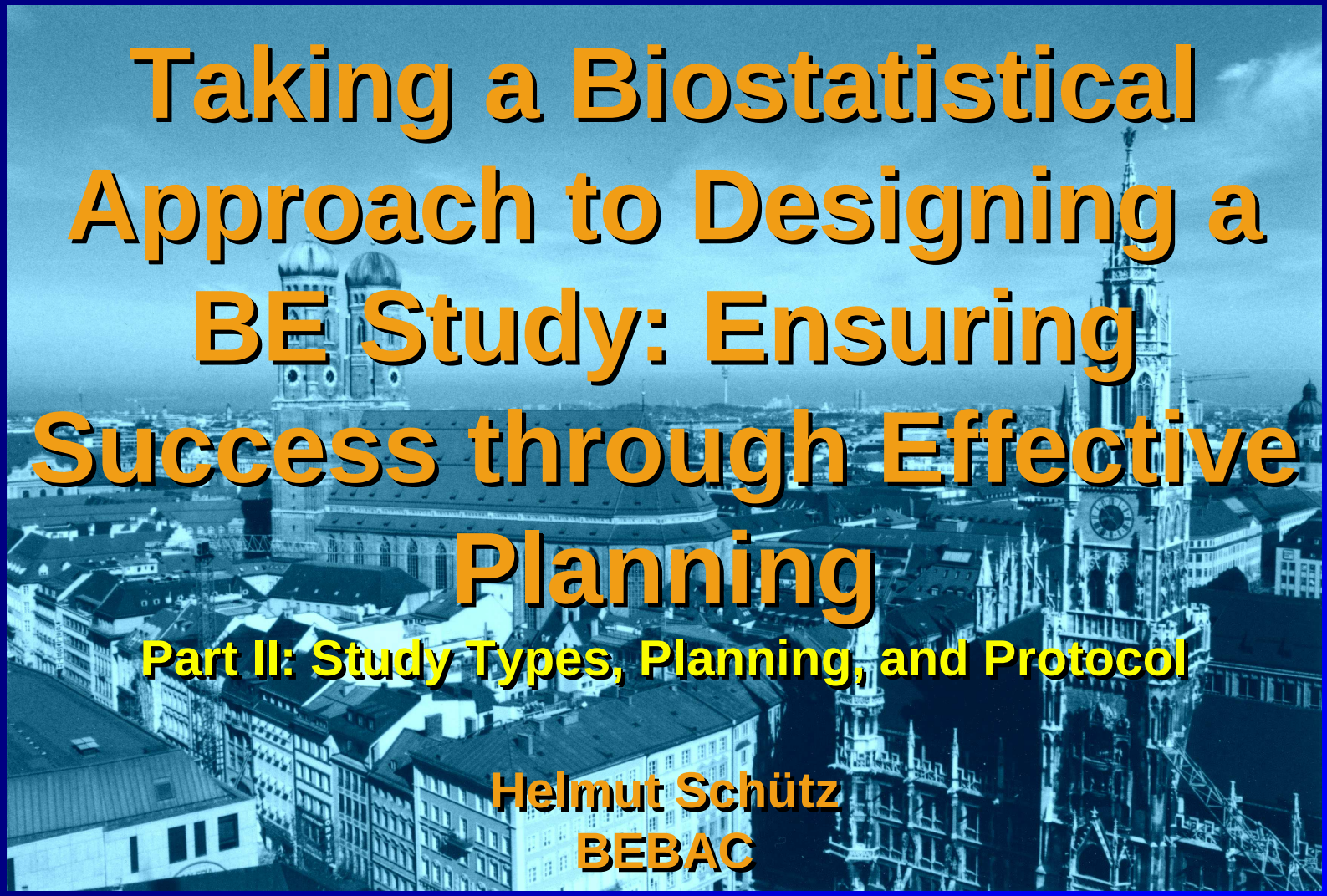


Taking a Biostatistical Approach to Designing a BE Study: Ensuring Success through Effective Planning

Part II: Study Types, Planning, and Protocol

Helmut Schütz
BEBAC

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)

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

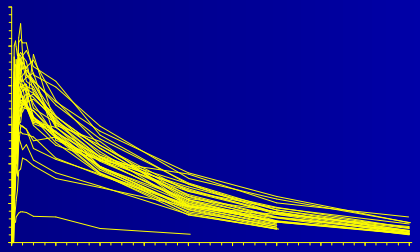
- Types of studies (cont'd)
  - Food effect
  - PK interaction
- Design Issues
  - Dose regimen
  - Fasted / fed state
  - Type of standard meals
- Bioanalytics (*not* GLP!)
  - Parent drug / metabolite(s) / enantiomers / pro-drugs
  - Validation / routine application

Overview

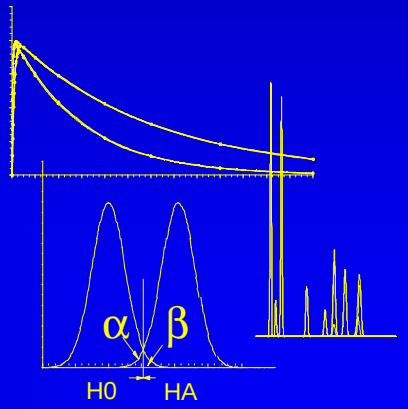
- Ethics (GCP!)
  - Dose levels / number of administered doses
  - Number / volume of blood samples
  - Drug and/or adverse effects
- Clinical performance (GCP!)
  - CRO selection
  - Responsibilities of sponsor / investigator
  - Audits / monitoring

