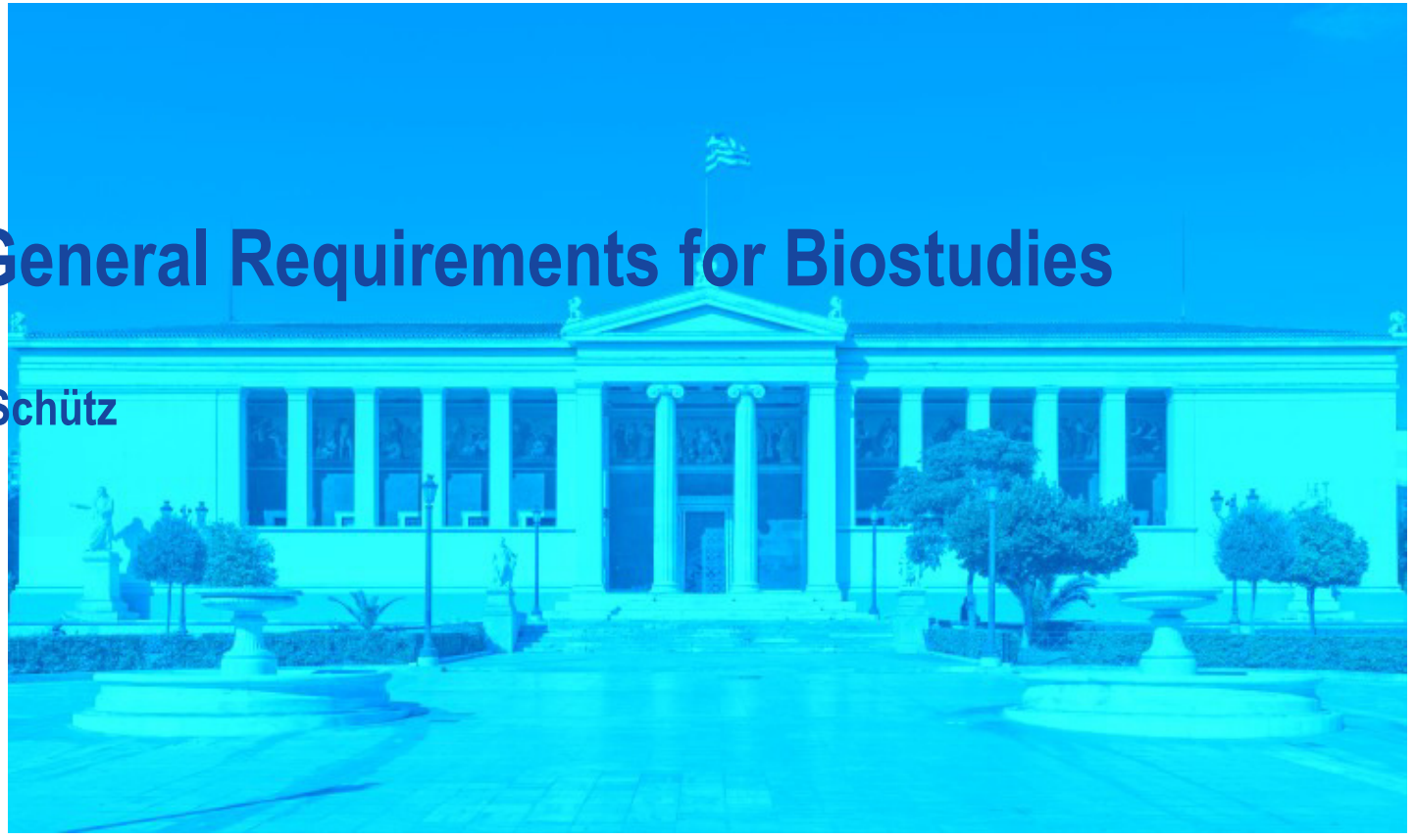
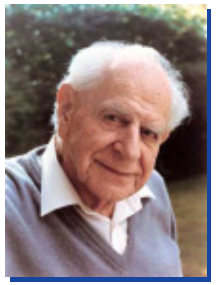
The General Requirements for Biostudies

Helmut Schütz



To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood 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*!

