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# Pharmacokinetic and bioanalytical issues in patients studies

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AGAH Workshop – Beyond the Guidelines
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# Why are patient populations critical?

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## Bioequivalence concept

- comparison of *in-vivo* performance of drug products
- assessment of equivalence in peak and total exposure ...
- ... conclusion of therapeutic equivalence possible

## Requirements

- properties of formulation of interest
- exclusion/reduction of factors potentially interfering with PK
- particular role of concomitantly applied therapies

## Adjuvant therapies in patients

- treatment of underlying disease required
- potential for co-/multimorbidity (concomitant diseases)
- higher incidence for experiencing adverse events

# Regulatory background in Europe

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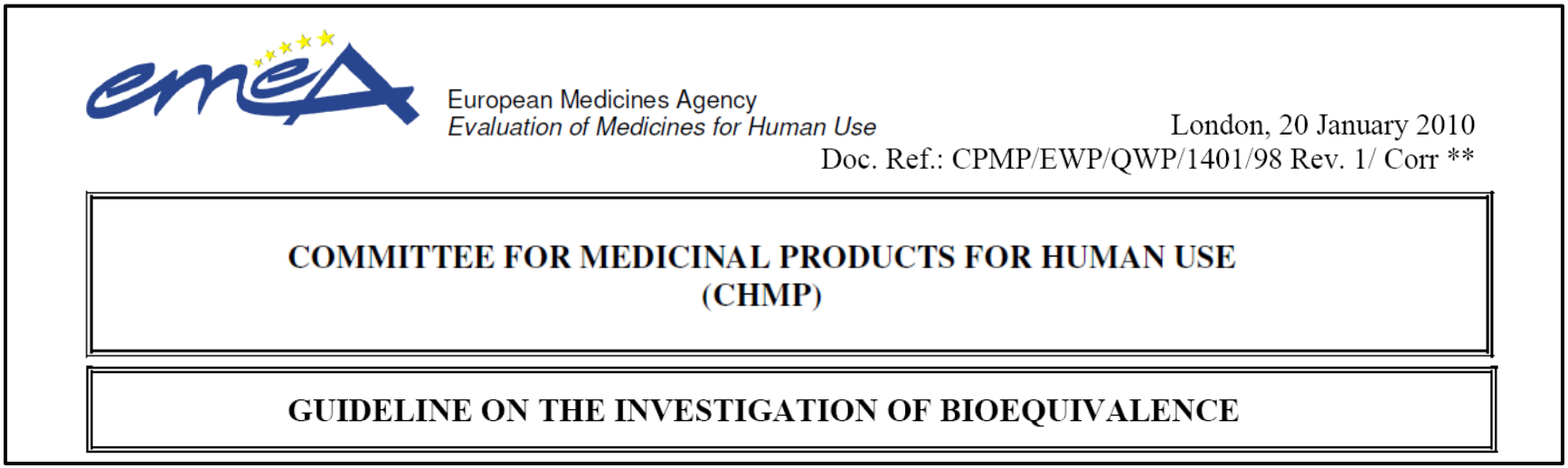

European Medicines Agency
*Evaluation of Medicines for Human Use*

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

**GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE**

- patient populations generally allowed ...
  ... e.g. unacceptable risks for healthy subjects
- preferably no concomitant medication; however
- ... if unavoidable (e.g. treatment of AEs, safety/tolerability)
  - address possible impact on study outcome
  - address risk for potential interaction and bioanalytical interferences
- decision upon exclusion from statistical analysis prior to BA

# Regulatory background in Europe

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMEA/CHMP/EWP/192217/2009
Committee for Medicinal Products for Human Use (CHMP)

Guideline on bioanalytical method validation

- validation of bioanalytical method (almost) completed prior start of measurements
- investigation of method selectivity - interference caused by metabolites, degradation products, co-medication(s)
- "Co-medication ... which may potentially interfere should be taken into account at the stage of method validation"

# Regulatory background in the U.S.

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**Guidance for Industry**

**Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations**

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2003

- admission of patients (intended indication) may be useful
- concomitant medication not specifically addressed but "monotherapy" preferred by US-FDA

