General Principles of Biostudies

Pharmakokinetic Issues   A Basic Refresher

Regulatory Demands on BE   An Introduction

To bear in Remembrance...

Whenever a theory appears to you
as the only possible one, take this as
a sign that you have neither under-
stood the theory nor the problem
which it was intended to solve.
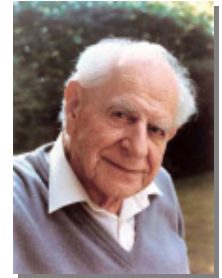
Karl R. Popper

Even though it's applied science
we're dealin' with, it still is – science!

Leslie Z. Benet

Fundamentals of Pharmacokinetics

- φαρμακός (drug) + κινητικός (putting in motion)
  - Term introduced by Friedrich H. Dost in 1953
    Der Blutspiegel: Kinetik der Konzentrationsabläufe in der Kreislaufflüssigkeit
  - Pharmacokinetics may be simply defined as
    what the body does to the drug, as opposed to
    pharmacodynamics which may be defined as
    what the drug does to the body.
    - Leslie Z. Benet 1984
      Pharmacokinetics: Basic Principles and Its Use
      as a Tool in Drug Metabolism

Pharmacokinetic Process (1)
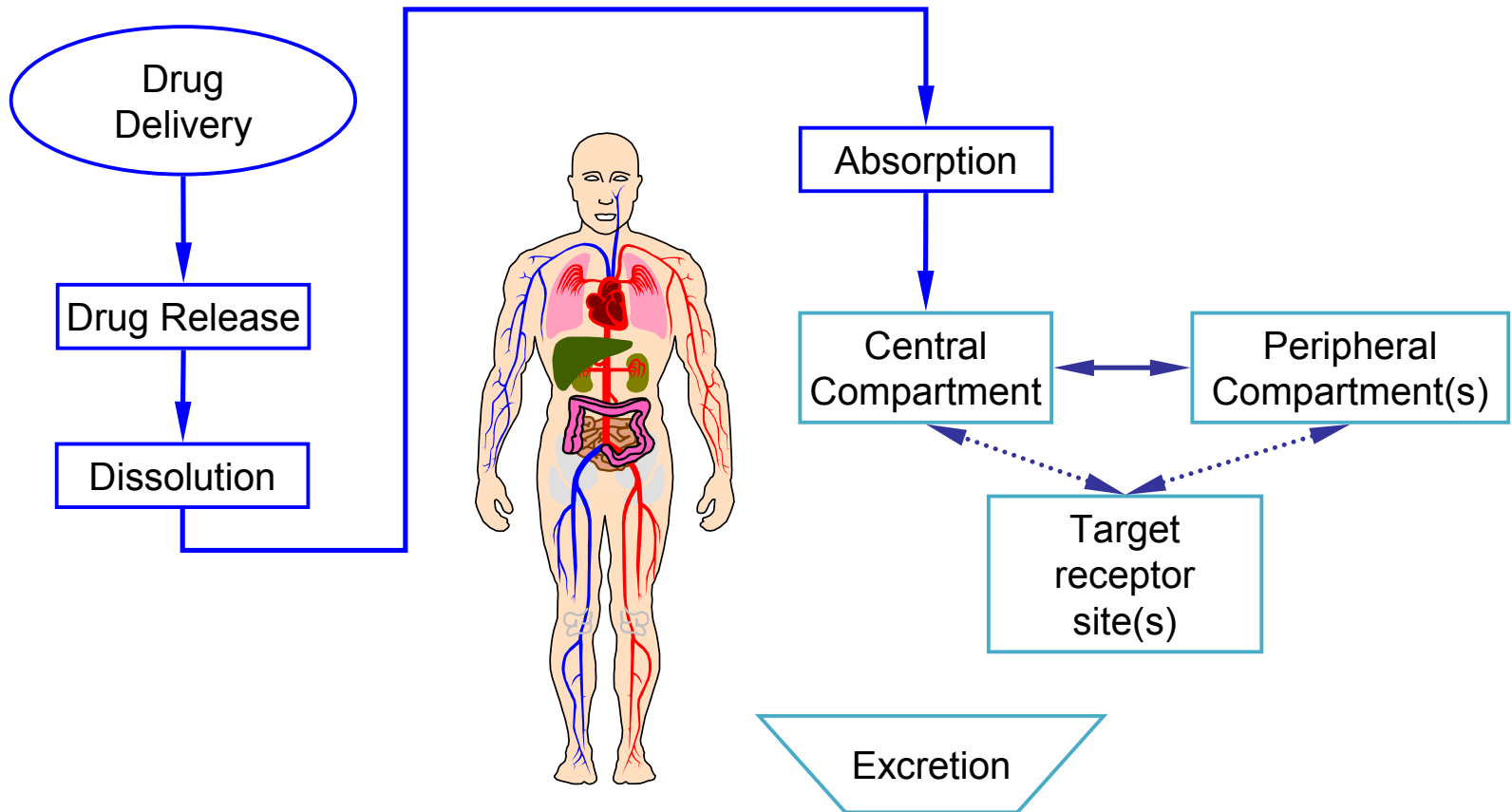
Pharmacokinetic Process (2)
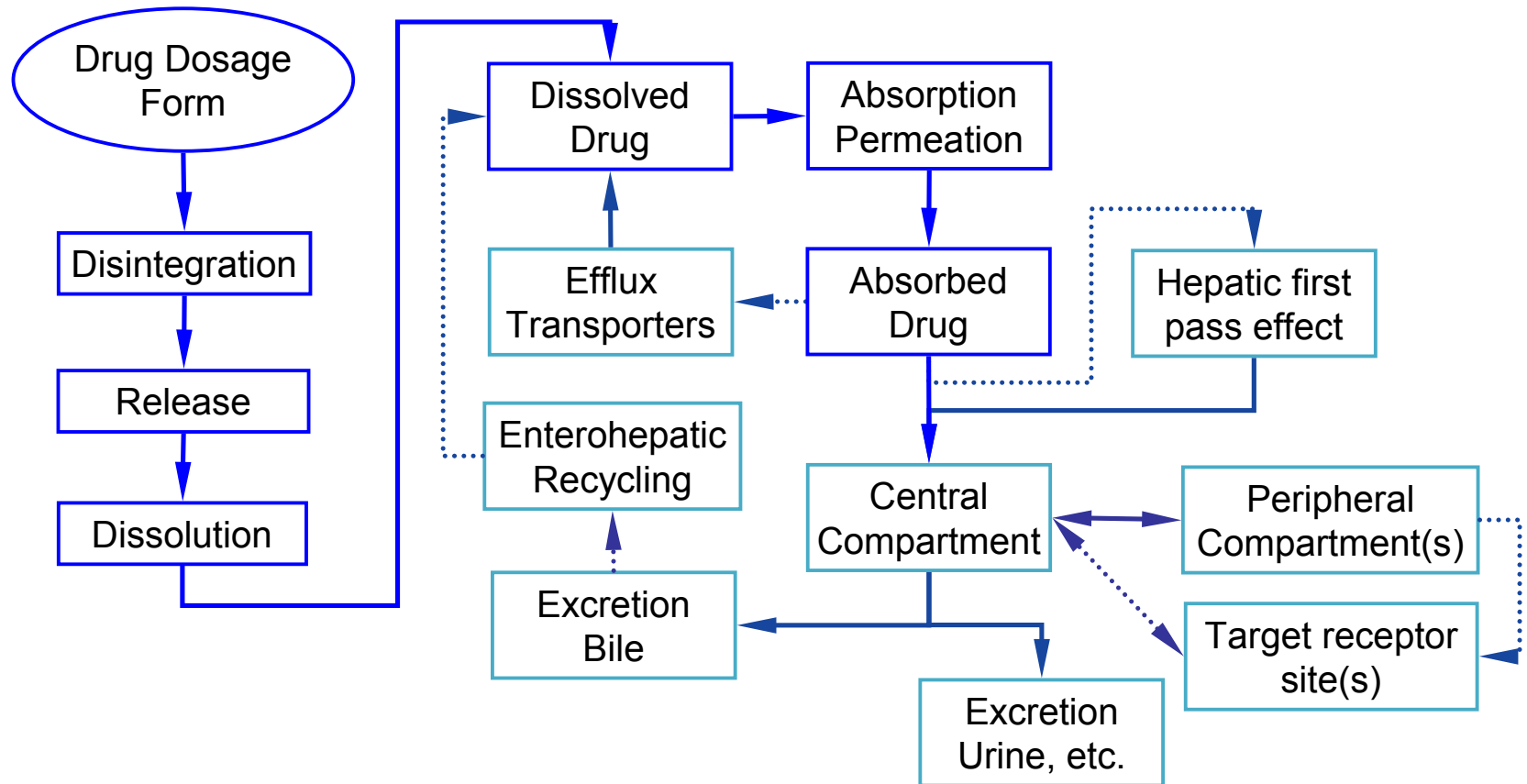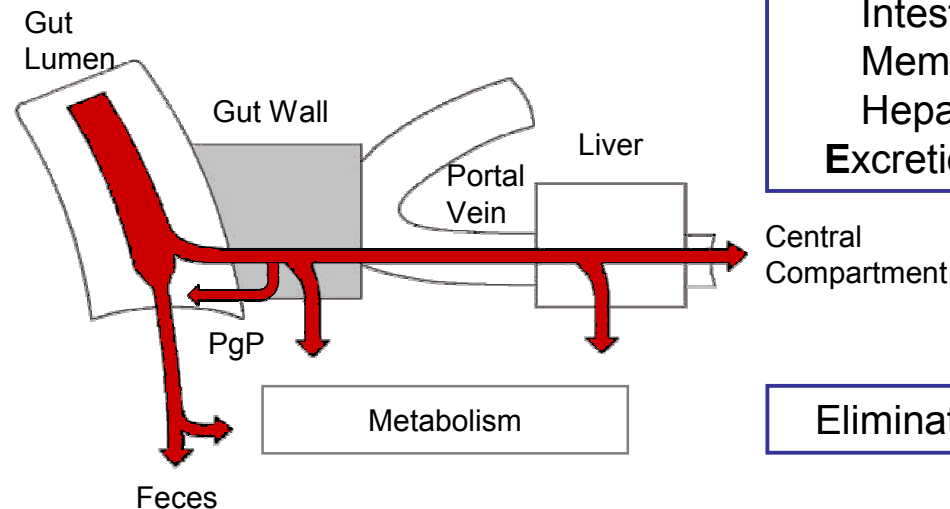
Pharmacokinetic Process (3)