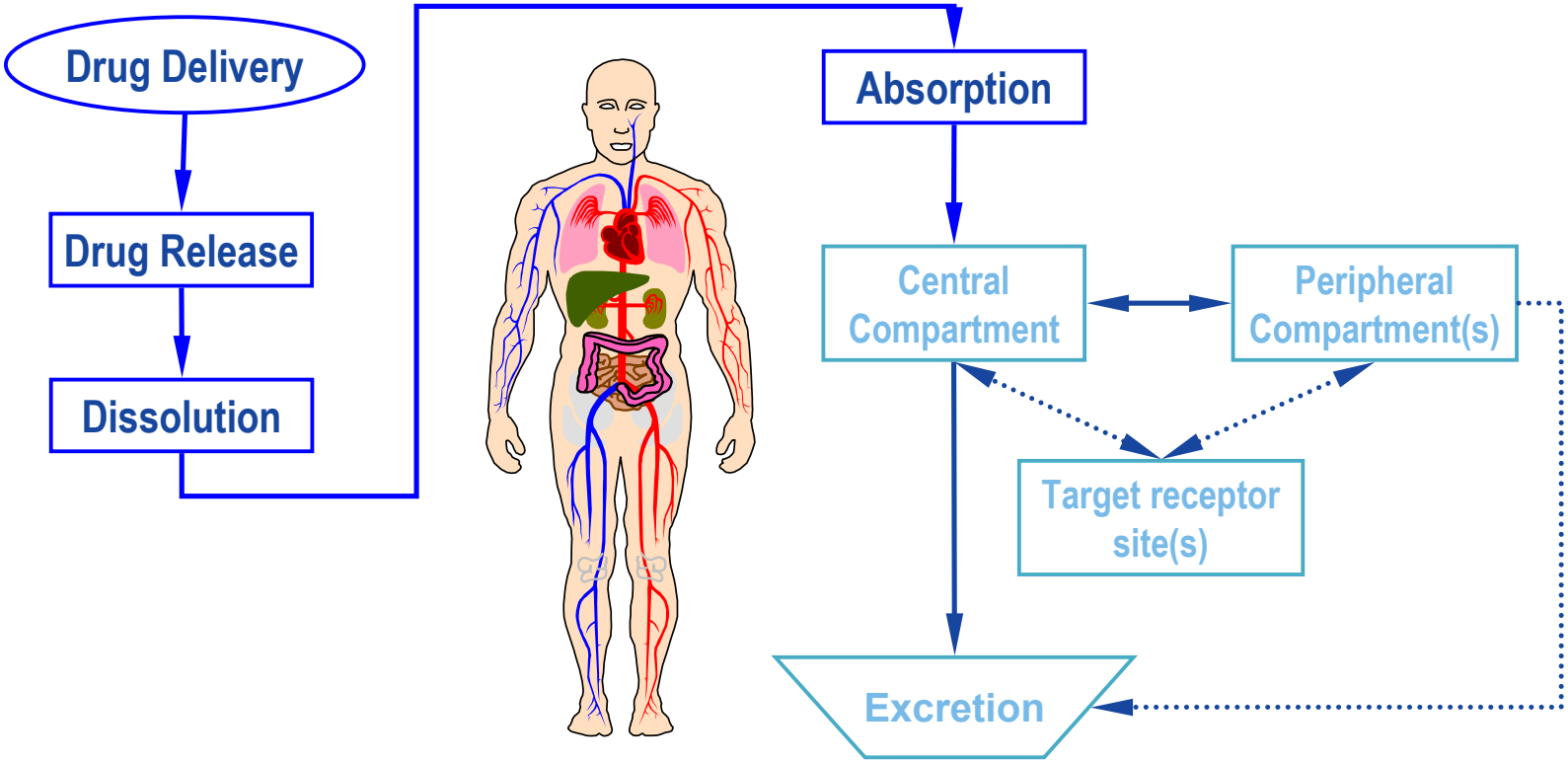
Leslie Z. Benet

Fundamentals of Pharmacokinetics

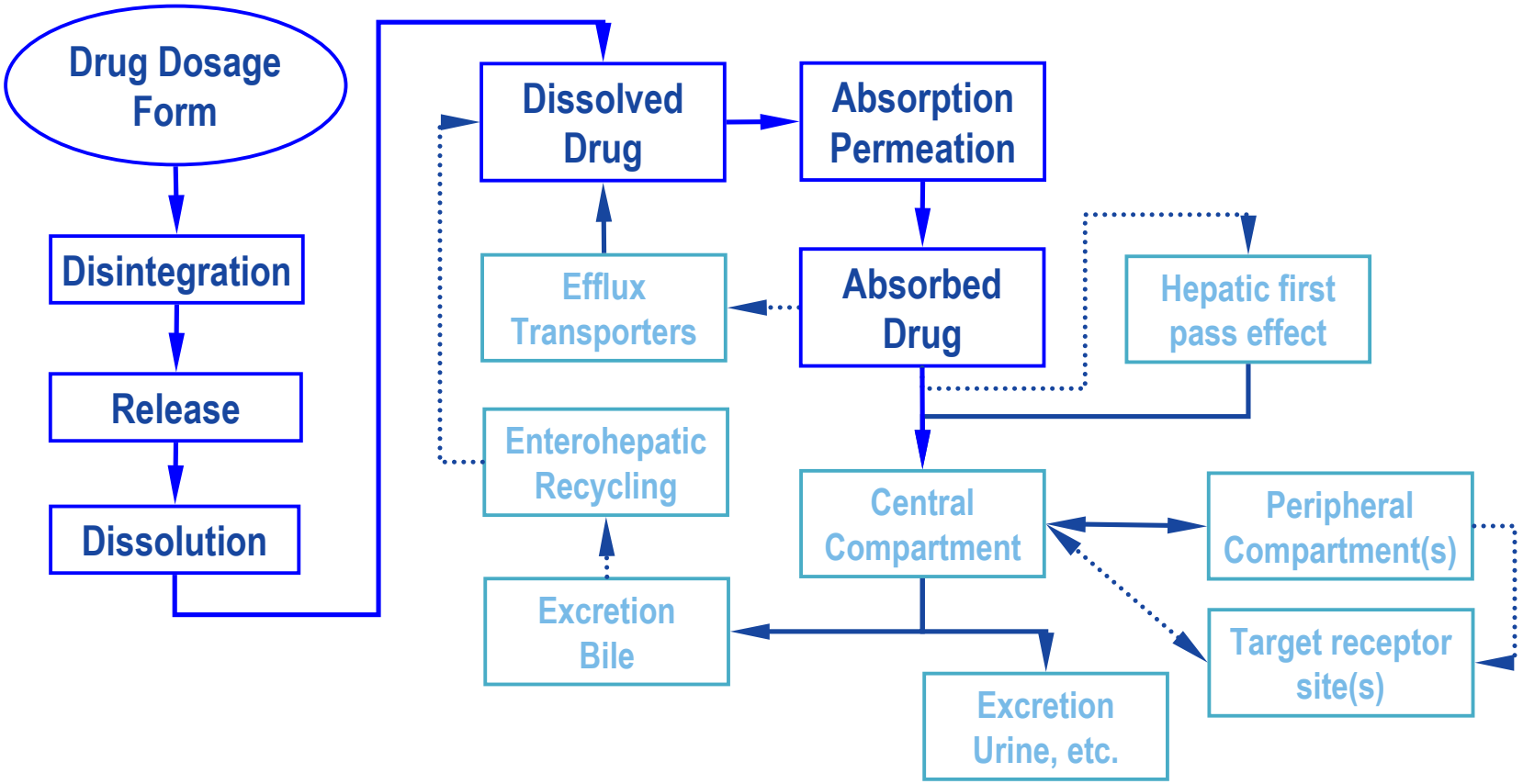
φαρμακός (drug) + κινητικός (putting in motion)

- Term introduced in 1953.
  - Friedrich H Dost 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



Pharmacokinetic process



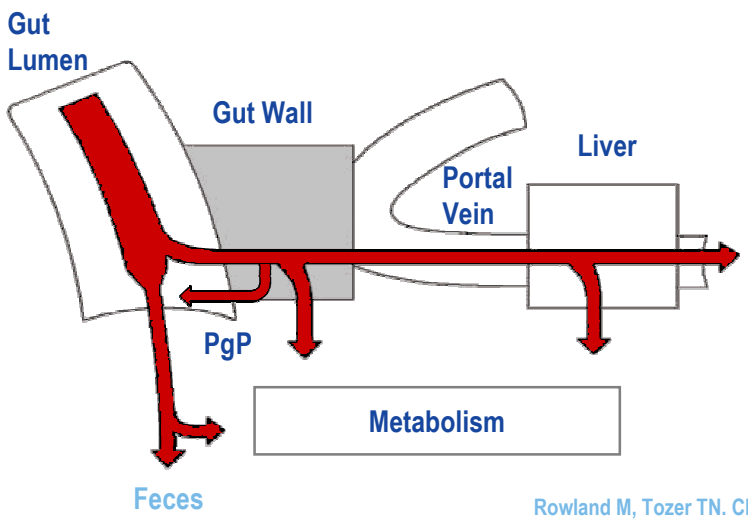
Pharmacokinetic process

(L)ADME

Biopharmaceutical phase
- Disintegration
- Release
- Dissolution

} **L**iberation

Pharmacokinetic phase
- **A**bsorption
  - Passive diffusion
  - Active transport
- **D**istribution
- **M**etabolism
  - Intestinal first pass
  - Membrane first pass
  - Hepatic first pass
- **E**xcretion

