Üdvözöljük!

Design and Evaluation of BE Studies

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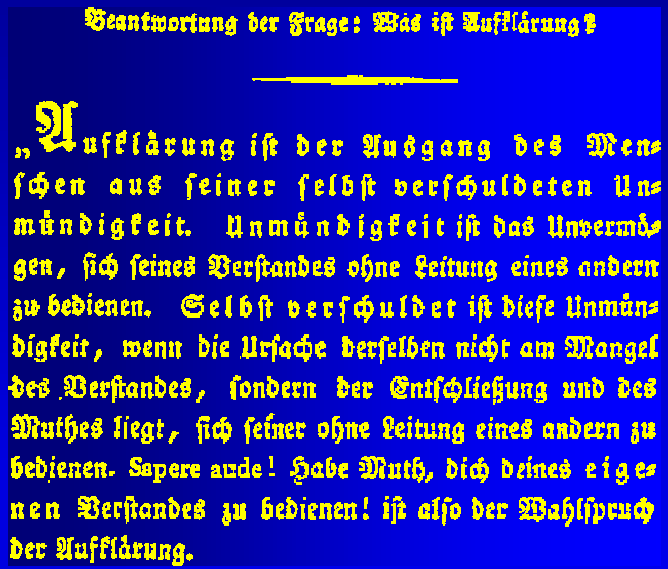
Answering the Question: What is Enlightenment?


Beantwortung der Frage: Was ist Aufklärung?

„Aufklärung ist der Ausgang des Menschen aus seiner selbst verschuldeten Unmündigkeit. Unmündigkeit ist das Unvermögen, sich seines Verstandes ohne Leitung eines andern zu bedienen. Selbst verschuldet ist diese Unmündigkeit, wenn die Ursache derselben nicht am Mangel des Verstandes, sondern der Entschließung und des Muthes liegt, sich seiner ohne Leitung eines andern zu bedienen. Sapere aude! Habe Muth, dich deines eigenen Verstandes zu bedienen! ist also der Wahlspruch der Aufklärung.

„Enlightenment is man's emergence from his self-imposed immaturity for which he himself was responsible. Immaturity and dependence are the inability to use one's own intellect without the direction of another. One is responsible for this immaturity and dependence, if its cause is not a lack of intelligence, but a lack of determination and courage to think without the direction of another. **Sapere aude!** Have courage to use your own understanding! is therefore the slogan of Enlightenment."

Immanuel Kant (1784)

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

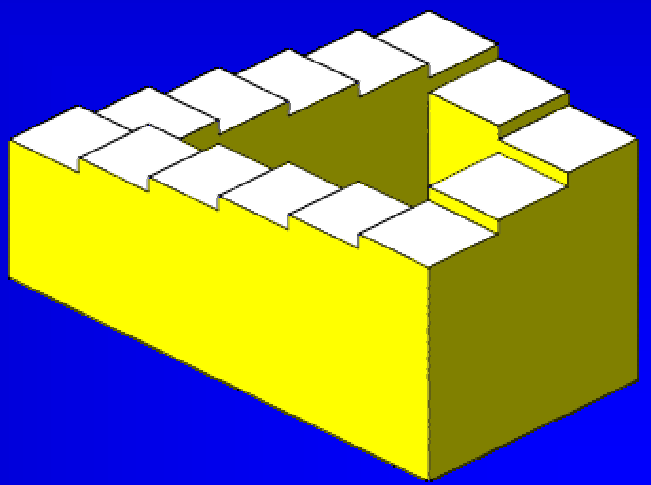
***Statistics* – A subject which most statisticians find difficult but in which nearly all physicians are expert.**