Assumptions

World *'Truth'*

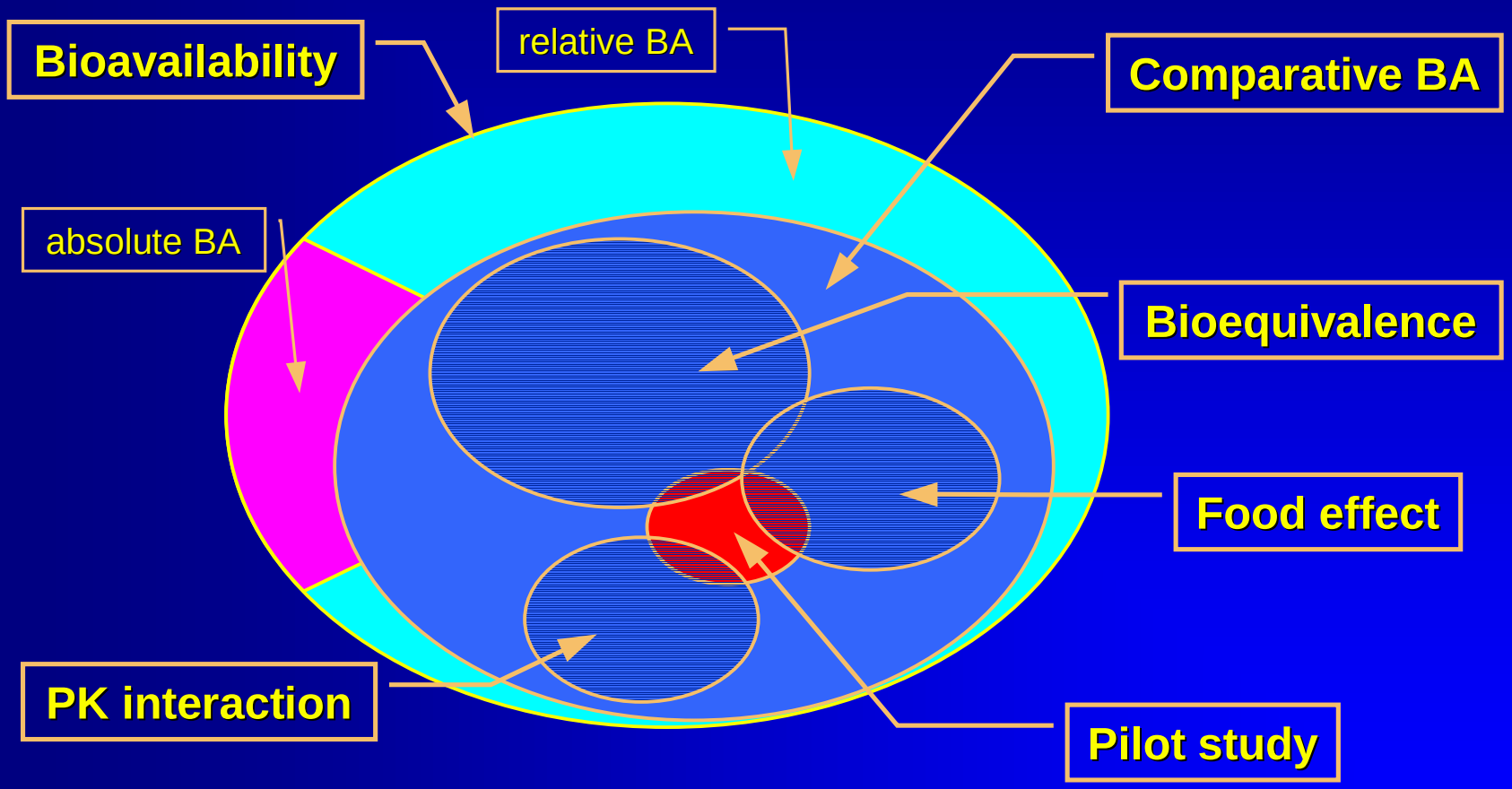


Model *'Data'*

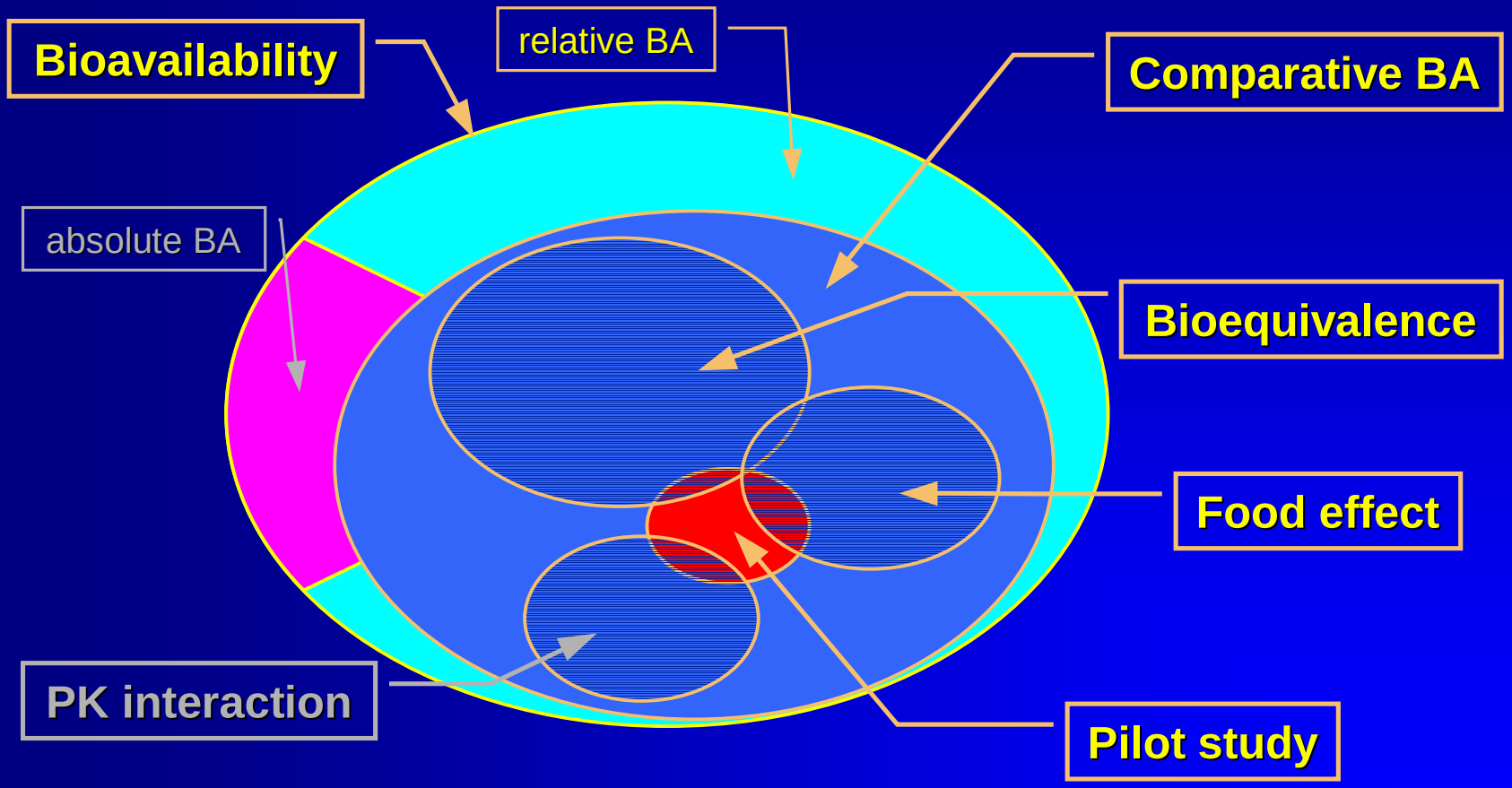


Theory *'Reality'*

Terminology



Terminology



Definition

- EMEA NfG on BA/BE (2001)

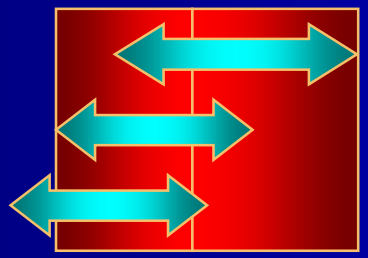
  ‘A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products.’

  - 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%]

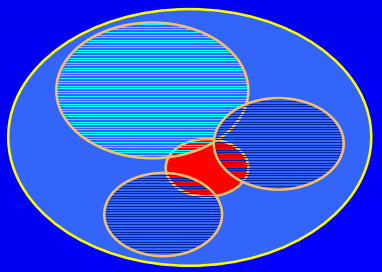
#2: BE [80%–110%]

#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!

α- *vs.* β-Error

- All formal decisions are subjected to two types of error:
  - Error Type I (α-Error, Risk Type I)
  - Error Type II (β-Error, Risk Type II)

  Example from our justice system:

Verdict	Defendant innocent	Defendant guilty
Presumption of innocence not accepted (guilty)	**Error Type I**	**Correct**
Presumption of innocence accepted (not guilty)	**Correct**	**Error Type II**

α- *vs.* β-Error

- … in more statistical terms:

Decision	Null Hypothesis True	Null Hypothesis False
Null Hypothesis rejected	**Error Type I**	**Correct**
Failed to reject Null Hypothesis	**Correct**	**Error Type II**

- In BE-Testing the 'Null-Hypothesis' is that of bioinequivalence!