(L)ADME

Biopharmaceutical phase
Disintegration ⎫
Release ⎬ Liberation
Dissolution ⎭

Pharmacokinetic phase
Absorption
Passive diffusion
Active transport
Distribution
Metabolism
Intestinal first pass
Membrane first pass
Hepatic first pass
Excretion

Gut Lumen

Gut Wall

Portal Vein

Liver

Central Compartment

PgP

Metabolism

Feces
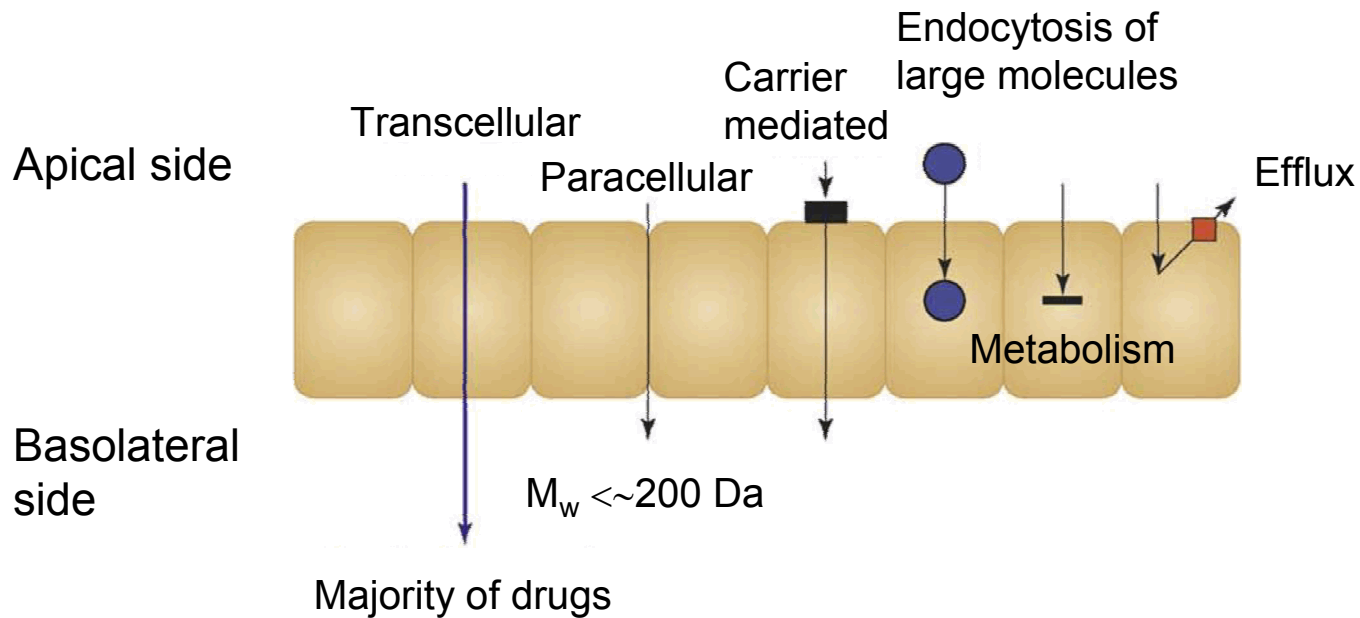
Elimination = **M** + **E**

Rowland M, Tozer TN. Clinical PK and PD. Philadelphia: Wolters Kluwer; 2011.