Stephen Senn

Bioequivalence Studies

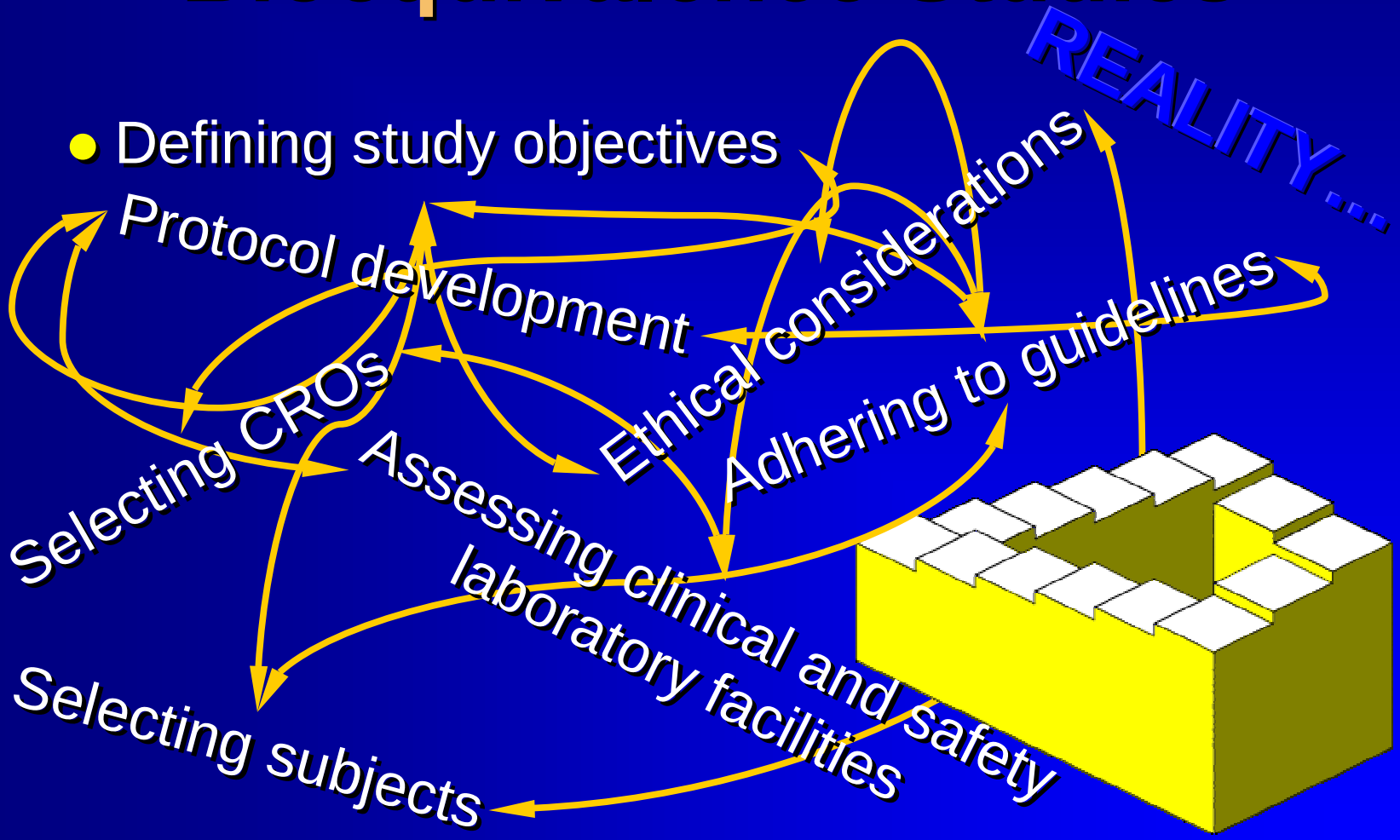
DREAM...

- Defining study objectives
- Selecting CROs
- Protocol development
- Ethical considerations
- Assessing clinical and safety laboratory facilities
- Selecting subjects
- Adhering to guidelines



Bioequivalence Studies

- Defining study objectives



Overview

- Bioequivalence
  - Surrogate of clinical equivalence or
  - Measure of pharmaceutical quality?
- Types of studies
  - Pharmacokinetic (PK)
  - Pharmacodynamic (PD)
  - Clinical (equivalence and/or safety/efficacy)

Overview

- Types of studies (cont'd)
  - Healthy Subjects
  - Patients
  - Single dose
  - Multiple dose
  - Cross-over
  - Parallel
  - Reference product (another modified release formulation, IR, solution)