# Regulatory background in the U.S.

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## Substance specific Guidances (e.g. Capecitabine, 2010)

"Cancer patients with monotherapy are generally recommended for the BE studies. However, cancer patients receiving concomitant drug(s) are allowed to participate, provided:

- The concomitant medication is the same for both study periods and clearly documented.
- The subjects should follow the same dosing regimen for the concurrent medications for both periods of the BE study. Each concurrent medication should be well documented and clearly stated on the protocol.
- Patients do not change their concurrent medication during the BE study."

# Regulatory background in the U.S.

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**Guidance for Industry**

**Bioanalytical Method Validation**

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2003

- investigation of methods selectivity
- potentially interfering substances: endogenous matrix components, metabolites, decomposition products, and in the actual study, concomitant medication

# Pharmacokinetic issues

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## Pharmacokinetic considerations

- pharmacological / non-pharmacological adjuvant therapies
- interaction affecting *in-vivo* drug disposition

| | Possible interactions | Examples |
|---|---|---|
| Absorption | GI-pH, complexation, active membrane transport (P-gp), first-pass metabolism | Antacids ($Mg^{2+}$/ $Al^{3+}$) →capecitabine (↓); macrolides→ saquinavir (↑); carbamazepine→ paclitaxel, vincristine (↓) |
| Distribution | Transporter, plasma proteins | Barbiturates → methotrexate (↑) |
| Metabolism | Inhibition/induction of metabolising enzymes, (genetic polymorphism) | Clarithromycin → ciclosporin (↓); paroxetin → tamoxifen (↑) |
| Excretion | Transportes (P-gp in kidneys, OATP in the liver) | Ciclosporin → digoxin (↑) |

→ impact on peak and/or total exposure should be addressed

# Bioanalytical issues

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## Bioanalytical considerations

- especially pharmacological adjuvant therapies
- interaction affecting selectivity of bioanalytical method

*" ... ability of analytical method to differentiate and quantify the analyte in presence of other components in the sample."*

FDA Guidance for Industry, 2001

## Consequences

- suppression/enhancement of signal of analyte or internal standard, change in retention times
- impact on accuracy and precision
- questioning method validity
- unreliable bioanalytical results
- impede evaluation/interpretation of study results

# Continuous consideration

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## Planning and set-up of trial design

- define type of study population
- identify possible/potential of concomitant therapies
- define inclusion/exclusion criteria and restrictions
- predefinition of allowed medication to overrule AEs
  → communication to bioanalytical laboratory

## Conduct of clinical trial

- thorough anamnesis of prior and concomitant medication
- ongoing
  - recruitment / screening
  - hospitalisation
  - end of clinical phase

# Anamnesis of medication

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## Recruitment and screening

- adjuvant therapies required during study?
  - check of IC/EC and restrictions

## Hospitalisation

- pharmacological treatment started in the meantime?
- further/other treatments planned during the study periods?
- records required: type, dose, dosing regimen, duration

## End of treatment periods (prior to bioanalysis)

- medications actually administered during the trial? (therapy of underlying/concomitant diseases or AE)
- records required: type, dose, dosing regimen, duration