Pharmacokinetic Process (4)

Absorption revisited

Endocytosis of large molecules

Carrier mediated

Transcellular

Apical side

Paracellular

Efflux

Basolateral side

Metabolism

$M_w < \sim 200$ Da

Majority of drugs

Pharmacokinetic Models (1)

- The body is simplified to one – or more –
  'Compartments' where the drug is distributed
  - One compartment model
    - Drug is homogeneously distributed within the entire body
  - Two compartment model
    - The first (central) compartment is loosely related to the blood and heavily perfused organs
      - Liver
      - Kidneys
      - Lung
      - Muscles
    - The second (peripheral) compartment describes less perfused tissues
   - Fat
      - Bones

Pharmacokinetic Models (2)

- Compartment models
  - Compartments are
    - described by a volume and
    - pathways which link them
  - These links may be
    - unidirectional (absorption, excretion) or
    - bidirectional (*e.g.*, central ↔ peripheral)
  - Most common models are 'mammillary', *i.e.*,
    - absorption to the central compartment,
    - distribution to peripherial and back to the central compartment, and
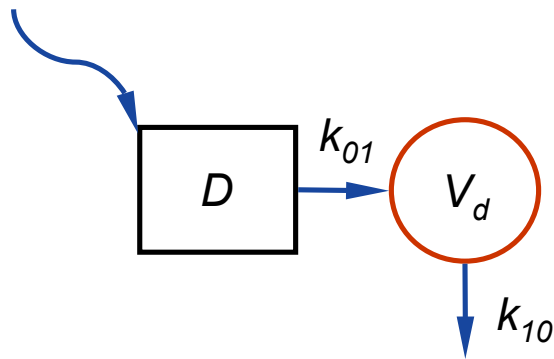   - elimination from the central compartment

Pharmacokinetic Models (3)

Examples

One comp. IV

One comp. EV

Two compartments EV

D

k_{01}

V_d

V_d

V_1

V_2

k_{12}

k_{21}

k_{10}

k_{10}

D

D

M + E

A + M + E
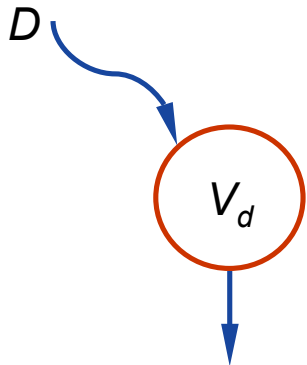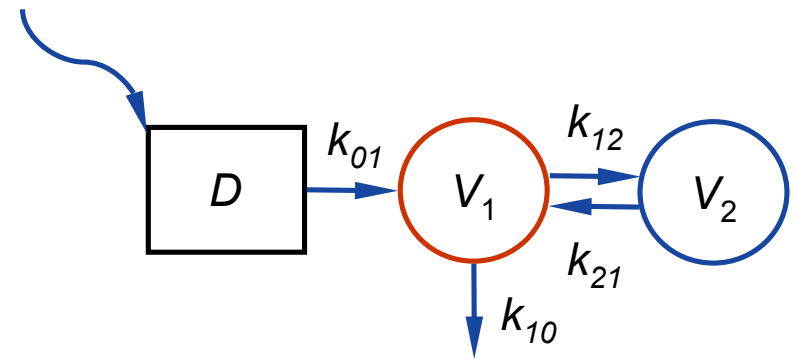
A + D + M + E