Overview

- Types of studies (cont'd)
  - Food effect
  - PK interaction
- Design Issues
  - Dose regimen
  - Fasted / fed state
  - Type of standard meals
- Bioanalytics (*not* GLP!)
  - Parent drug / metabolite(s) / enantiomers / pro-drugs
  - Validation / routine application

Overview

- Ethics (GCP!)
  - Dose levels / number of administered doses
  - Number / volume of blood samples
  - Drug and/or adverse effects
- Clinical performance (GCP!)
  - CRO selection
  - Responsibilities of sponsor / investigator
  - Audits / monitoring

Overview

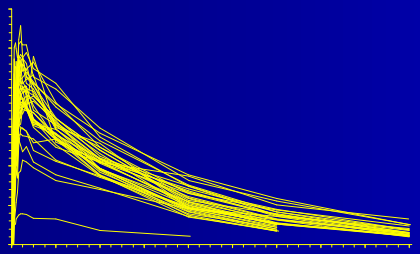
- NCA / PK (PD)
  - Sampling schedule
  - Metrics (AUC, C_{max}; AUEC, Ae_{max},…)
  - Design, methods, evaluation
- Sample size
  - Estimation from previous and/or pilot studies, literature
  - Highly variable drugs
- Biostatistics
  - Models & assumptions
  - Protocol, evaluation, report

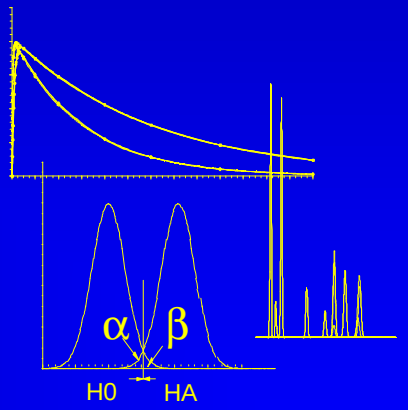
Overview

- ‘What if’-scenarios
  - Common pitfalls
  - Blind review
  - ‘Failed’ studies
  - Deficiency letters