# Assessment of concomitant medication

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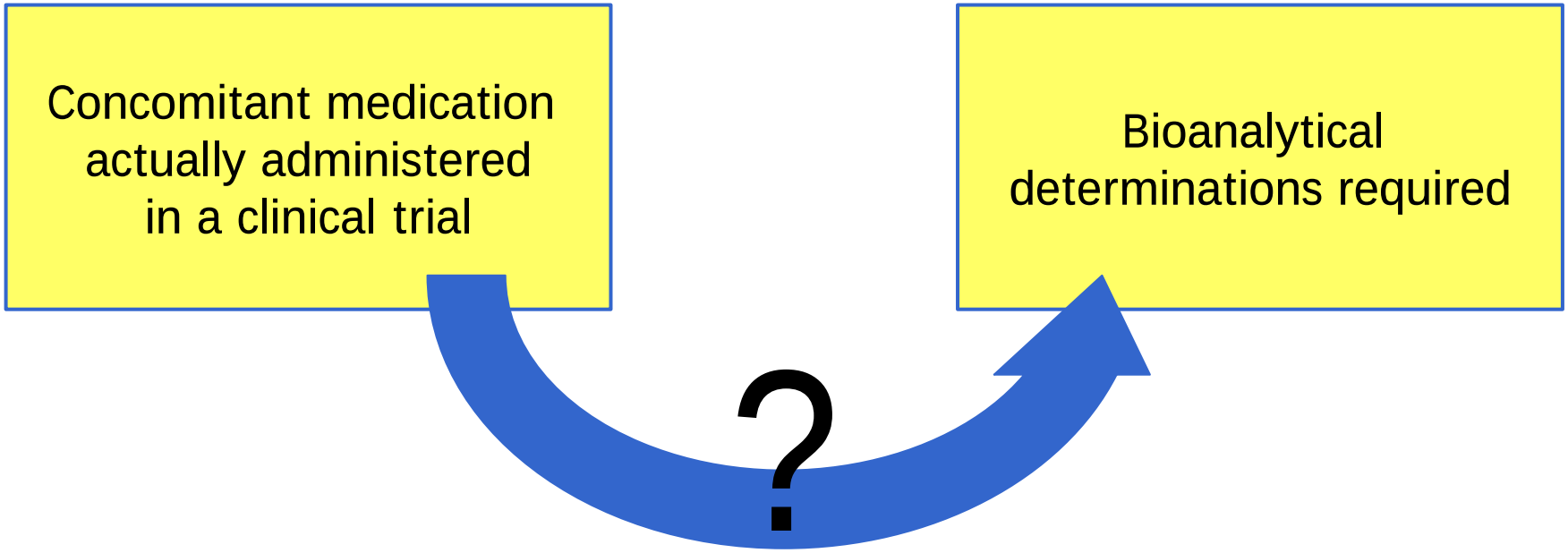
## Pharmacokinetic aspects

- relevant PK interaction suspected → Exclusion / Withdrawal

## Bioanalytical aspects

- risk for bioanalytical interference expected



# Risk for bioanalytical interference

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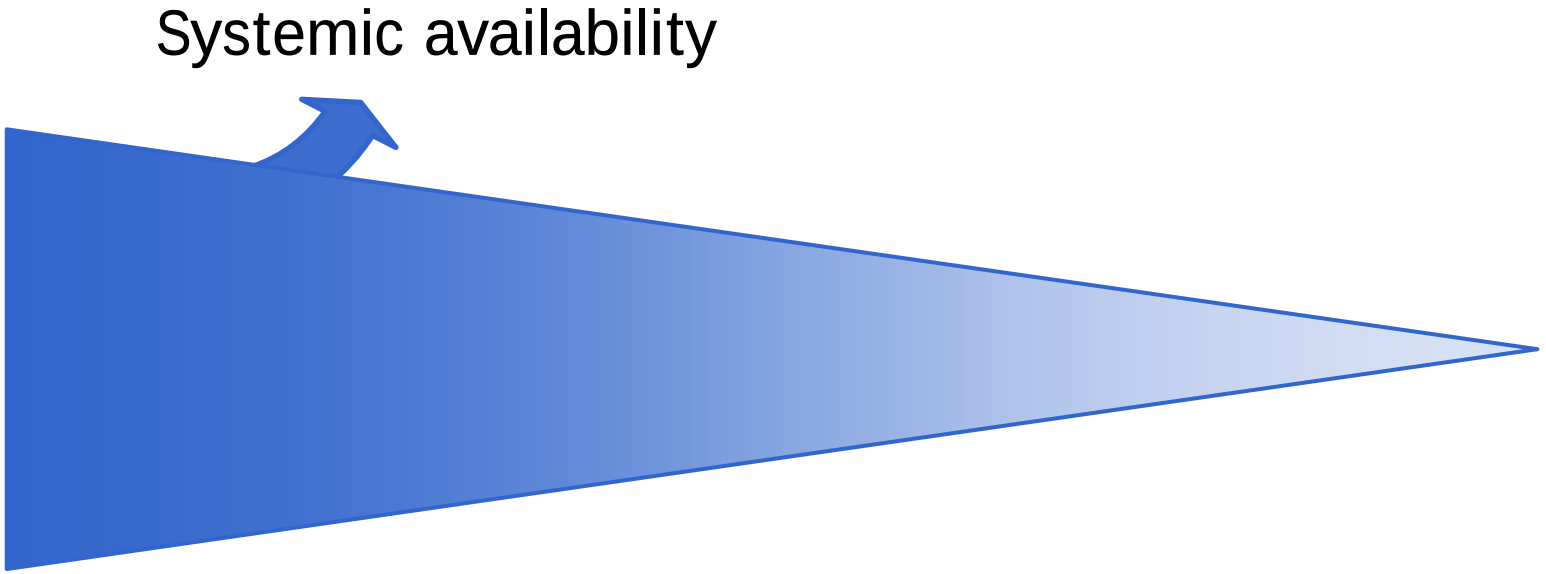
Actual concomitant medication

