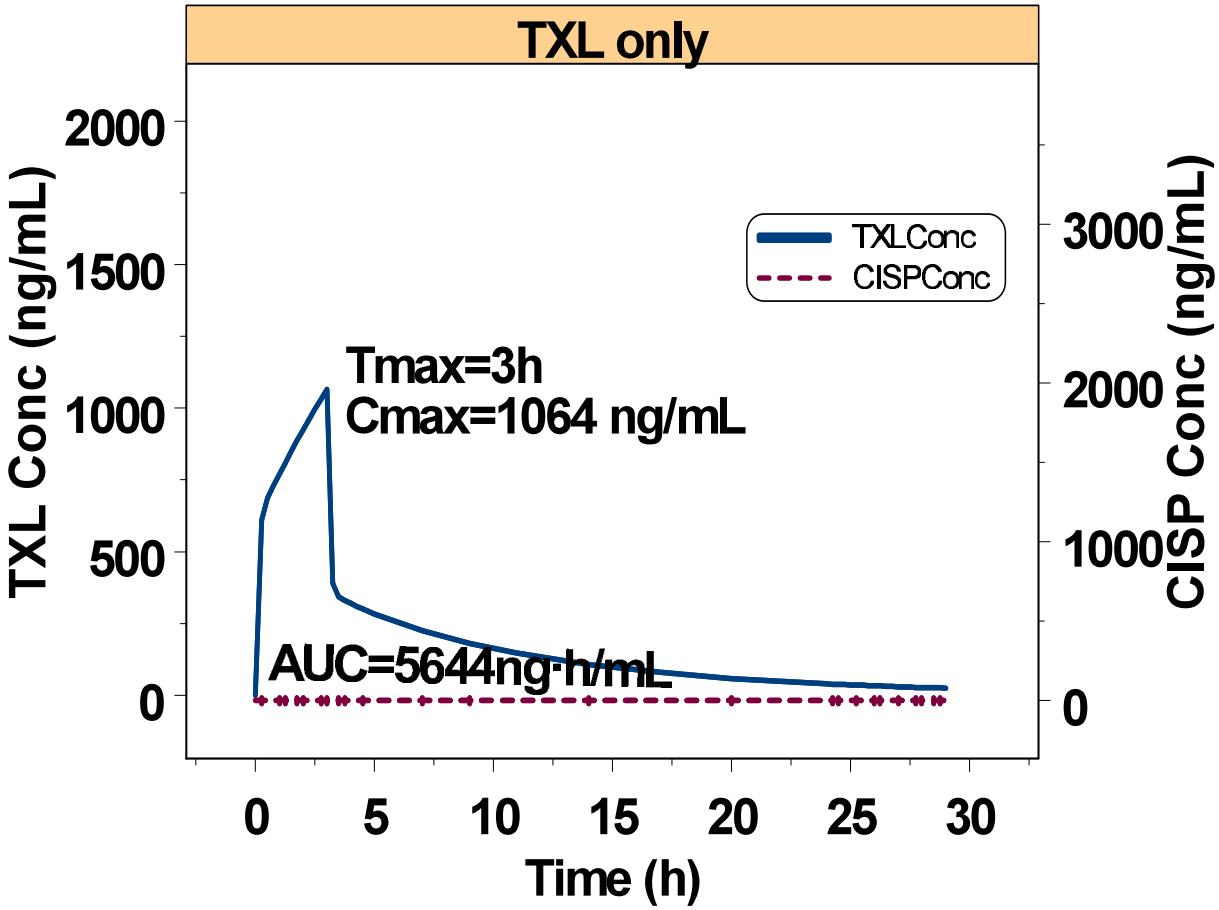
- Dosing history of comedications should be accurately recorded
- Sampling scheme should be reasonable
- Sample size and samples per subject should be adequate

TXL – CISP Interaction

- Sequence-dependent influence of cisplatin on paclitaxel*.
- Neutropenia mean nadir absolute neutrophil count
  - CISP → TXL: 770/μL
  - TXL → CISP: 1,002/μL.
- Significant decrease in paclitaxel clearance when patients were pre-treated with cisplatin

*Rowinsky et.al. J Clin Oncol 9: 1692-703, 1991.