Excursion into Hydrodynamics

- Driving force for draining a tank:
  Hydrostatic pressure (height of liquid column & gravity)
- Emptied volume decreases with time
- Same *proportion* is emptied in the same time interval
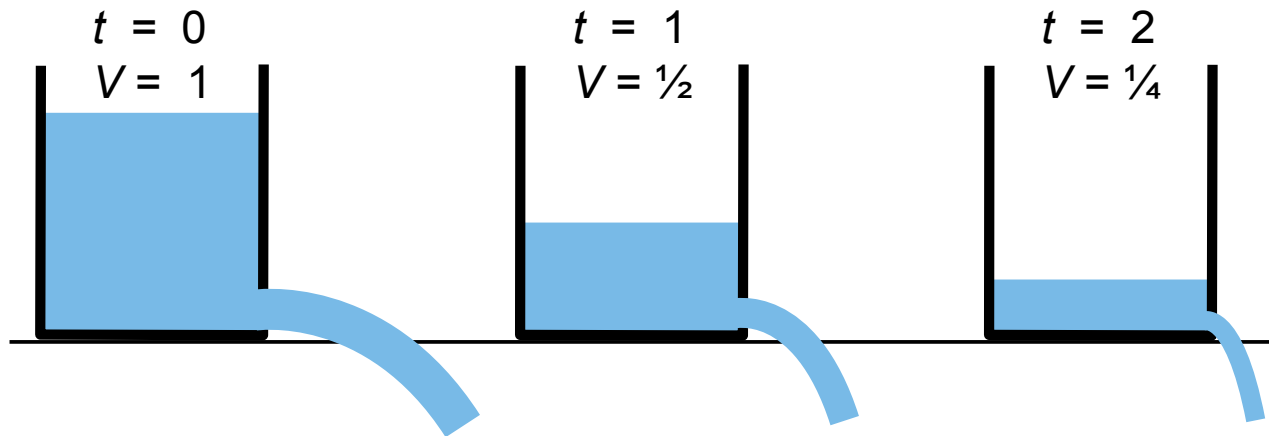
One Compartment Model, IV dose (1)

- **The whole body is simplified to one 'compartment'**
  - Practically instantaneous distribution
  - Homogenous within all tissues
  - Concentrations decline exponentially
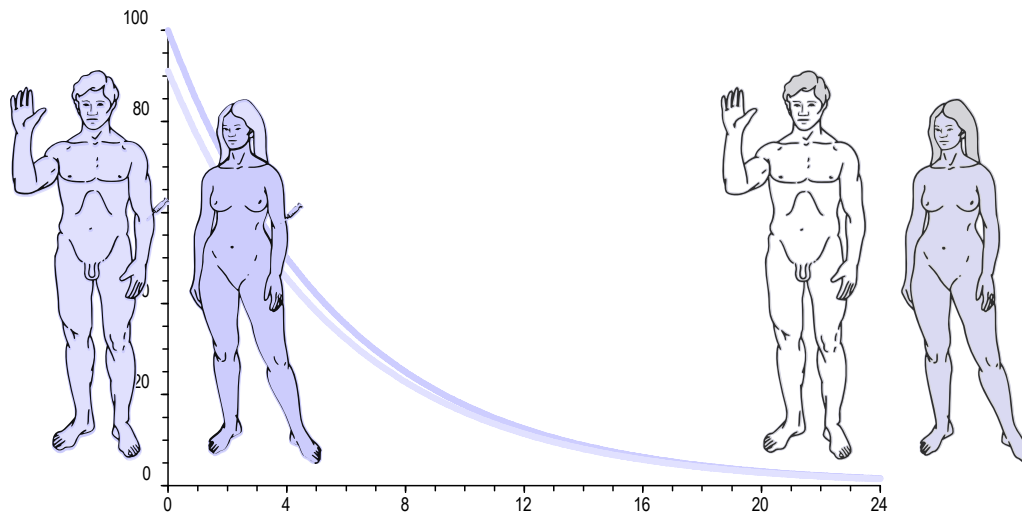
Mod. from Pioneer Plaque: Designed by Carl Sagan & Frank Drake, artwork by Linda Salzman Sagan (1972)

One Compartment Model, IV dose (2)

- Half life
    - Troughout the profile concentration drops to ½ of its previous value within one 'half life' ($t_{½}$)
    - In a semilogarithmic plot the profile shows a straight line with
        - a slope of $-\ln(2)/t_{½}$, which is the elimination rate constant k_e and
        - the intercept is related to the initial concentration by $C_0 = e^{intercept}$

