Bioavailability and Bioequivalence

Their Role as Surrogate for Clinical Investigations

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Outline

- Pharmacodynamics and Pharmacokinetics
- Measures of Bioavailability/Bioequivalence
- Assumptions and Limitations
- Regulatory Aspects

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Pharmaco-*Dynamics* and -*Kinetics*

- Pharmacodynamics:

  „what the drug does to the system“
- Pharmacokinetics:

  „what the system does to the drug“

Both properties of the drug are assessed in *Clinical Studies*. Presumably there is a link between them, expressed as PK/PD relationship.

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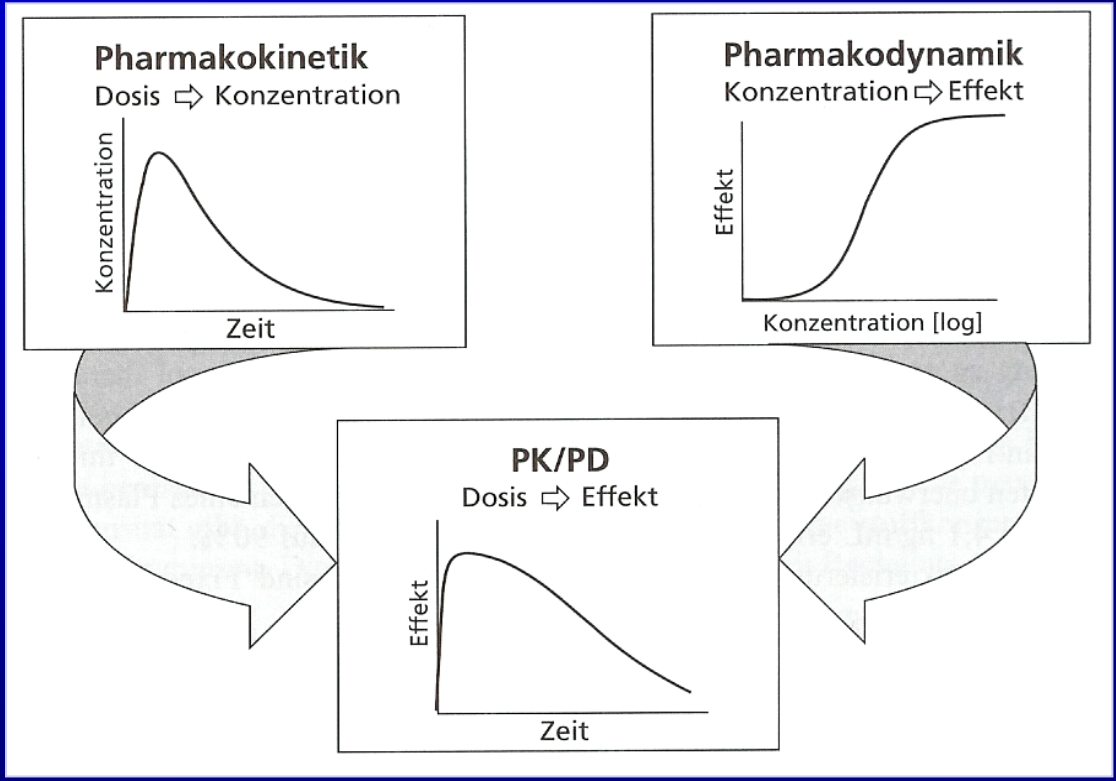
Link between PK and PD



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From Pharmacodynamics to Pharmacokinetics to Bioavailability

- Emphasis is on the time course of drug appearance, (distribution), and elimination
- As a rule the bioavailability is *product* specific
- Originally meant as surrogate for PD, today the BA of a product is a pivotal quality characteristic
- (In turn, BA to be mimicked by *in vitro* data)

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Bioavailability and Bioequivalence: Definitions

- BA: rate and extent of the therapeutically active drug that reaches the systemic circulation (*and is available at the site of action*)
- BE: drug products are bioequivalent when they have similar bioavailabilities, i.e. are not significantly different with respect to rate and extent of absorption, when given in the same molar dose and under similar experimental conditions

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Bioavailability: Conceptual Assumptions and Limitations

- Originally: in linear section of dose response curve
- Linear pharmacokinetics, no time dependence, no enzyme induction, etc.
- Scientifically „poor“ definition, because it comprises two independent characteristics
- Not valid for locally acting drugs
- Extension of BA quality to *in vitro* data

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Bioequivalence: Assumptions and Limitations

- Definition, strictly speaking, valid for like products only. Different importance of „rate“ and „extent“. Example: IR vs. MR product
- Demonstration of bioequivalence in chronic studies or even with a pharmacodynamic test parameter
- Biowaivers possible for certain products based on *in vitro* performance

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Definitions (from CPMP guidance)

Bioavailability

- Absolute bioavailability
- Relative bioavailability
- Suprabioavailability

Products

- Pharmaceutical equivalence
- Pharmaceutical alternatives
- Essentially similar products
- Therapeutic equivalence

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Nomenclature / Abbreviations

in the context of BA/BE Studies

Not always consistent:

- *in vivo* study, absorption study, etc.
- „Clinical studies“, Phase I studies

Abbreviations

- Similar inconsistency
- Listing to be included in report

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Factors of Influence for the Assessment of BA/BE

- Science
- Ethics
- Cost/benefit ratio
- Regulatory requirements

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Regulatory Aspects

- Human data vs. data from animal studies
- Emphasis on C_{max}/T_{max} and AUC as primary BA and BE indicators, additional PK parameters are to be reported as secondary characteristics
- Guidances as opposed to guidelines
- Available on websites from FDA and EMEA
- Harmonization of regulatory requirements, acceptance of „foreign“ data, however special aspects of target patients (age, sex, race, etc.) to be addressed

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Regulatory Aspects (cont'd)

- Detailed recommendations for BA/BE assessment
- ✓ Study objective(s)
- ✓ In vitro quality of drug products
- ✓ Number and nature of study subjects
- ✓ Plasma/urine sampling points
- ✓ Quality of analytical method
- ✓ Statistical analysis of data
- ✓ Content and format of report
- GCMP, Helsinki Declaration, Informed Consent, Review of Ethical Committee

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