Decision	Null Hypothesis True	Null Hypothesis False
Null Hypothesis rejected	**Patient's Risk**	**Correct (BE)**
Failed to reject Null Hypothesis	**Correct (not BE)**	**Producer's Risk**

α- *vs.* β-Error

- α-Error: Patient's Risk to be treated with a bioinequivalent formulation
  - BA of the test compared to reference in a particular patient can be *either* below 80% *or* above 125%.
  - If we keep the risk of particular patients at 0.05 (5%), the risk of entire the population of patients (<80% *and* >125%) is 2×α (10%)
    That's where the 90% confidence interval comes from (CI = 1 – 2×α = 0.90)…
  - α is generally *set* to 0.05 (but may be smaller: NTDIs in Brazil, multiplicity, interim analyses).

α- *vs.* β-Error

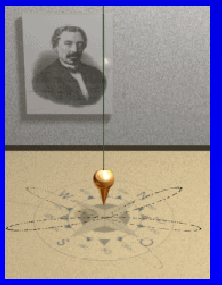
- β-Error: Producer's Risk to get no approval for a bioequivalent formulation
  - Generally *set* in study planning to ≤0.2, where power = 1 – β = ≥80%
  - No guidelines about power ('appropriate'), but
    - 70% only in exceptional cases
    - >90% *may* raise questions from the Ethics Committee (suspection of 'forced bioequivalence')
  - If power is set to 80 %

    One out of five studies will fail just by chance!