$$C(t) = C_0\, e^{-k_e \cdot t}$$

$$\ln\big(C(t)\big) = \ln\big(C_0\big) - k_e \cdot t$$
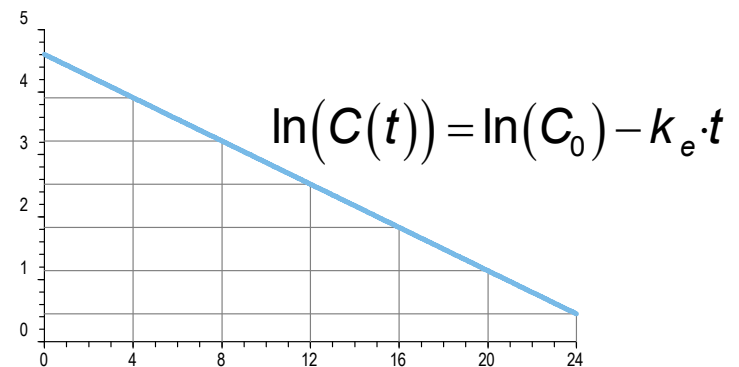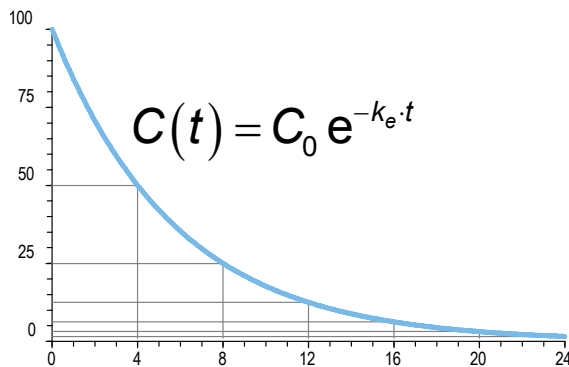
One Compartment Model, IV dose (3)

- ## Volume of distribution
  - At administration the entire dose (D) is assumed to homogenously dissolve in the 'Volume of distribution' (V_d)
  - Only concentrations can be measured
    - At $t = 0$ we get $V_d = \dfrac{C_0}{D}$
    - Beware: V_d is a *hypothetical* compartment, whereas in reality the distribution is not homogenous!
      Some lipophilic drugs have a V_d of hundreds of liters…
    - Classical PK is *not* directly related to physiology

Essentially, all models are wrong,
but some are useful. *George Box*

One Compartment Model, IV dose (4)

- **Clearance**
  - Instead of describing elimination by the rate constant k_e (unit: 1/time) we can also ask for the *fraction* of V_d which is completelly 'cleared' of the drug per unit of time
  - This parameter is called 'Clearance' CL (unit: volume/time), which leads to basic equations of pharmacokinetics:

$$CL = V_d \cdot k_e \text{ or } \frac{D}{AUC}, \text{ where } AUC = \int_{t=0}^{t=\infty} C(t)\,\mathrm{d}t$$

$$\left[\text{volume/time}\right] = \frac{\left[\text{mass}\right]}{\left[\text{time} \times \text{mass/volume}\right]}$$

Assumptions in Bioequivalence

- ## All (!) models rely on assumptions
  - Bioequivalence as a surrogate for therapeutic equivalance
    - Studies in healthy volunteers in order to minimize variability
      (*i.e.*, lower sample sizes than in patients)
    - Current emphasis on *in vivo* release
      ('human dissolution apparatus')
  - Concentrations in the sample matrix reflect concentrations
    at the target receptor site
    - In the strict sense only valid in steady state
    - *In vivo* similarity in healthy volunteers can be extrapolated
      to the patient population(s)
  - $f = \mu_T / \mu_R$ assumes that
    - $D_T = D_R$ and

$$AUC_T = \frac{f_T \cdot D_T}{CL}, AUC_R = \frac{f_R \cdot D_R}{CL}$$

    - inter-occasion clearances are constant

Regulatory Demands for Study Design in BE

- Definitions
  - EMA (BE GL, 2010)
    - Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, *i.e.* similarity in terms of safety and efficacy.
  - WHO (TRS 992, Annex 6, 2017)
    - Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (C_{max} and t_{max}) and extent of absorption (area under the curve (AUC)), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Regulatory Demands for Study Design in BE

- ## Definitions (cont'd)
  - ### FDA (CFR 21–320.23(b)(1), 2019)
    - Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.