Bioanalytical determinations required?



# Systemic availability

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## Determining systemic availability of co-medication

**Route of administration**
(intravenous, oral, topical/transdermal, nasal, ocular, ...)

**Physicochemical characteristics of drug substance**
(molecular size, solubility, permeabilty)

**Pharmacokinetic characteristics of drug substance**
(extent of absorption, metabolism)

# Risk for bioanalytical interference

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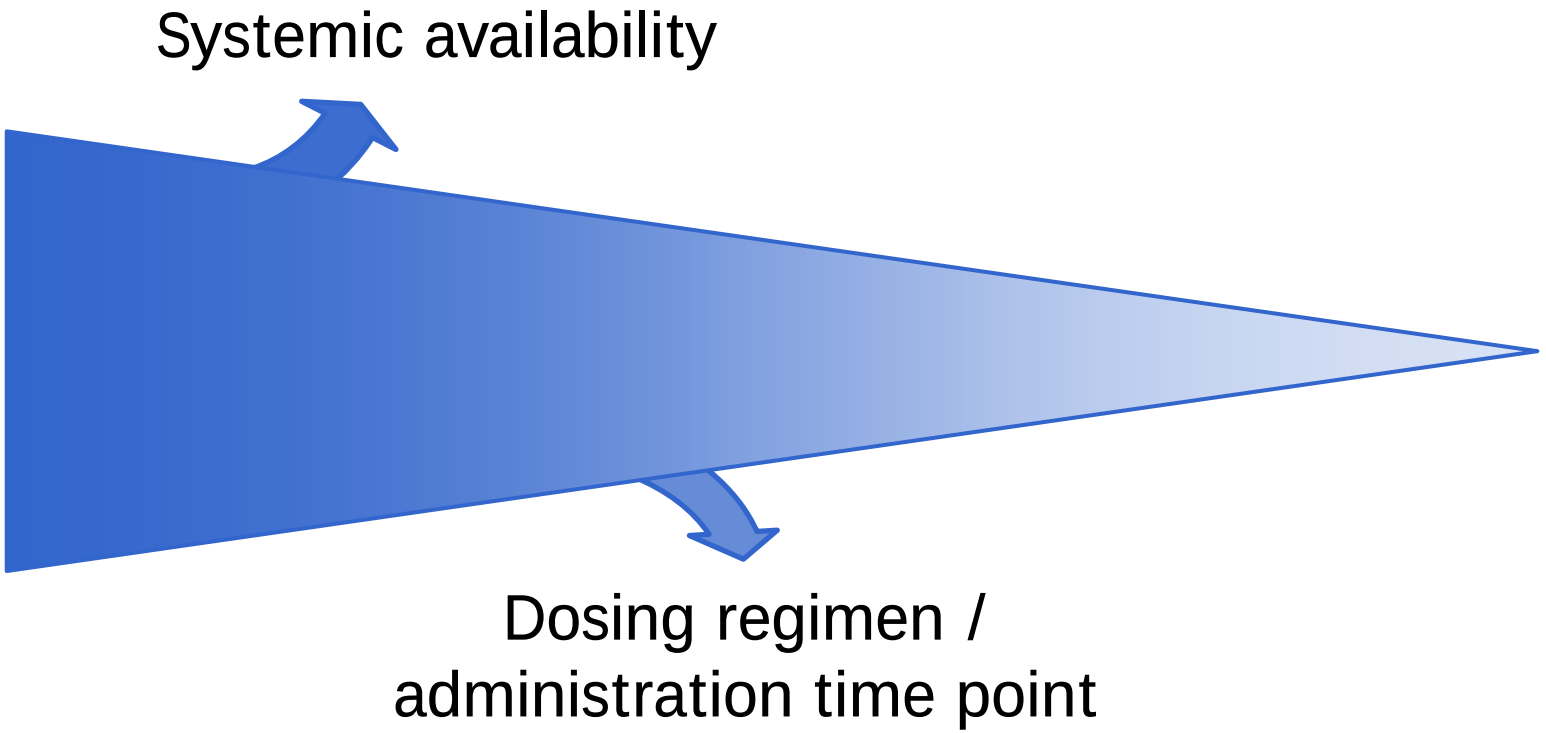
Actual concomitant medication