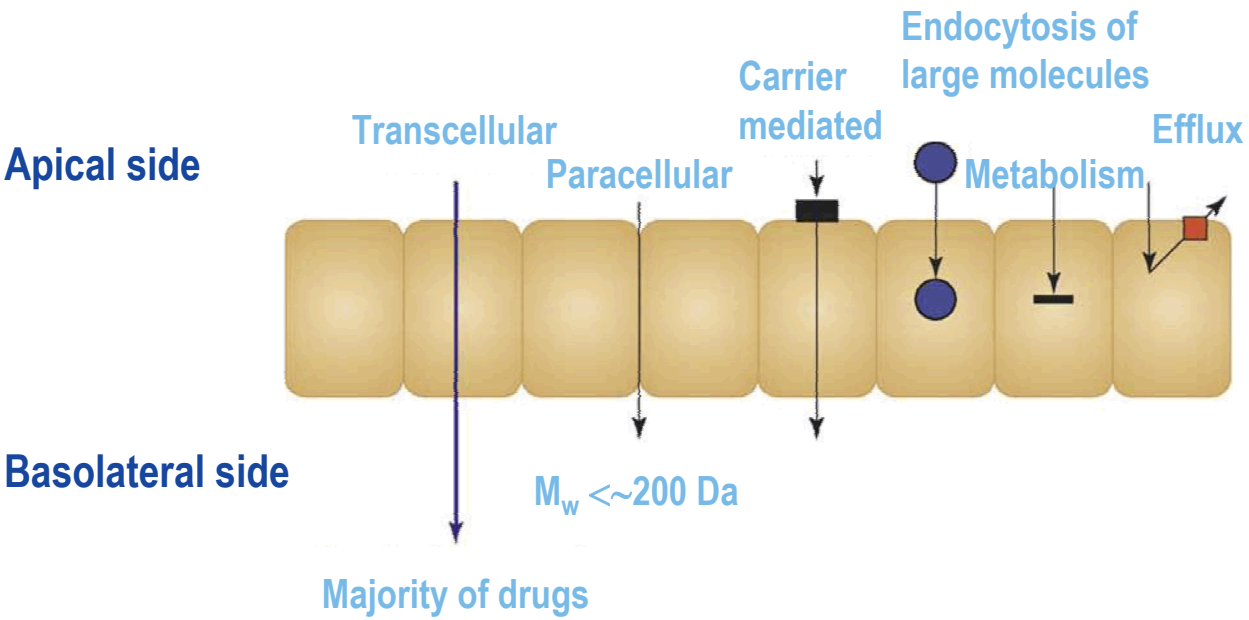


Elimination = M + E

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

Pharmacokinetic process

Absorption revisited



Pharmacokinetic models

The body is simplified to one – or more – 'Compartments' where the drug is distributed

- One compartment model
  - Drug is distributed homogeneously 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, (brain).
  - The second (peripheral) compartment describes less perfused tissues (fat, bones, …).

Pharmacokinetic models

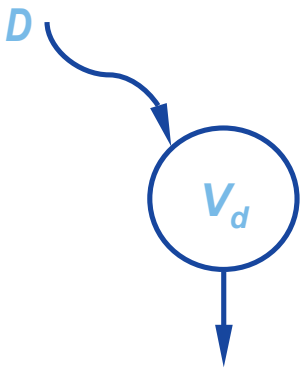
Compartment models

- Compartments are
  - described by a volume and
  - pathways which link them.
- These links may be
  - unidirectional (absorption, excretion) or
  - bidirectional (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