Background of BE

- BE = (desired) result of a comparative BA study
  - Generally only for extravascular routes. Exceptions for IV:
    - Excipients which may interact with the API (complex formation)
  - Case-by-case: Liposomal formulations, emulsions
  - Same active substance
    - Focus on the 'core' API (different salts, esters, isomers, complexes are considered the same active substance)
  - Same molar dose, same conditions
  - Clinically not relevant difference: Δ 20%, except
    - Narrow Therapeutic Index Drugs $\leq$10%
    - Highly Variable Drugs / Drug Products $\geq$20%
  - $100(1 - 2\alpha)$ confidence interval of PK-metrics within $[1 - \Delta, (1 - \Delta)^{-1}]$
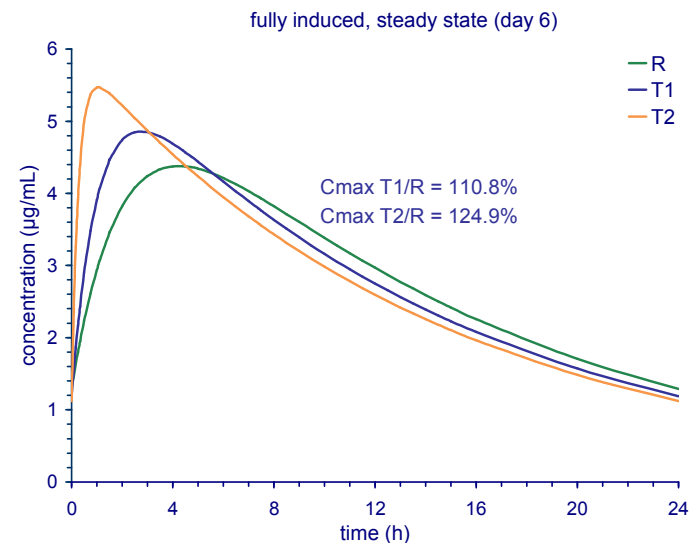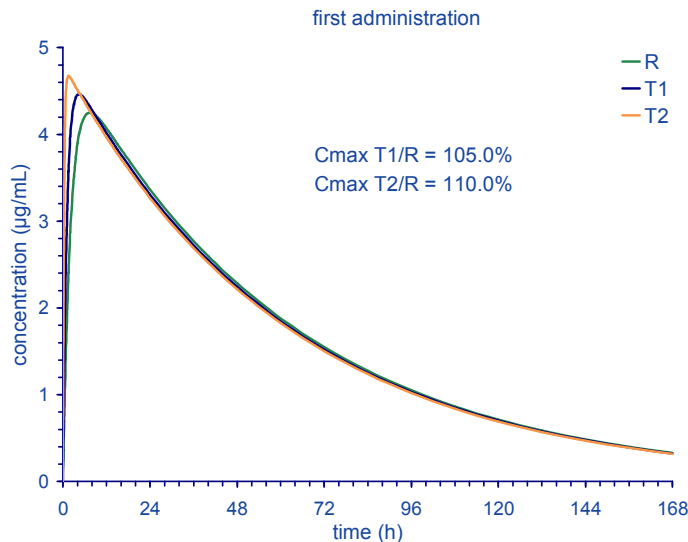
Background of BE

- Design should allow accurate (unbiased) assessment of the treatment effect
  - Generally healthy volunteers (lower variability); except:
    - Not ethical due to effects or AEs → study in patients
  - Cross-over design preferred
    - Each subject serves as its own 'reference'
      - Hence, the comparison is performed *within* subjects
      - More powerful (fewer subjects needed) than in a parallel design
  - Parallel design as an alternative
    - Studies in patients were the disease state is not stable
    - Studies of drugs with (very) long half lives
    - Comparison is performed *between* subjects
      - Less powerful than cross-over
      - Requires high degree of standardization

Background of BE

- ## Assessment of the treatment effect (cont'd)
  - Cross-over design
    - Assumes that the treatment effect is independent from the sequence of administration
      - Sufficiently long washout between periods
        - » No residual concentrations in higher period(s)
        - » No remaining effect which may influence ADME
        - » Patients: Stable disease
    - Period effects are not relevant (adjusted in the statistical model)
  - Parallel design
    - Assumes lacking difference in groups
      - Similar anthropometric properties (sex, age, BMI, …)
      - If the drug is subjected to polymorphism, geno-/phenotyping is strongly recommended

Background of BE

- Assessment of the treatment effect (cont'd)
  - Carbamazepine ($k_{a(R)}$ 0.472 h^{-1}, $k_{a(T1)}$ 0.94 h^{-1}, $k_{a(T2)}$ 3.6 h^{-1})
    - $t_{½}$ after first administration 43 h (↘ 10 h after full auto-induction)
    - A rare [*sic*] example where a multiple dose study is more sensitive to detect differences in the rate of absorption than single dose

first administration

Cmax T1/R = 105.0%
Cmax T2/R = 110.0%

fully induced, steady state (day 6)

Cmax T1/R = 110.8%
Cmax T2/R = 124.9%

Background of BE

- Assessment of the treatment effect (cont'd)
  - Parent *vs.* metabolite(s)
    - Absorption of parent expected to be the best measure of Liberation and Absorption (formulation dependent)
    - Parent may be difficult to measure (pro-drugs: low concentrations together with fast elimination)
      - Alternative: Metabolite (irrelevant whether active or inactive)
      - If possible the *first* metabolite in the chain should be measured
      - The further 'downstream' a metabolite is, the less it is able to detect differences in absorption of the parent
  - Fasting *vs.* fed conditions
    - Fasting generally considered the most sensitive
      - Exceptions
        » Intake with food required according to the reference's label
        » Fasting *and* fed for controlled release products (EMA and some of the FDA's product-specific guidances)