Bioanalytical determinations required?



# Dosing of concomitant medication

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## Duration of treatment

- stable long-term treatment; similar during study periods
  - possible interference detectable at pre-dose level
- occasional (SD or MD) administrations
  - no identification from pre-dose samples possible
  - need to be addressed from bioanalytical perspective

## Administration time (relative to IMP administration)

- course of study periods, real dosing time to be considered
- (shortly) prior to IMP administration (not concomitant)
- during period of PK sampling (e.g. 72h postdose for IR)
- during washout period

## Pharmacokinetics of co-medication

- $t_{max}$, $T_{1/2}$, metabolism, ...

# Dosing of (concomitant) medication

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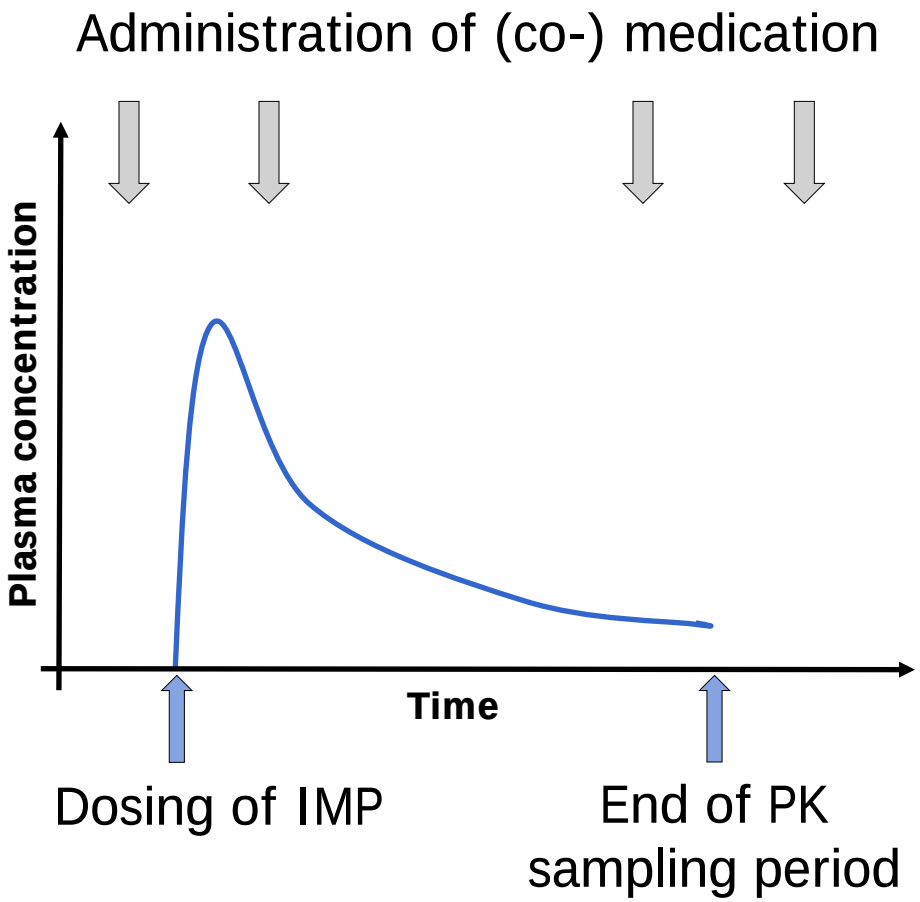