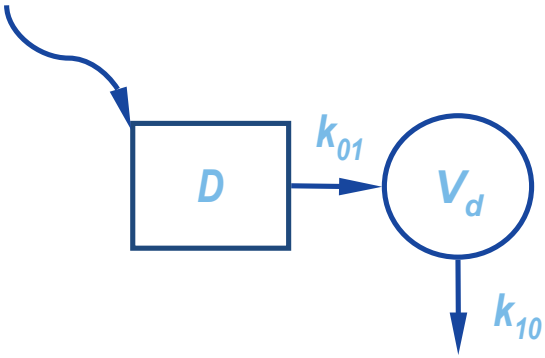
Examples

One comp. IV



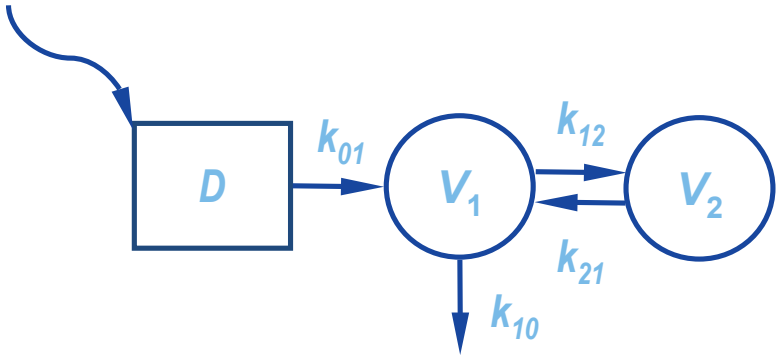
M + E

One comp. EV



A + M + E

Two comp's EV

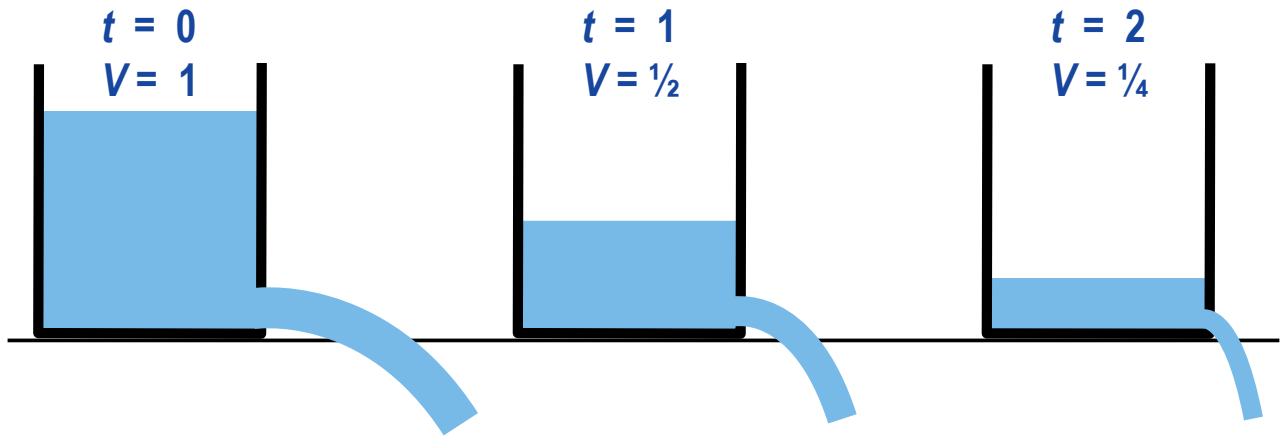


A + D + M + E

One compartment model, IV dose

Excursion into Hydrodynamics

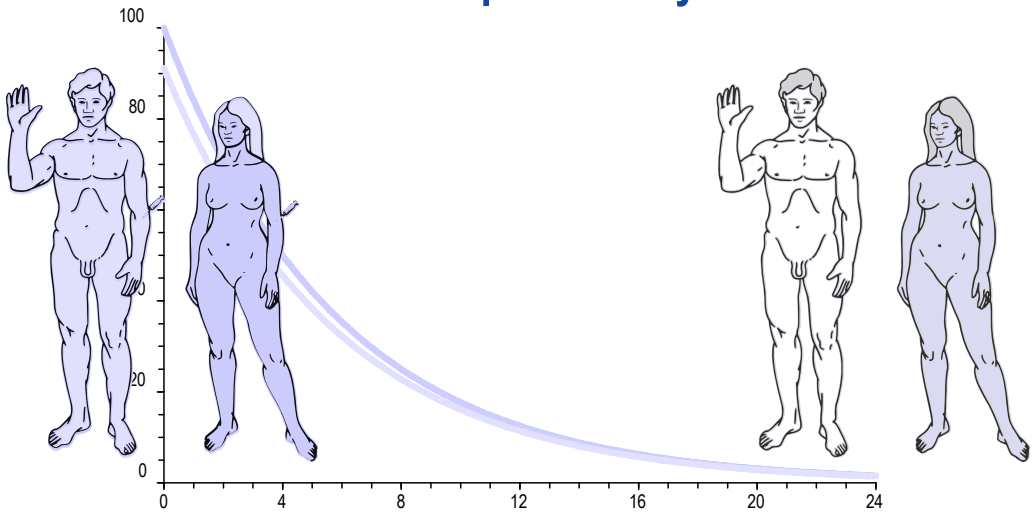
- Driving force for draining an *open* tank:
  Hydrostatic pressure (height of liquid column & gravity).
- Emptied volume decreases with time.
- Same *proportion* is emptied in the same time interval.