Assumptions

World *'Truth'*

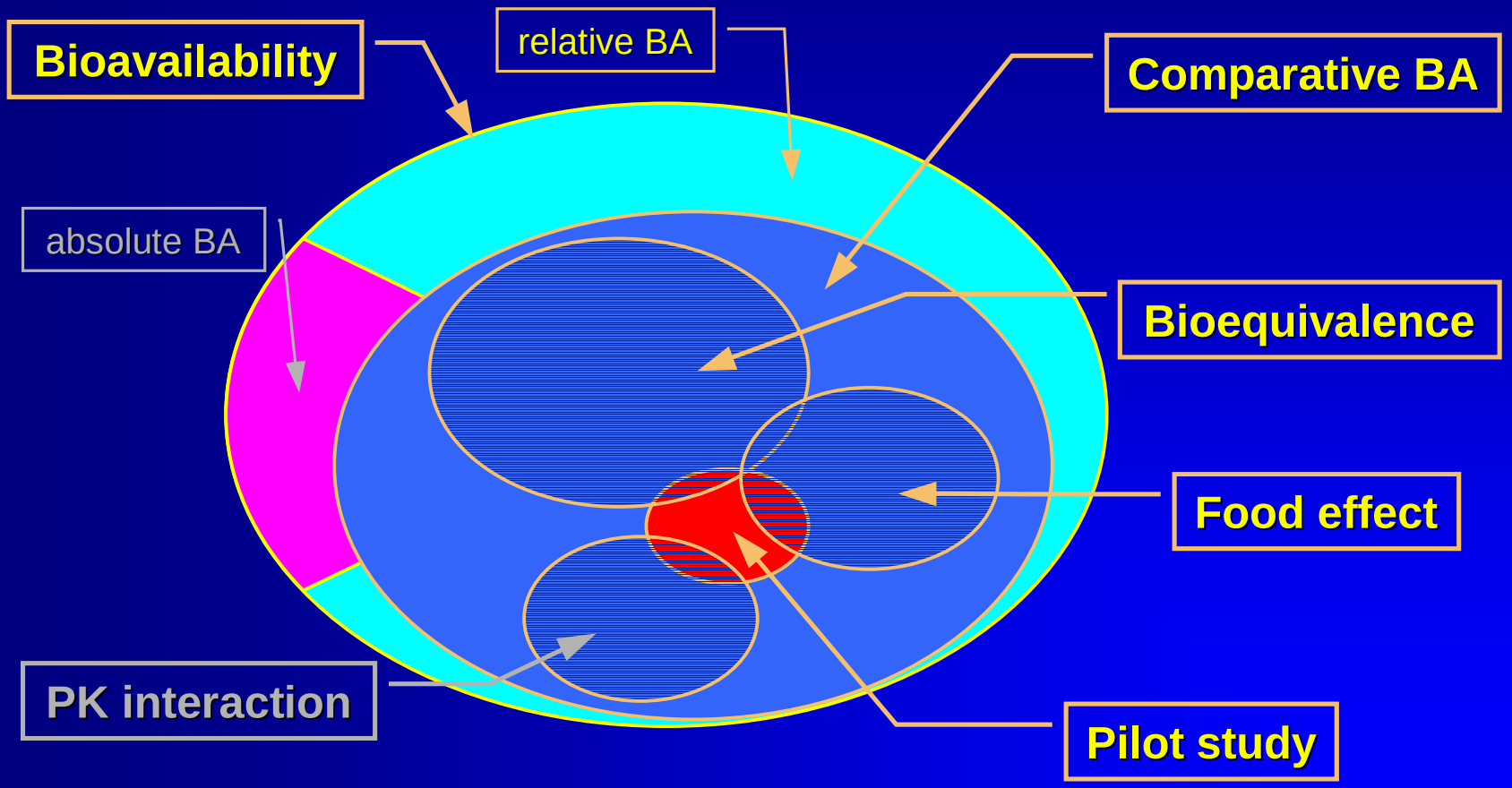




Model *'Data'*

Theory *'Reality'*

Terminology



Definition

- EMEA NfG on BA/BE (2001)

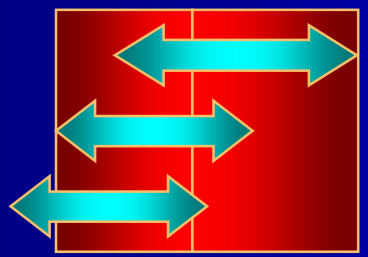
  ‘A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products.’

  - Comparative BA,
  - designed to demonstrate BE,
  - reference = innovator’s product.

EMEA Human Medicines Evaluation Unit / CPMP
Note for Guidance on the Investigation of Bioavailability and Bioequivalence (2001)
http://bebac.at/downloads/140198enfin.pdf

Bioequivalence…

- Comparative BA
  - true experiment; no bibliographic comparison
- Designed to demonstrate BE
  - variability,
  - deviation of test from reference,
  - drop-out rate,…
    - ➔to be able (statistical power!) to demonstrate BE
- Reference = Innovator's product



#1: BE [90%–125%]

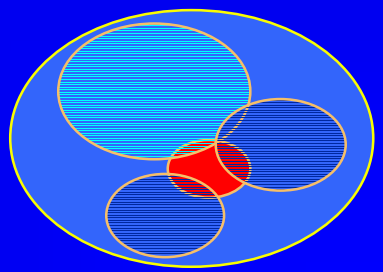
#2: BE [80%–110%]

#3: not BE [76%–103%]; (but 'BE' to #2)

Bioequivalence…

- EMA GL on BE (2010)

  ‘Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavail-abilities (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.’



Global Harmonization?

- In almost all regulations two metrics are necessary to demonstrate BE, namely
  - extent (AUC_t *or* AUC_∞) and
  - rate (C_{max}) of exposure.
- One exception: US-FDA (where AUC_t *and* AUC_∞ must demonstrate extent of exposure)
  - Although stated in the GL, such a requirement is statistically flawed.
    - Multiplicity issues (what is the patient's risk?)
    - Impossible α-adjustment (interdependence)

There can be only one!