α 0.05	BE
not BE	β 0.20

History of BE

- Bioequivalence
  - Surrogate of clinical equivalence (1985+)
    - 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%

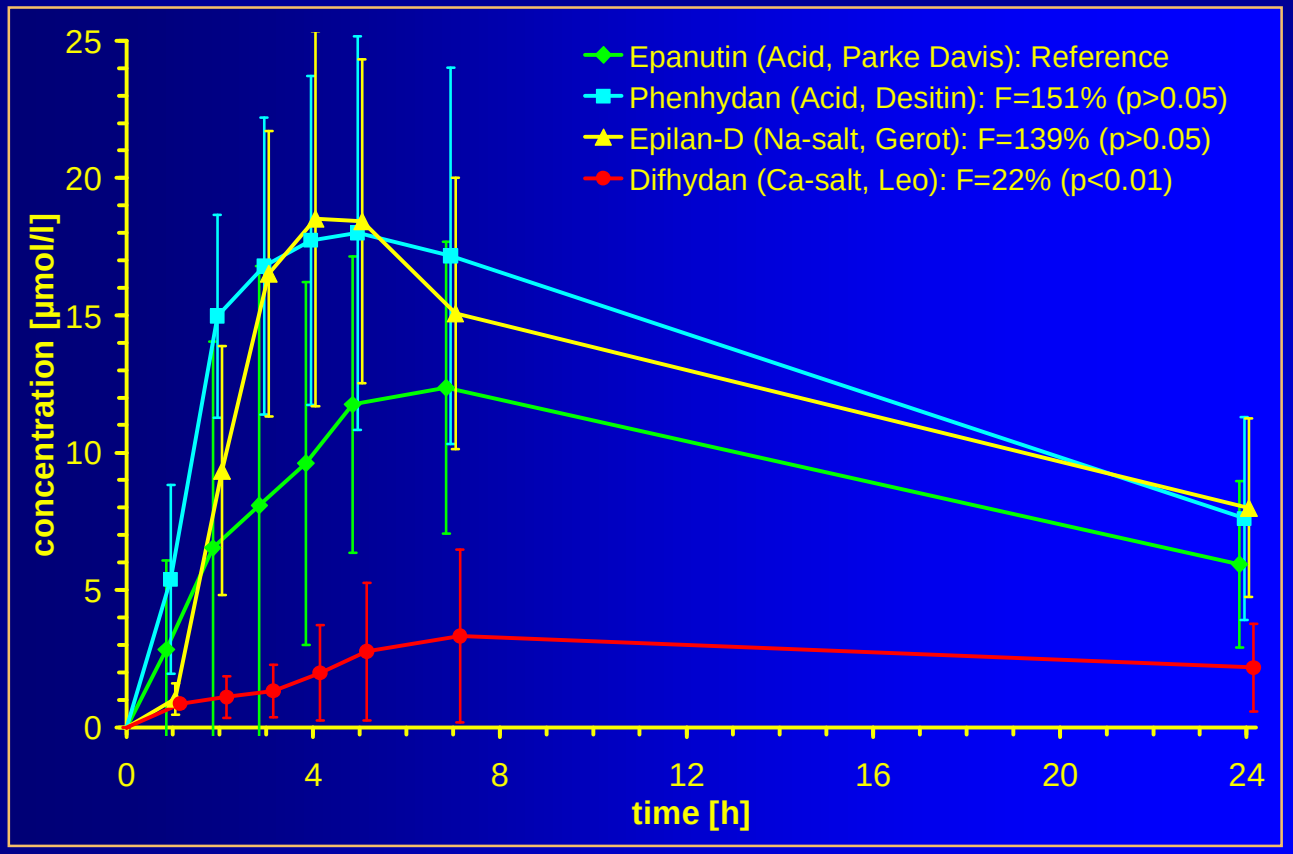
BE Cabana
Assessment of 75/75 Rule: FDA Viewpoint
J Pharm Sci 72, 98-99 (1983)
JD Haynes
FDA 75/75 Rule: A Response
J Pharm Sci 72, 99-100 (1983)

Mid 1980s

- 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 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)

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 …

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

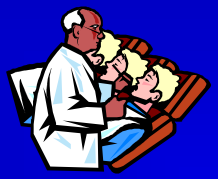
  - … should be representative for the population of patients.

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

Human Guineapigs II

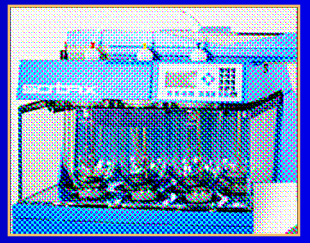
- BE studies as a special case of documented pharmaceutical quality
  - The *in vivo* release in the biostudy …

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



  - … 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

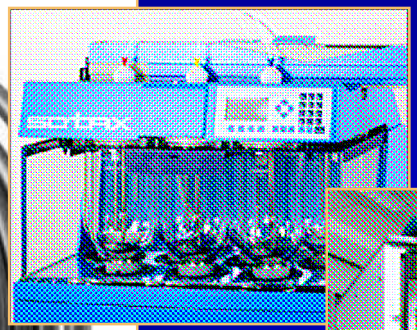
- We can't compare bioavailabilities in the entire population of patients
  - Scientific Reductionism (based on assumptions)
    - 'Similar' concentrations in healthy subjects will lead to 'similar' effects in patients.
    - Equal doses and inter-occasion clearances!