One compartment model, IV dose

The whole body is simplified to one ‘compartment’

- Practically instantaneous distribution.
- Homogenous within all tissues.
- Concentrations decline exponentially.

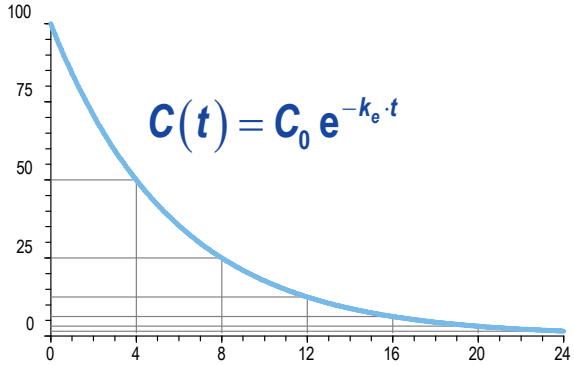


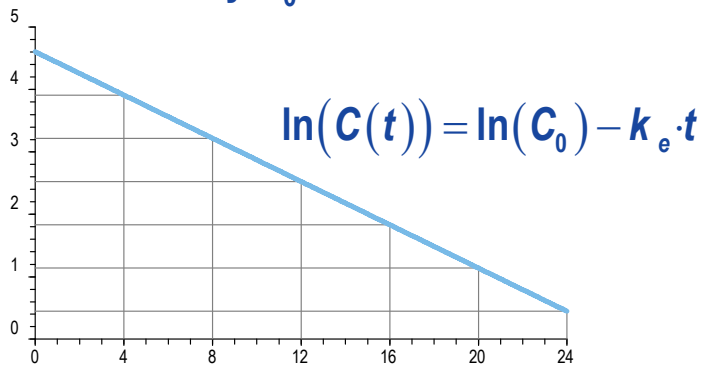
Mod. from Pioneer Plaque: Designed by Carl Sagan & Frank Drake, artwork by Linda Salzman Sagan (1972)

One compartment model, IV dose

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 $C_0 = e^{intercept}$.





One compartment model, IV dose

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 $V_d = \frac{C_0}{D}$.
  - Cave: V_d describes a *hypothetical* compartment, whereas in reality the distribution might not be 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

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:

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

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

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*
  - inter-occasion clearances are constant.

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

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.
- **FDA (CFR 21–320.1, 2016)**
  - Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Regulatory demands for study design in BE

BE = (Desired) result of a comparative bioavailability 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.
- Clinically not relevant difference: Δ 20% (NTIDs 10%, HVD(P)s >20%).
- 100(1 – 2α) confidence interval of PK-metrics within $[1 - \Delta, (1 - \Delta)^{-1}]$.
  - AUC_{0-t} (extent of absorption)
  - C_{max} (rate of absorption)
  - t_{max}, $AUC_{0-\tau}$, $C_{max,ss}$, $C_{min,ss}$, $C_{\tau,ss}$, %*PTF*, partial *AUC*s, …

Regulatory demands for study design in 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.