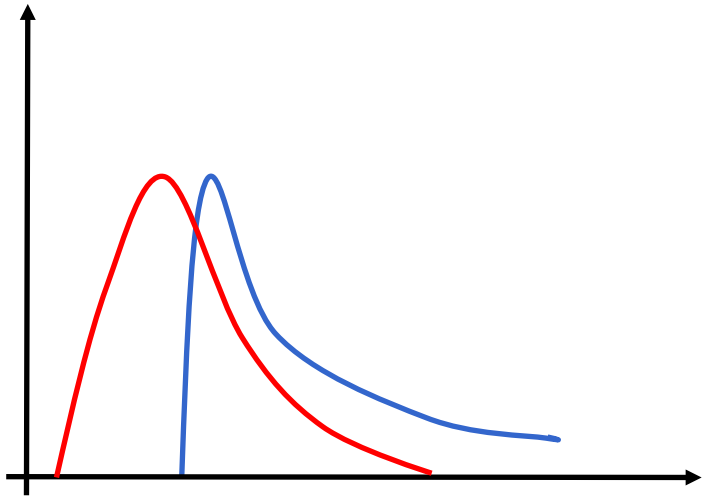

# Dosing of (concomitant) medication

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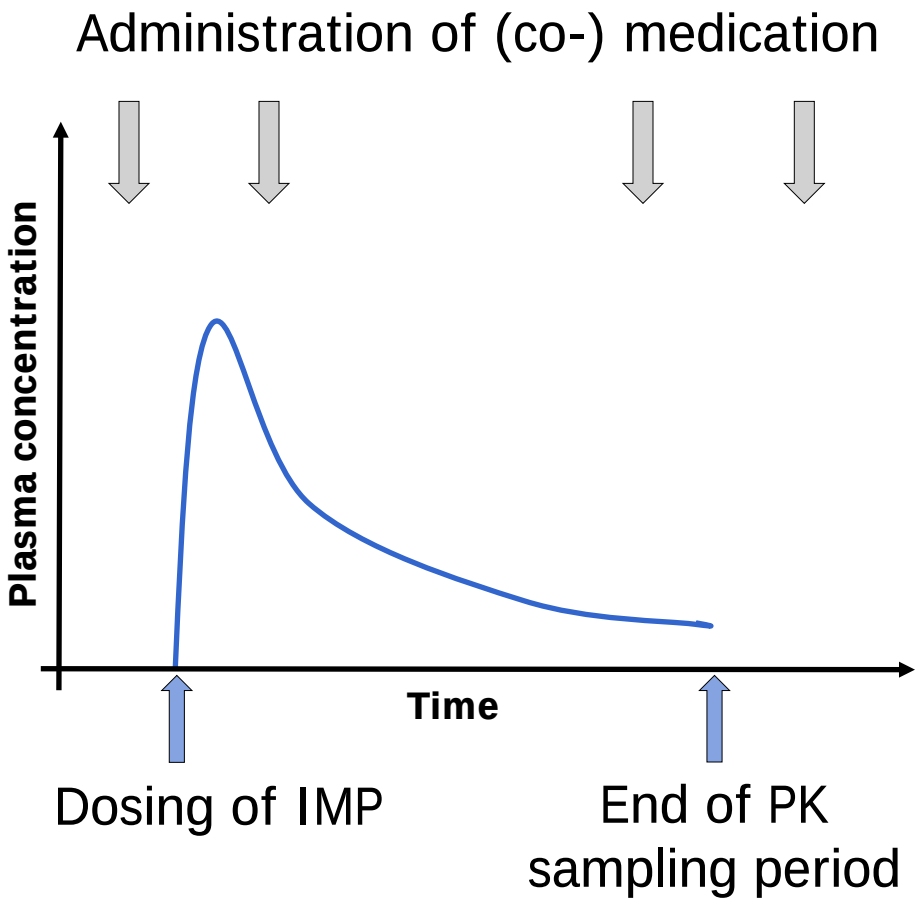