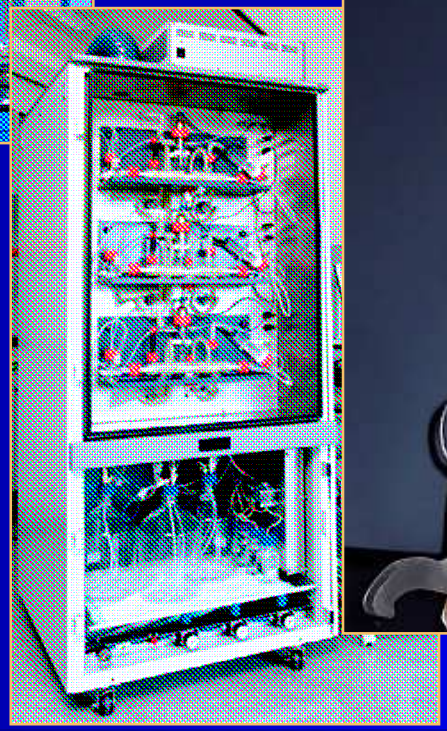
$$AUC_T = \frac{D_T \cdot F_T}{CL_T}, AUC_R = \frac{D_R \cdot F_R}{CL_R}$$

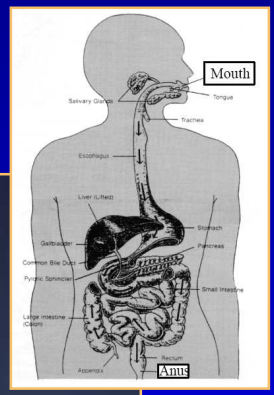
$$[D_T \cong D_R, CL_T \cong CL_R]$$

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

Models *vs.* Reality





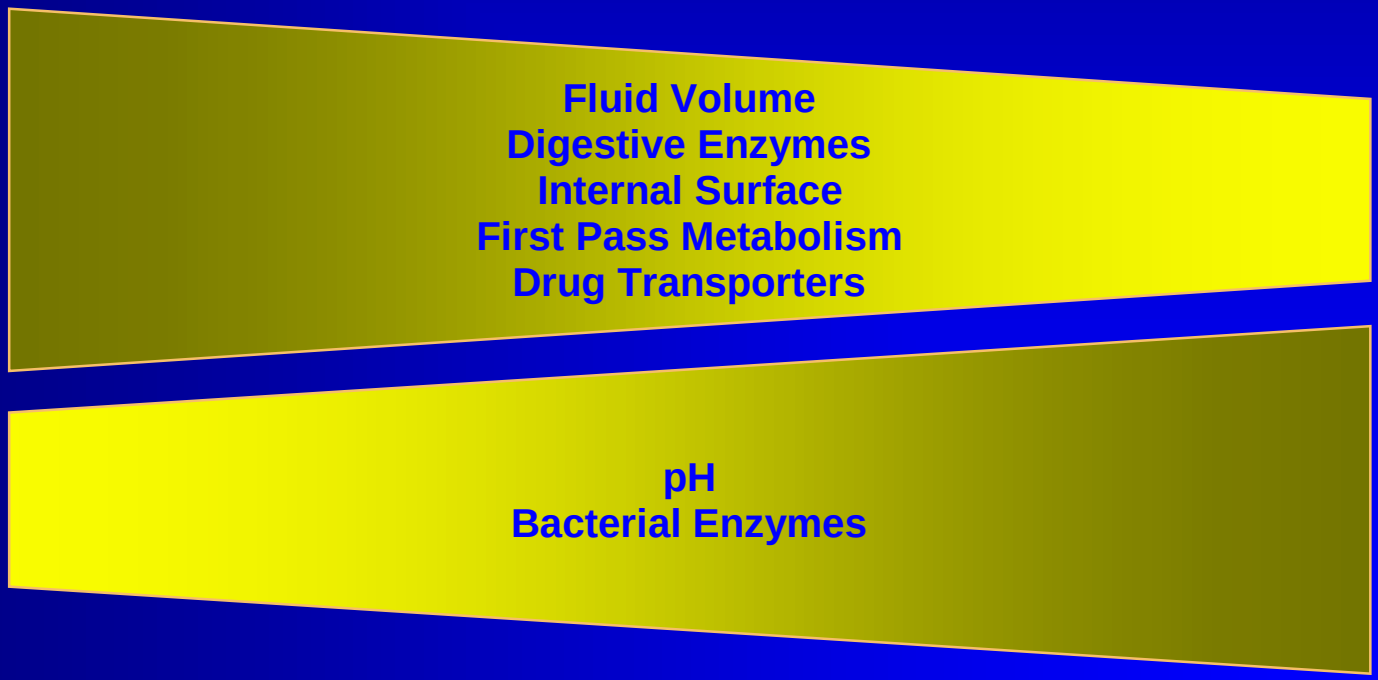


Protocol Development

- Study Design
  - Based on
    - Human pharmacokinetic data (except FIM studies)
    - Parallel groups / cross-over / replicate design
    - Study type (exploratory / confirmatory)
    - Study target (metric, variability)
    - Pharmacology of the drug (both effects *and* AE profile)
    - Single dose / multiple dose
    - Study Population (healthy volunteers, patients, special population, geno-/phenotyped subjects, …)
    - Method of evaluation ('classical PK', Population PK, NCA, comparative BA / BE)
    - Sample size (based on all of the above *and* logistics)

Protocol Development

- Study Design based on PK
  - Differences in Absorption Conditions along the Gut