Regulatory demands for study design in BE

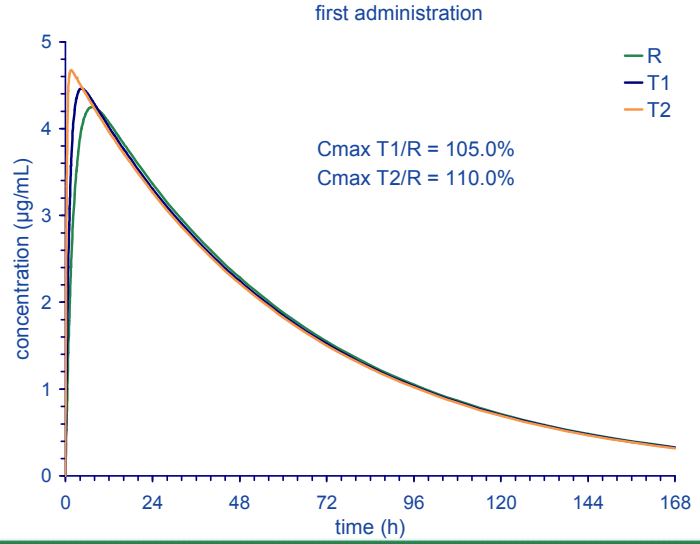
Design should allow accurate (unbiased) assessment of the treatment effect.

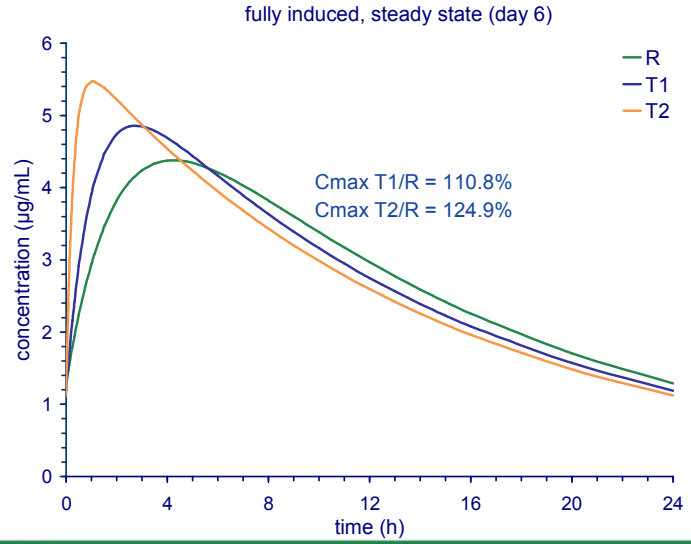
- Cross-over design.
  - Assumes that the treatment effect is independent from the period and sequence of administration.
    - Sufficiently long washout between periods:
      - » No residual concentrations in higher period(s).
      - » No remaining effect which may influence ADME.
      - » Patients: Stable disease.
- Parallel design.
  - Assumes lacking difference in groups.
    - Similar anthropometric properties (sex, age, BMI, …).
    - If the drug is subjected to polymorphism, geno-/phenotyping is mandatory.

Regulatory demands for study design in BE

Design should allow accurate (unbiased) assessment of the treatment effect

- 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 MD is more sensitive to detect differences in the rate of absorption than SD





Regulatory demands for study design in BE

Design should be able to detect differences in formulations.

- 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 measure the *first* metabolite in the chain. The further 'downstream' a metabolite is, the less it is able to detect differences in absorption of the parent.
- Fasting *vs.* fed.
  - Generally fasting since considered the most sensitive.
    - Exceptions:
      - » Intake *with* food required according to the reference's SmPC.
      - » Fasting *and* fed for MR products (EMA, some product-spefic guidance by the FDA).

Regulatory demands for study design in BE

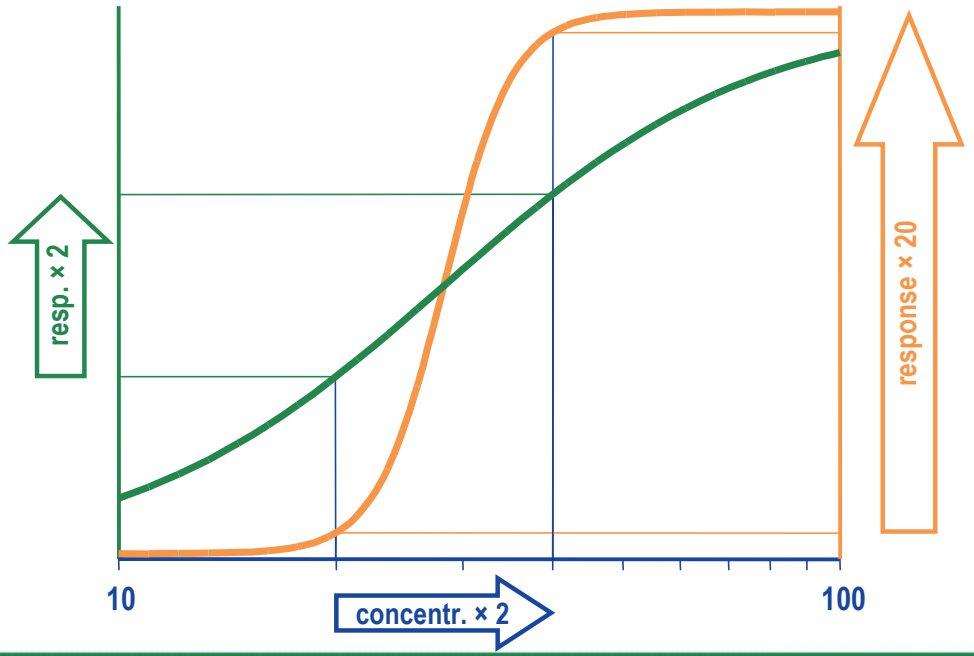
Design should be able to detect differences in formulations.