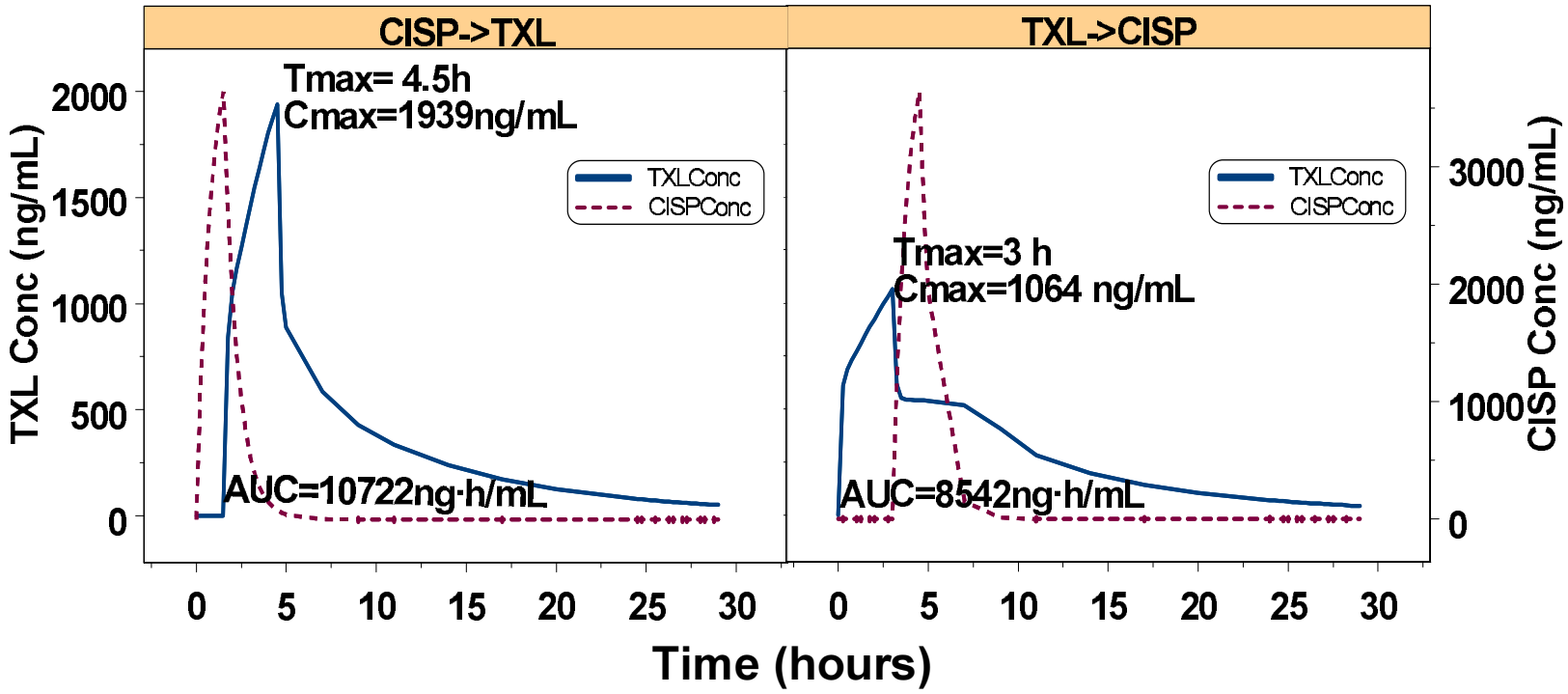
TXL – CISP Simulation



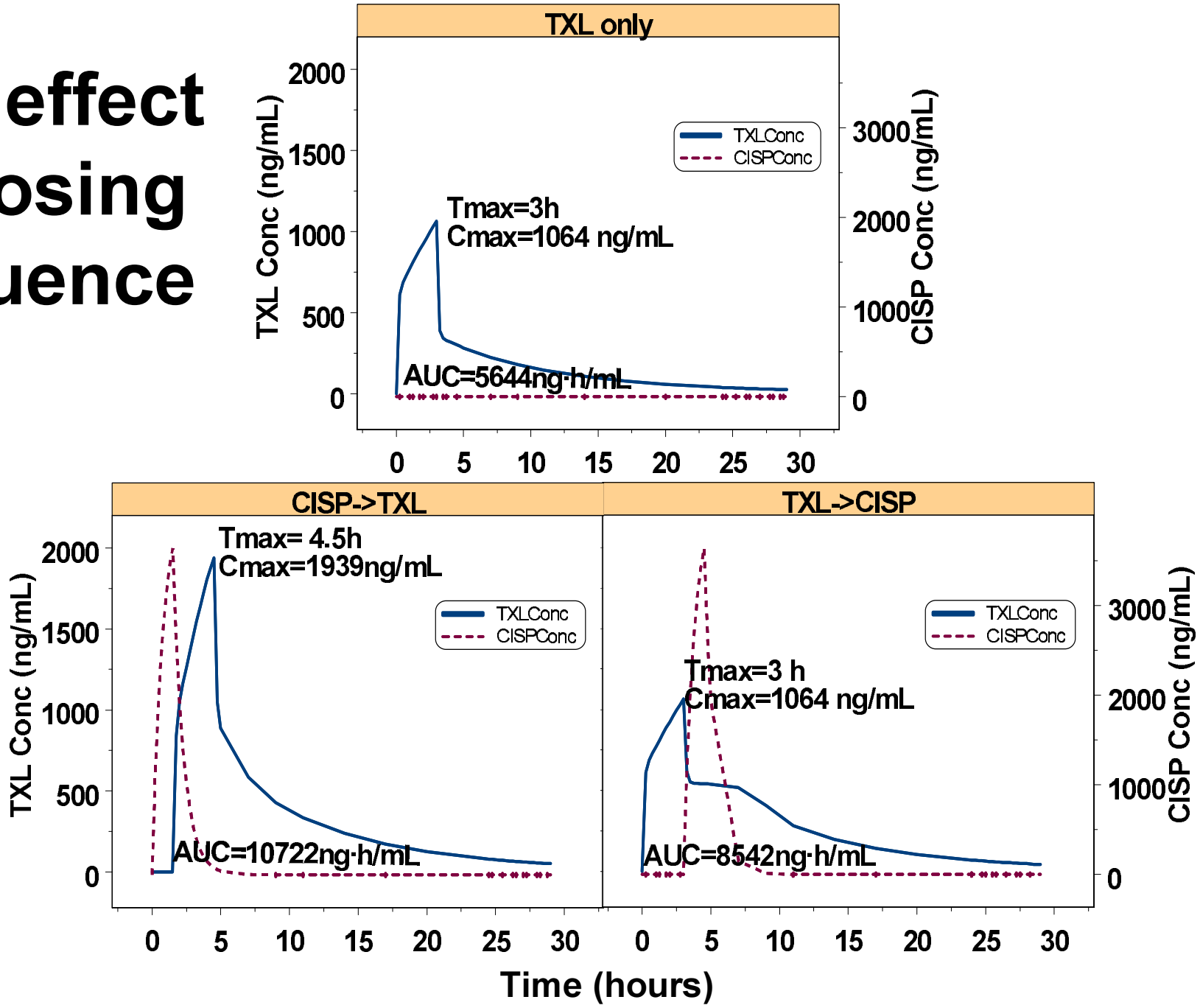
TXL: three compartment model with saturable metabolism and saturable distribution. Karlsson et. al Drug Metabolism and Disposition. 1999; 27(10):1220-23.

TXL – CISP Simulation

- **CISP: one compartment model Hanada et. al Jpn J Clin Oncol 2001; 31:179-184**
- **Arm 1. TXL alone.**
- **Arm 2. CISP → TXL.**
- **Arm 3. TXL → CISP.**