Protocol Development

- Study Design based on PK (cont'd)
  - Processes affecting BA/BE of orally administered drugs/formulations
    - (Liberation from drug product)
    - (Dissolution of drug)
    - Gastrointestinal degradation
    - Changes in hepatic blood flow (food, posture,…)
    - Binding to gut contents
    - Absorption by transporters
    - Secretion by transporters
    - Intestinal first past metabolism (presystemic)
    - Hepatic first past metabolism

Protocol Development

- Study Design based on PK (cont'd)
  - Reasons for 'true' differences in bioavailability
    - Different pharmaceutical properties *in vivo* resulting in
      - different drug concentrations at
      - different sites of release

      +
    - different overall amounts released by respective formulations

      and / or
    - different excipients influencing absorption

      and / or
    - absorption characteristics of the drug vary along the GUT

Protocol Development

- Study Design based on PK (cont'd)
  - Difficulties in demonstrating bioequivalence
    - Intraindividual variability of the drug itself (HVD – Highly Variable Drug: CV_{intra} of a solution ≥30%)
    - Intraindividual variability of the formulation(s) (test and/or reference, HVDP – Highly Variable Drug Product: CV_{intra} of formulation >30%)
    - Variability caused in the clinical performance of the study
    - Variability caused by sampling technique, sample preparation, storage, shipment,…
    - Analytical variability

M Gaffney
Variance Components in Comparative Bioavailability
J Pharm Sci 1/4, 315-317 (1992)

Protocol Development

- Study Design based on PK (cont'd)
  - Points to consider (cont'd)
    - Frequent sampling in the area of C_{max}
    - Lag-time expected?
    - Spead samples evenly between t=0 and t_{max}
    - Sample according to a geometric progression after C_{max}-area:

$$t_i = t_{i-1} \times (t_n/t_1)^{1/(n-1)}$$

i index of the respective time points ($2, 3, \ldots, n$)
n number of time points
t_i calculated time point at i
t_{i-1} previous time point
t_1 first time point
t_n last time point

Sampling schedule adjusted according to clinical practicability!

Protocol Development

- Study Design based on PK (cont'd)
  - Points to consider (cont'd)
    - Simulations help in setting the working range of the analytical method. Ideal:
      - LLOQ ~ C_{last} and ≤5% of C_{max}
      - ULOQ ~ C_{max} (of any subject – not the mean!)
      - AUC_t/AUC_∞ ≥80% (dependent on the design)
    - Cooling prior to centrifugation (Stability testing mandatory part of bioanalytical method validation)
    - Prevent sample mix-up at plasma separation (barcode system, four-eye-principle, …)
    - Adsorption to surfaces (PP, glass, stoppers)
    - Stabilize instable compounds

Protocol Development

- Study Design based on PK (cont'd)
  - Design not only based on PK/statistical necessities but also dictated by Guidelines…
    - Points to consider
      - Selection of reference formulation
      - Sample size (previous studies, pilot studies, literature,…)
      - Average BE (cross-over, parallel), Sequential design, Reference Scaled Average BE (RSABE)
      - Assumptions ($CV_{WT} = CV_{WR}$, T/R-ratio, constant Clearances in cross-over, Power, drop-out rate,…)
      - For new formulations include additional informations, *e.g.*,
        - urinary excretion
        - pharmacodynamic parameters
        - genotypes

Protocol Development

- Study Design based on PK (cont'd)
  - Points to consider (cont'd)
    - Light sensitive compound – check first!
      Example nifedipine (clinical phase)
      - Glas vials (vacutainers) shield almost perfectly against UV-radiation.
      - The entry-depth of light into whole blood is in the range of a few millimeters only.
      - Similar absorption wavelength as compared to albumin; the compound is well protected after centrifugation in plasma / plastic tubes.
      - Working in the clinical phase under light protection (*e.g.*, sodium vapour lamps) may lead to difficulties in venipuncture, sampling errors, etc.

Protocol Development

- Study Design based on PK (cont'd)
  - Points to consider (cont'd)
    - Light sensitive compound – check first!
      Example nifedipine (analytical phase)
      - Stock solutions and sample extracts are much more susceptible to light-degradation than plasma samples.
      - Validate all sample preparation steps under varying light conditions (daylight through – closed – windows, fluorescent light, dimmed light, sodium vapour light) and different light protection measures (glass vials, brown glass vials, PP vials, etc).
      - Don't forget to close the lid of the autosampler…

Protocol Development

- Study Design based on PK (cont'd)
  - Points to consider (cont'd)
    - Inhouse storage (capacity, back-up)
    - Sample shipment
      - Enough dry ice
      - Electronic data logger
      - Accepted carrier
      - Expect delays at US-customs anyhow (samples of biological origin!)
      - Personell available at the analytical site at date of delivery (holidays?)

Ethical Considerations

- Cross-over design not always feasible
  - Long half live drugs
  - Patients: change in disease state
  - Safety considerations
- Paediatrics
  - Bioequivalence studies in children not acceptable!
  - PK studies for NDAs: Population PK with sparse sampling preferred

Ethical Considerations

- Healthy subjects *vs.* patients
  - Healthy subjects generally preferred, except if main effect and/or adverse reactions unacceptable (anti-psychotics, chemotherapeutic agents,…)
  - Hormones in postmenopausal women (driven by analytical requirements)

Ethical Considerations

- Polymorphism
  - Phenotyping
    - In all parallel design studies (fast metabolizers only)
    - Slow metabolizers not a problem in cross-over studies, but sampling period may be too short to show $AUC_t/AUC_\infty \geq 80\%$
    - Safety: in steady-state studies (fast metabolizers only; example: paroxetine)
  - Genotyping?
    - Pro: No additional administration of a 'model drug'.
    - Cons: Very restrictive in some countries (informed consent, data protection,…).