- 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.

Narrow therapeutic index drugs and HVDP(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 curve! NTID (steep curve), HVD (flat curve):



Narrow therapeutic index drugs and HVDP(s)

Clinically not relevant difference.

- Based on PK but extrapolated to similarity of safety and efficacy in the patient population.
  - Predefined by the authority.
    - Generally 20%.
      - » Leads to BE-limits of 80.00–125.00%.
    - Lower for NTIDs.
      - » EMA: 10% leads to 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

Narrow therapeutic index drugs and HVDP(s)

Clinically not relevant difference.

- Based on PK but extrapolated to similarity of safety and efficacy in the patient population.
  - Predefined by the authority.
    - Higher for HVD(P)s. Scaled based on the variability of the reference.
      - » EMA: IR C_{max} only; MR (additionally $C_{max,ss}$, $C_{min,ss}$, $C_{T,ss}$, partial *AUC*s).
      - » FDA: C_{max}, *AUC*.
      - » HC: *AUC* only.

EMA	
CV_{wR}	BE limits (%)
≤30	80.00 – 125.00
35	77.23 – 129.48
40	74.62 – 143.02
45	72.15 – 138.59
≥50	69.84 – 143.19

FDA	
CV_{wR}	BE limits (%)
≤30	80.00 – 125.00
35	73.83 – 135.45
40	70.90 – 141.04
45	68.16 – 146.71
50	65.60 – 152.45
60	60.96 – 164.04

HC	
CV_{wR}	BE limits (%)
≤30	80.00 – 125.00
35	77.23 – 129.48
40	74.62 – 143.02
45	72.15 – 138.59
50	69.84 – 143.19
≥57.4	66.67 – 150.00

Plasma levels or alternatives

Recap the main assumption:

- Concentrations in the sample matrix reflect concentrations at the target receptor site.
  - In exceptional cases neither the parent or a metabolite can be reliably measured. Needs good justification – a simple claim is not sufficient!
  - Urine may be used as an alternative matrix, if
    - the drug shows high absolute bioavailability and
    - is mainly excreted unchanged in the urine.
  - With the current analytical technology of historical interest.
    - Example: Bisphosphonates (very low and highly variable absorption).
      - » *AUC* as the PK metric for extent of absorption could not be reliably measured in plasma.
        The amount excreted in urine was employed instead.
      - » However, C_{max} in plasma was still required as the PK metric for the rate of absorption.

Plasma levels or alternatives

Recap the main assumption:

- Concentrations in the sample matrix reflect concentrations at the target receptor site.
  - Sometimes the receptor site is *not* directly linked to the circulation.
    - Example: Pulmonary delivery of antiasthmatics.
      - » Receptors are located in the lung.
      - » Drug acts *locally*.
      - » By inhalation the dose is fractionated:
        (a) deposited in the lung (reponsible for the effect) and subsequently absorbed (bypassing first-pass metabolism),
        (b) absorbed in the oral cavity (bypassing first-pass metabolism),
        (c) swallowed and absorbed in the GIT (subjected to metabolism).
      - » Only (a) reflects the effect.
      - » EMA: By administering charcoal we block (b) and (c). Now can measure the drug in plasma (absorbed through the lung only).
      - » FDA: Measurement of a *pharmacodynamic* surrogate (FEV_1).

The General Requirements for Biostudies

Thank You!
Open Questions?

Helmut Schütz

BEBAC

Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria

helmut.schuetz@bebac.at