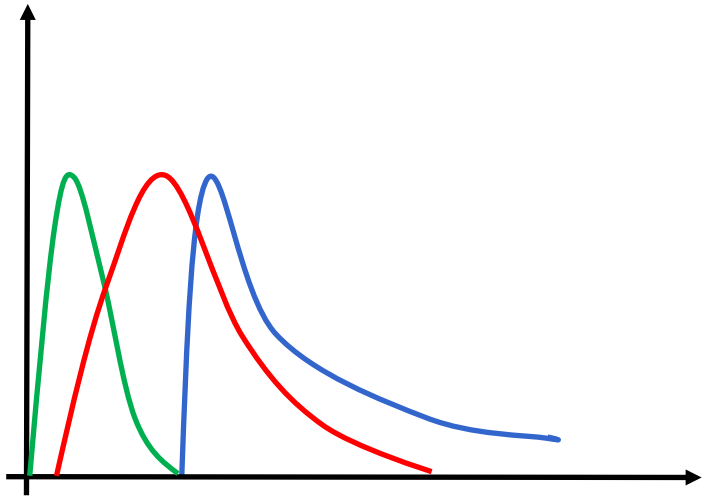

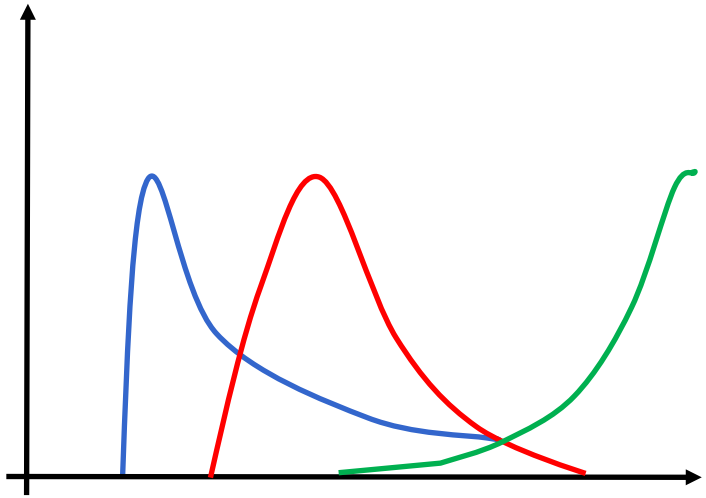

# Risk for bioanalytical interference

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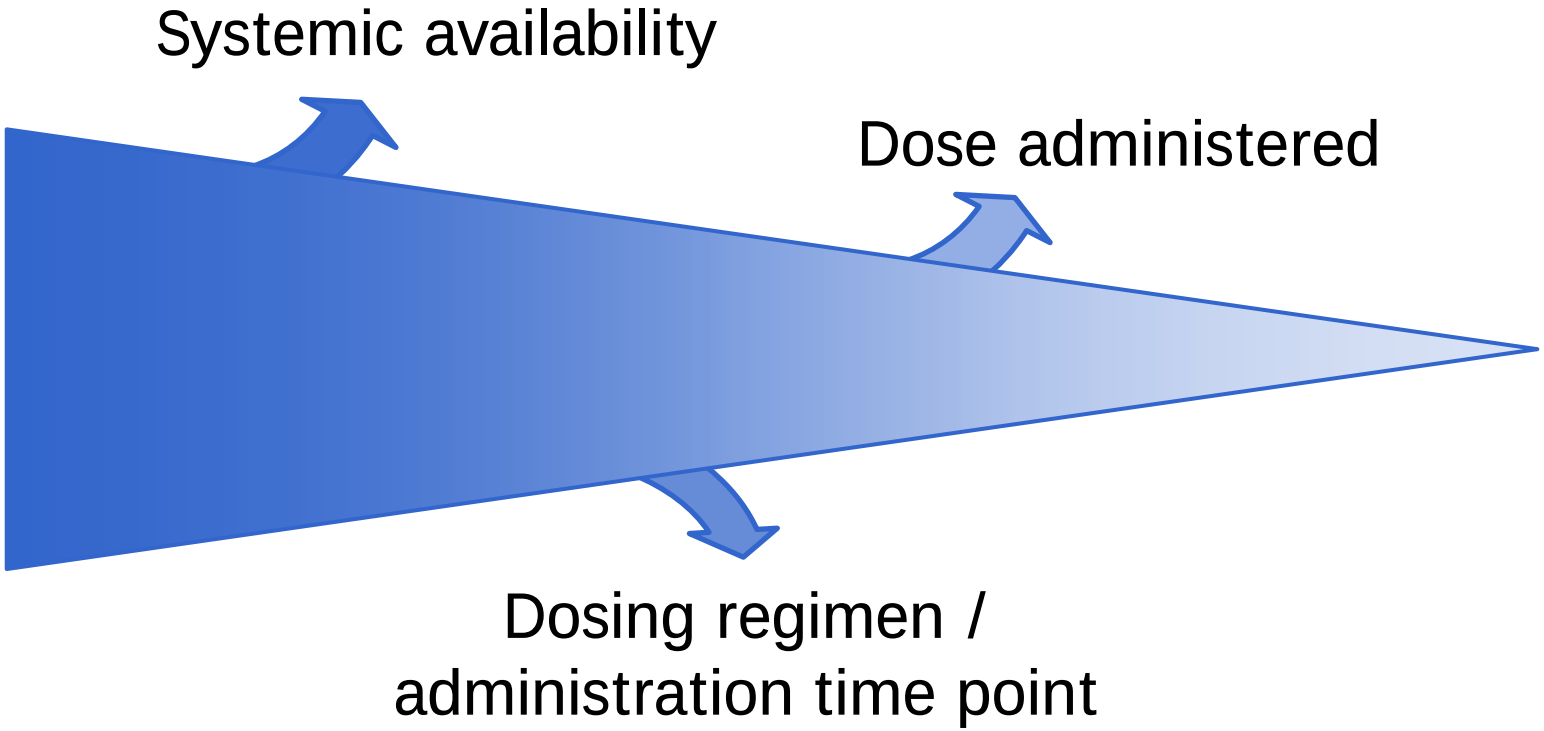
Actual concomitant medication

Bioanalytical determinations required?



# Bioanalytical determinations required?

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## How to proceed?

- communication of critical co-medication (and possible metabolites) to bioanalytical lab
- theoretical assessment of likelihood of interactions based on molecular structure and degradation scheme due to MS-detection
- critical: retention times, MW of MS fragment, ionisation behaviour → additional experiments may be necessary

## Testing selectivity

- signal of LLOQ samples prior and after spiking with defined concentration of co-medication
- absence of interference: response <20% of LLOQ signal of analyte and <5% for IS

# Conclusions

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## Consequences for clinical trials

- comprehensive knowledge of characteristics of IMP and co-medication required
- need to deal with co-medication throughout the whole clinical trial → rapid identification of problems allows proper intervention
- close collaboration with bioanalytical experts
  - allowed/known co-medication should be addressed during validation
  - communication of actual co-administered medication possible

## Recommendation

- early start of communication,
- preferably prior to start of sample analysis
  → adaption of bioanalytical method possible (if required)

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