Background of BE

- Assessment of the treatment effect (cont'd)
  - Dose strength
    - The strength which is considered to be most sensitive
    - Linear PK
      - Generally highest strength
      - If highly soluble, a lower strength is acceptable
      - A lower strenght is also acceptable if safety/tolerability issues in healthy subjects (requires justification)
    - Nonlinear PK
      - Higher than proportional increase in AUC over the dose range
        » Generally highest strength. Similar exceptions as for linear PK
      - Lower than proportional increase in AUC over the dose range
        » Lowest *and* highest strength
        » Under certain conditions testing only the lowest strength can be justified

Special Cases: NTIDs and HVD(P)s

- ## Clinically not relevant difference?

  - Based on PK but extrapolated to similarity of safety and efficacy in the patient population

    - Depends on the dose-response curves: NTID (steep), HVD (flat)
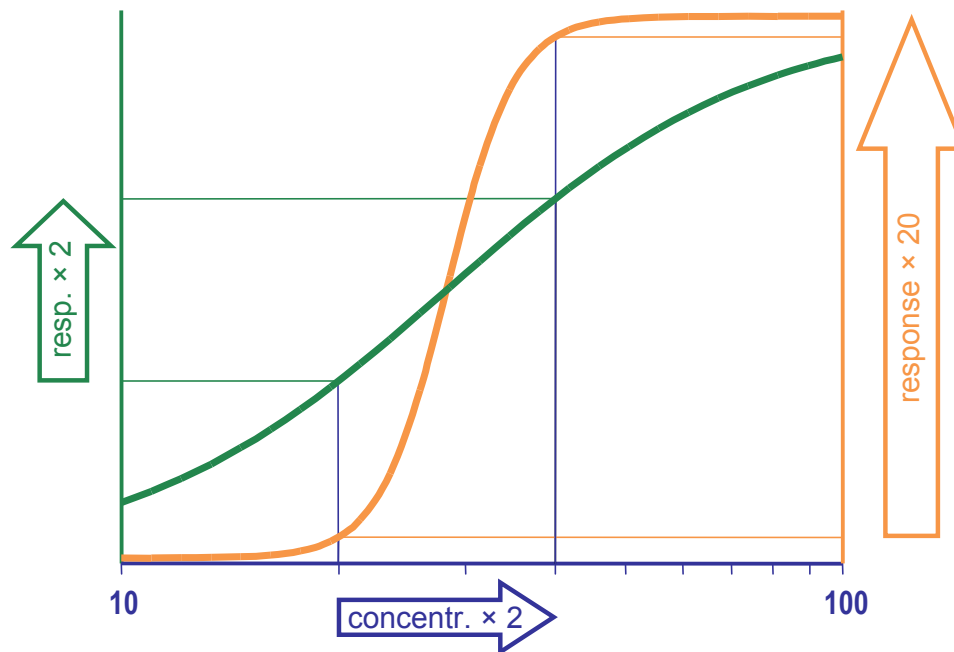
Special Case: NTIDs

- **Clinically not relevant difference**
  - Predefined by the authority
    - Generally 20%
      - Leads to BE-limits of 80.00 – 125.00%
    - Lower for NTIDs
      - EMA, WHO   10% $\rightarrow$ BE-limits of 90.00 – 111.11%
      - FDA   Scaled based on the variability of the reference

CV_{wR}	BE-limits (%)
5.00	94.87 – 105.41
7.50	92.41 – 108.21
10.03	90.00 – 111.11
15.00	85.46 – 117.02
20.00	81.17 – 123.20
21.50	80.00 – 125.00

Special Case: HVD(P)s

- **Clinically not relevant difference**
  - Predefined by the authority
    - >20%
      - Leads to BE-limits of wider than 80.00–125.00%
      - GCC   25% → BE-limits of 75.00 – 133.33% (C_{max} only)
      - EMA   Scaled based on CV_{wR} (C_{max} only)
      - WHO   Like EMA (if justified, also AUC)
      - FDA   Scaled based on CV_{wR} (AUC and C_{max})

EMA, WHO		FDA	
CV_{wR}	BE limits (%)	CV_{wR}	BE limits (%)
≤30	80.00 – 125.00	≤30	80.00 – 125.00
35	77.23 – 129.48	35	73.83 – 135.45
40	74.62 – 143.02	40	70.90 – 141.04
45	72.15 – 138.59	45	68.16 – 146.71
≥50	69.84 – 143.19	50	65.60 – 152.45
		60	60.96 – 164.04