History of BE

- Bioequivalence
  - Problems first noticed with NTIDs (Narrow Therapeutic Index Drugs) in the late 1970s
  - Intoxications (and even some fatallities!) were reported (warfarin, digoxin, phenytoin)
    - Warfarin, digoxin: Patients switched between formulations which were got approval solely based on *in vitro* data (innovator ↔generic)
    - Phenytoin: The innovator's API was changed from a microcrystalline to an amorphous form resulting in 10times higher plasma concentrations in steady state

History of BE

- Bioequivalence
  - Surrogate of clinical equivalence (1980+)
    - Studies in steady state in order to reduce variability
    - Studies based on active metabolite
    - Wider acceptance range if clinical justifiable (not FDA!)
  - Measure of pharmaceutical quality (2000+)
    - Single dose studies preferred
    - Generally parent drug
    - Widening of acceptance range exceptional (except FDA HVDs and EMA C_{max} of HVDs)

Early 1980s

- First method
  - FDA's 75/75 Rule
    BE, if 75% of subjects show ratios of 75%-125%.
    Not a statistic, variable formulations may pass by chance…

	T	R	T/R	75%-125%
1	71	81	87.7%	yes
2	61	65	93.8%	yes
3	80	94	85.1%	yes
4	66	74	89.2%	yes
5	94	54	174.1%	no
6	97	63	154.0%	no
7	70	85	82.4%	yes
8	76	90	84.4%	yes
9	54	53	101.9%	yes
10	99	56	176.8%	no
11	83	90	92.2%	yes
12	51	68	75.0%	yes
				75.0%

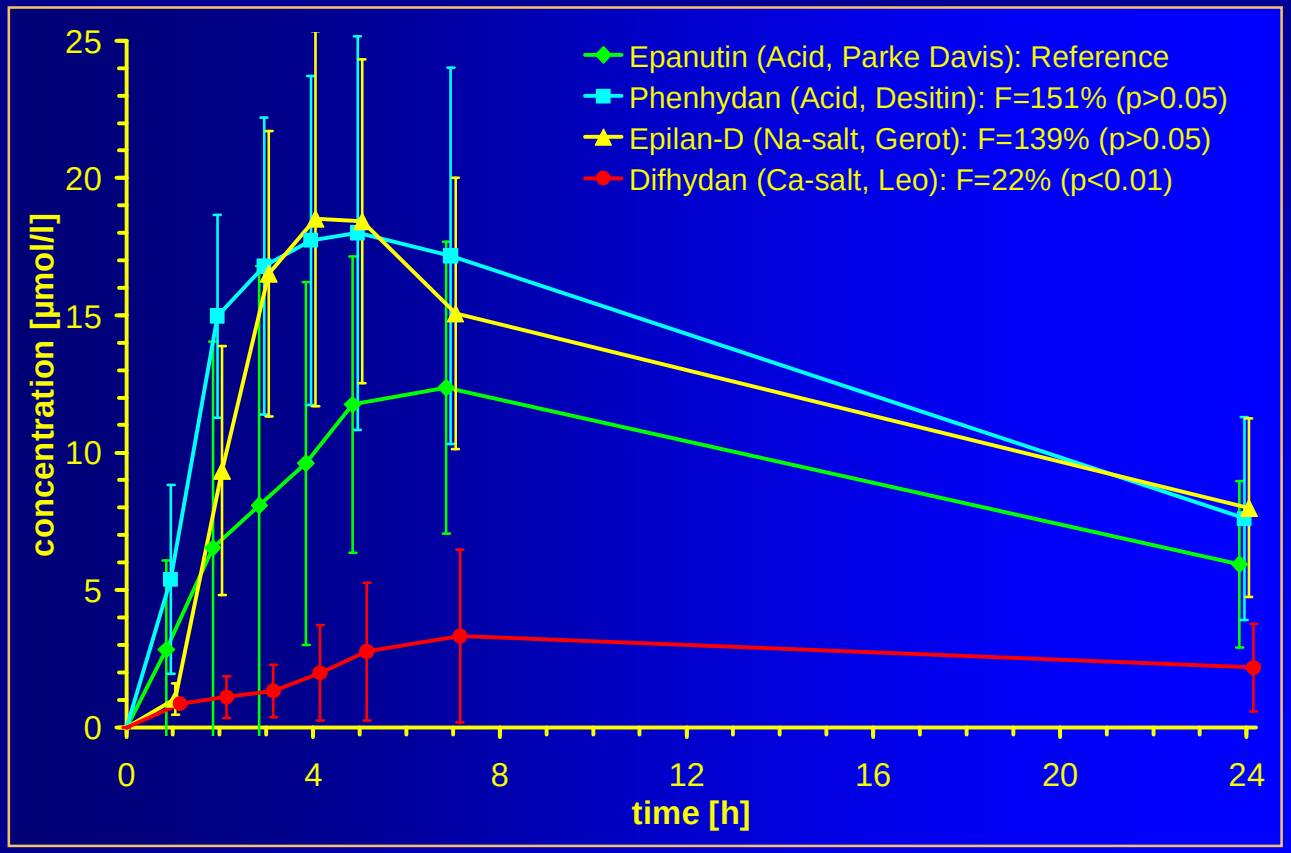
BE Cabana
Assessment of 75/75 Rule: FDA Viewpoint
J Pharm Sci 72, 98-99 (1983)
JD Haynes
FDA 75/75 Rule: A Response
J Pharm Sci 72, 99-100 (1983)