The effect of dosing sequence



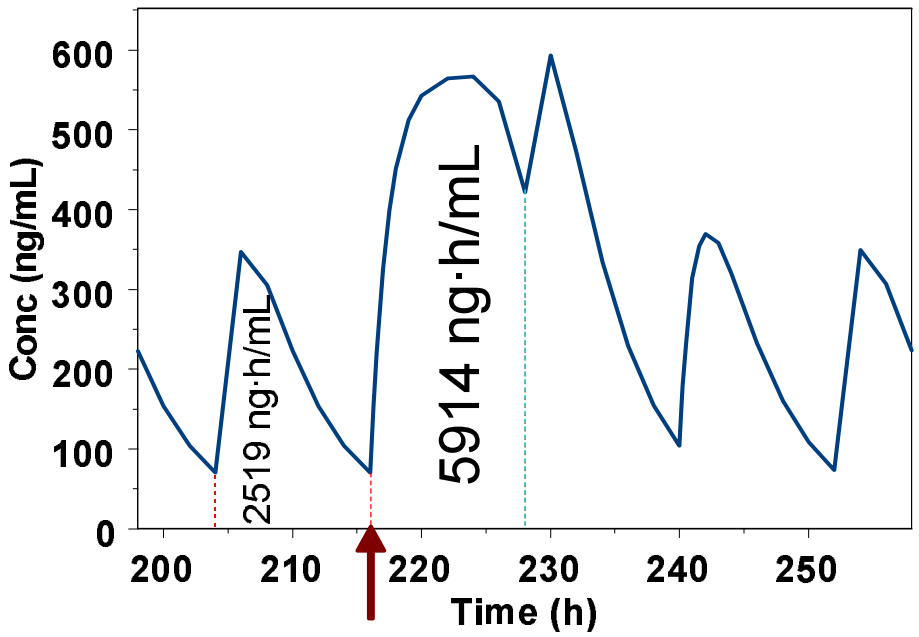
Relative Dosing Time

- Dosing time can affect the onset and the magnitude of the effect
- If not controlled, mixture of different relative dosing times could lead to an underestimation of effect
- Explorations of ‘what-if’ scenarios might be beneficial when planning to administer multiple drugs

Robust Design

- Dosing history of comedications should be accurately recorded
- Sampling scheme should be reasonable
- Sample size and samples per subject should be adequate

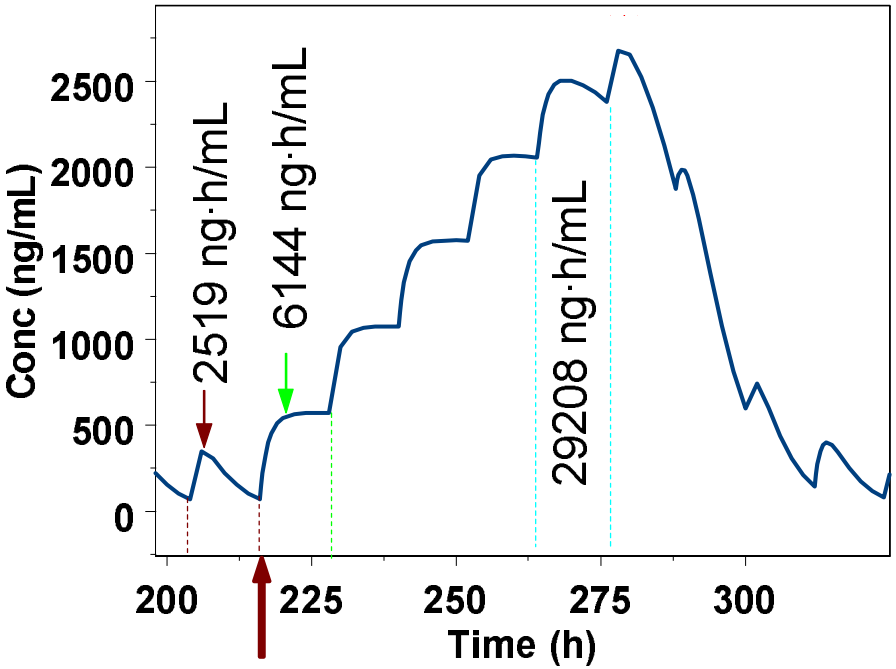
Sampling Schedule



Dose of Comed

- Sampling during the interval after the dose of COMED might capture the drug interaction reasonably well
  - Provided the kinetics are relatively fast

Sampling Schedule



Dose of Comed

- Sampling during the interval after (a single dose) of COMED **will not** capture the drug interaction
  - Comedication could have slow absorption and elimination. e.g.: Induction of risperidal CL by carbamazepine takes weeks
  - Sampling needs when multiple doses of comedication are given might be different

Optimal Sampling

- Should capture the complete interaction potential
  - Sampling scheme may vary when comedication is given
- Can be explored using simulations

Robust Design

- Dosing history of comedications should be accurately recorded
- Sampling scheme should be reasonable
- Sample size and samples per subject should be adequate
  - Addressed by several researchers, not discussed here

Regulatory Decision

- Effectiveness, safety and *in vitro* data dictate the final decision about DDIs, even if explorative

When can sponsors successfully use PPK to claim labeling statements?

- Systematic evaluation of the various factors affecting the interpretation of PPK analyses assessing drug-drug interactions, although intuitive, is necessary

- Hopefully, a clearer expectation about use of PPK to assess DDI was provided

Thank you