Selecting Subjects

- EU GL on BE (Section 4.1.3)

  The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical.

Selecting Subjects

- EU GL on BE (Section 4.1.3 cont'd)

  Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered.' (acc. to ICH, but BfArM…)
  […] preferably […] non-smokers […].

Is the API meta-bolized by cytochrome P450 1A1?

EMA
Gender Considerations in the Conduct of Clinical Trials
EMEA/CHMP/3916/2005 – ICH, London (Jan 2005)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500059887.pdf

Selecting Subjects

- US-FDA BE (Section III.A.5.)
  - 18 years of age or older and capable of giving informed consent.
  - Individuals representative of the general population, taking into account
    - age,
    - sex, and
    - race.
  - If the drug product is intended for use in both sexes, the sponsor [should] attempt to include similar proportions of males and females in the study.

'Caucasian' is an outdated racistic concept and has nothing to do with (pharmaco)genetics…

Selecting Subjects

- US-FDA BE (Section III.A.5.)
  - If the drug product is to be used predominantly in the elderly, we also recommend that the sponsor attempt to include as many subjects of 60 years of age or older as possible.
    We recommend that the total number of subjects in the study provide adequate power for BE demonstration, but it is not expected that there will be sufficient power to draw conclusions for each sub-group.

Selecting Subjects

Criterion	Potential Problem	Solution
Healthy	Variability by disease, age	Required (with exceptions)
Males only	Menstrual cycle, oral contraceptives, pregnancy, lactation period, family	Females required according to some guidelines…
Caucasians	None expected	Not required in cross-over!
Body weight	None (except extremes)	No narrow BMI limits in cross-over
Nonsmokers	Effect on metabolism (P450 1A1 only?)	Preferred; <10 cig./day (EU)

Study Performance

- Posture
  - Posture can influence the rate-limiting step in absorption (both whether it is gastric emptying or dissolution and, if it is gastric emptying, its rate), with respective consequences for the PK profile. Posture should be defined and maintained precisely, especially in the case of drugs which are absorbed rapidly and are subject to presystemic elimination. At least throughout the phase of absorption, any change of posture should be avoided.

C Queckenberg and U Fuhr
Influence of posture on pharmacokinetics
Eur J Clin Pharmacol 2008 (DOI 10.1007/s00228-008-0579-2)
http://www.springerlink.com/content/06r0nr88m54w6515/fulltext.pdf

Study Performance

Criterion	Potential Problem	Solution
Regular life	Parties, shift work, other studies	No parties? No shift workers? Try to prevent 'volunteer tourism'
No concomitant drugs	PK interactions, safety	Required (with exceptions)
No special diet	No meat (Vegetarians) No pork (Muslims) No beef (Hindu, BSE)	Chicken (GIT transit significantly longer in vegetarians)
No sports	Risk of injuries, effect on metabolism?	Unclear

Study Performance

- Standardization (Nutrition, Fluid intake)
  - All studies
    - Fasting period 10 hours pre-dose
    - Use pre-prepared meals (in-house or catering)
    - Standardize fluid intake to some extent
      - low calcium non-carbonated water
      - ambient temperature
      - no fluids 1 hour pre-dose until 1 hour post-dose
      - consider allowing some coffee/tea (headache upon caffeine withdrawal in up to 50% of the population – some subjects developing migraine). Cave: against guidelines!
    - No fruit or fruit juices (grapefruit!), limit some vegetables (cabage family)

Study Performance

- Standardization (Nutrition, Fluid intake)
  - Fluids in all studies of orally applied formulations

150 ml water	EU (2001), Australia, Canada
100 ml – 200 ml water	Japan (normally 150 ml)
150 ml – 250 ml water	WHO
≥150 ml fluid	Malaysia, Thailand, ASEAN States, EU (2010)
200 ml liquid	Brazil (generally water)
e.g. 200 ml fluid	South Africa
8 oz (237 ml) water	USA
240 ml (8 fl oz) water	PAHO States
200 ml – 250 ml water	Argentina
250 ml water	Mexico
sufficient fluid	Saudi Arabia
standardized	India, New Zealand

Study Performance

- Standardization (Nutrition, Fluid intake)
  - Fasting studies
    - No food until four hours post-dose
    - Consider to individualized food (males/females) – but any subject should consume the same amount in all treatment periods

Study Performance

- Standardization (Nutrition, Fluid intake)
  - Fed studies
    - Test meal
      - Well defined (described in protocol)
      - Light meal
        - EU according to the SmPC of the reference.
        - Japan a low fat diet of 700 kcal or less containing not more than 20% by energy of the lipid.
      - High-fat, high-calory meal
        - US-FDA ~800–1000 cal (150 cal protein, 250 cal carbohydrate, 500–600 cal fat). Test meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Other meals for NDAs (but one must be the test meal).