Mid 1980s I

- Early method
  - Testing for a significant difference (*t*-test) at α 0.05
    Problem:
    - High variability in differences
      $\rightarrow$ formulation will pass ($p \geq 0.05$)
    - Low variability in differences
      $\rightarrow$ formulation will fail ($p < 0.05$)
    - This is counterintuitive and the opposite of what we actually want!

	T	R	T–R
1	71	81	-10
2	61	65	-4
3	80	94	-14
4	66	74	-8
5	94	54	+40
6	97	63	+34
7	70	85	-15
8	76	90	-14
9	54	53	+1
10	99	56	+43
11	83	90	-7
12	51	68	-17
mean	75	73	+2
SD	16	15	23
CV%	21.4%	20.6%	940%
		t-table	2.2010
		t-calc	0.3687
			n.s.

Example



Nitsche V, Mascher H, and H Schütz
Comparative bioavailability of several phenytoin preparations marketed in Austria
Int J Clin Pharmacol Ther Toxicol 22(2), 104-107 (1984)

Mid 1980s II

- Later method
  - FDA's 80/20 rule
  - At least 80% power to be able to demonstrate a 20% difference (*t*-test) at α 0.05
    - Essentially the 75/75 rule in more statistical terms.
    - Power 71.5% < 80! (not BE)
    - In any study (even at 'true' T=R) with variability

      $$s\sqrt{2/n} > 6.44$$

      it is impossible to show BE!

	T	R	T–R
1	71	81	-10
2	61	65	-4
3	80	94	-14
4	66	74	-8
5	94	54	+40
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11	83	90	-7
12	51	68	-17
mean	75	73	+2
SD	16	15	23
		t-table	2.2010
		t-calc	0.3687
			n.s.
		power	71.59%

Late 1980s

- TOST (Two One-Sided Tests)
  - First formulation of the problem based on equivalence rather than a difference
    - Two One-Sided *t*-tests
    - Bioequivalent if
      $p(<80\%) + p(>120\%) \leq 0.05$
    - Equivalent to a 90% confidence interval within an acceptance range of 80% – 120%

	T	R	T–R
1	71	81	-10
2	61	65	-4
3	80	94	-14
4	66	74	-8
5	94	54	+40
6	97	63	+34
7	70	85	-15
8	76	90	-14
9	54	53	+1
10	99	56	+43
11	83	90	-7
12	51	68	-17
	p(<80%)		0.0069
	p(>120%)		0.0344
	p(total)		0.0414
		T/R	103.32%
	90% CI (lo)		88.35%
	90% CI (hi)		118.30%

