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Univariate and multivariate Bioequivalence of PK parameters

Thomas Jaki & Philip Pallmann

9:00 – 10:00	Non-compartmental estimation of PK parameters	Jaki
10:00 – 10:20	COFFEE BREAK	
10:20 – 10:40	Univariate Bioequivalence	Pallmann
10:40 – 10:50	Multiplicity and Bioequivalence	Jaki
11:50 – 11:20	Multivariate Bioequivalence	Pallmann
11:20 – 11:40	COFFEE BREAK	
11:40 – 12:30	Multivariate Bioequivalence	Pallmann

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Multiplicity and Bioequivalence

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Aims for the 10 minutes

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- Bioequivalence assessment as required by regulators
- Implications for analysis

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Current approach to establishing BE

- Use a single PK parameters
  - Often $AUC_{0,t}$
- Test if ratio of PK parameters is in [0.8, 1.25]

Guidances

> FDA's regulations generally define BA and BE in terms of rate and extent of absorption of the active ingredient or moiety to the site of action. . . . BA and BE frequently rely on PK measures such as AUC to assess extent of systemic exposure and Cmax and Tmax to assess rate of systemic absorption.

(FDA, 2014)

Guidances

> In studies to determine bioequivalence after a single dose, the parameters to be analysed are AUC(0-t), or, when relevant, AUC(0-72h), and Cmax.

(CHMP/EWP, 2010)

Guidances

> . . . two pharmaceutical products are bioequivalent if ...their bioavailabilities, in terms of rate (Cmax and tmax) and extent of absorption (area under the curve) ... are similar to such a degree that their effects can be expected to be essentially the same

(WHO Technical Report Series No. 996, 2016, Annex 9)

Practice

- Claiming equivalence for two PK measures, commonly AUC and Cmax independently, each at level α
- Or only one parameter used

Implications for correct analysis

- Simultaneous inference preferred
- Equivalence margins?
- Confidence regions rather then confidence intervals

References

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