DA Schuirmann
A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability
J Pharmacokin Biopharm 15, 657–680 (1987)

Human Guineapigs I

- BE studies as a surrogate for clinical efficacy / safety ('essential similarity')
  - We want to get unbiased estimates, *i.e.*, the point estimate from the study sample …

$$PE = \frac{\hat{X}_{Test}}{\hat{X}_{Reference}}$$

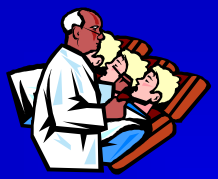
  - … should be representative for the population of patients.

$$F_{Pop} = \frac{\mu_{Test}}{\mu_{Reference}}$$

Human Guineapigs II

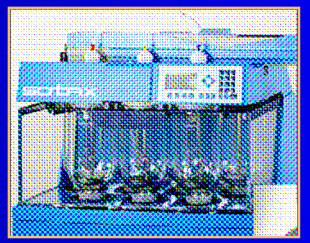
- BE studies as a special case of documented pharmaceutical quality
  - The *in vivo* release in the biostudy …

$$PE = \frac{\hat{X}_{Test}}{\hat{X}_{Reference}}$$



  - … should be representative for the *in vitro* performance.

$$f_2 = 50 \cdot \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\bar{R}(t) - \bar{T}(t) \right]^2}{n}}} \right]$$



Science → Regulations

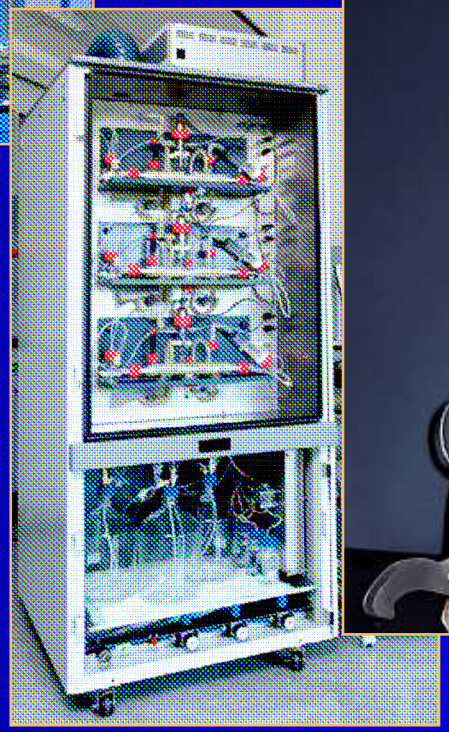
- We can't compare bioavailabilities in the entire population of patients
  - Scientific Reductionism (based on assumptions)
    - 'Similar' concentrations in healthy subjects will lead to 'similar' effects in patients.
    - Equal doses and inter-occasion clearances!

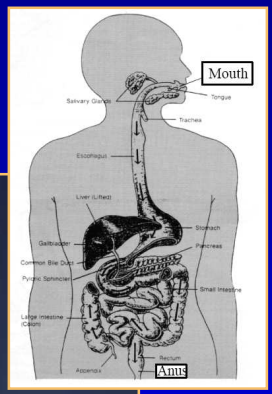
$$AUC_T = \frac{D_T \cdot F_T}{CL_T}, AUC_R = \frac{D_R \cdot F_R}{CL_R}$$

$$[D_T \cong D_R, CL_T \cong CL_R]$$

$$F_{rel}(BA) = \frac{F_T}{F_R} \cong \frac{AUC_T}{AUC_R}$$

Models *vs.* Reality





Another reminder

Rose
is a rose
is a rose
is a rose.

Gertrude Stein (1913)

Guidelines
are guidelines
are guidelines.

Henrike Potthast (ca. 2004)

In advanced engineering, you expected failure; you learned as much from failures as from successes – indeed if you never suffered a failure you probably weren't pushing the envelope ambitiously enough.

Stephen Baxter; Transcendent, Chapter 36 (2006)