Actually:
Protein 128 kcal (12%)
$(CH_2O)_n$ 308 kcal (29%)
Fat 631 kcal (59%)
Total 1067 kcal

Study Performance

- Standardization (Nutrition, Fluid intake)
  - Fed studies
    - Test meal
      - High-fat, high-calory meal (cont'd)
        - US-FDA: Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and *viscosity*. If the caloric breakdown of the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference.
        - Canada: Like US, but no substitutions!
        - Japan: A high fat diet of 900 kcal or more containing 35% lipid content.
        - EU: 800–1000 kcal: 150, 250, 500–600 kcal (prot., CH_2O, fat)

Study Performance

- Standardization (Nutrition, Fluid intake)
  - Fed studies
    - Test meal
      - High-fat, high-calory meal (cont'd)
        - India A high-fat breakfast before dosing. Such a breakfast must be designed to provide 950 to 1000 kcals. At least 50% of these calories must come from fat, 15 – 20% from proteins and the rest from carbohydrates. The vast ethnic and cultural variations of the Indian subcontinent preclude the recommendation of any single standard high fat breakfast. Protocol should specify the suitable and appropriate diet.
        - Others http://forum.bebac.at/forum_entry.php?id=20

Study Performance

- Standardization (Nutrition, Fluid intake)
  - Fed state mandatory (EU, 2010)
    - If administration in fed state mandatory according to the SmPC of the reference
      - If composition given, according to recommendations of the reference's SmPC.
      - If no composition given:
        - High-fat, high-calorie meal (800–1000 kcal with about 50% of calories derived from fat).
        - Composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

Study Performance

- Standardization (Confinement)
  - Hospitalize subjects in the evening before administration, if possible
  - Standardize smoking
  - Limit gambling & exciting movies – especially during the early parts of the treatments
  - Posture (try to find literature on your drug) – if no data available, similar between periods
  - Consider assessment of AEs even in open studies in a blinded manner (or at least by the same investigator)

Study Performance

Subject	Adverse Event	Duration
01	Impairment of short memory	271
02	Obstipation	241
02	Impairment of short memory	246
02	Reduced capability of concentration	248
02	Dry mucosa of mouth	241
02	Fatigue	271
03	Obstipation	252
03	Impairment of short memory	261
03	Dry mucosa of mouth	241
03	Fatigue	95
04	Euphoria	58
04	Impairment of short memory	73
05	Nausea	249
05	Diarrhoea	104
05	Loss of appetite	262
05	Vertigo	125
05	Reduced capability of concentration	246
05	Impairment of short memory	245
05	Dry mucosa of mouth	224
05	Dry mucosa of nose	224

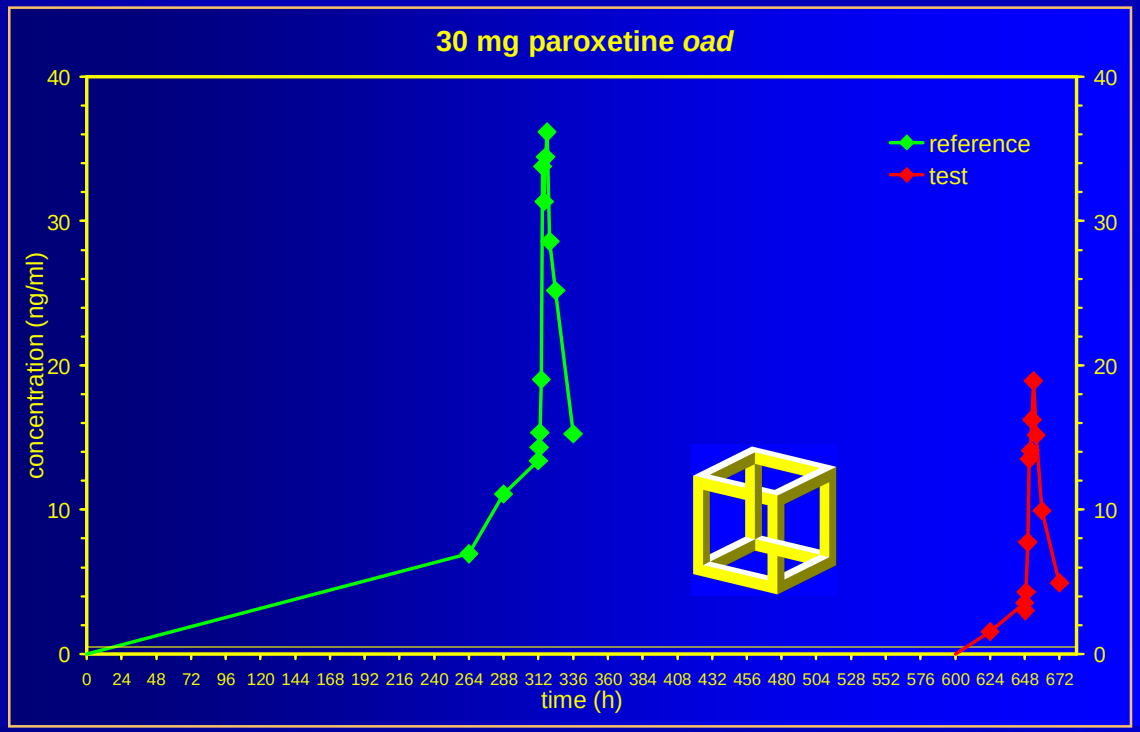
Subject	Adverse Event	Duration
06	Dry mucosa of mouth	52
06	Increased appetite	57
06	Fatigue	103
06	Reduced capability of concentration	75
07	Nausea	266
07	Diarrhoea	101
07	Vertigo	122
07	Impairment of short memory	152
07	Reduced capability of concentration	176
07	Loss of appetite	168
07	Dry mucosa of mouth	172
07	Dry mucosa of nose	172
08	Disturbance of concentration	256
08	Impairment of short memory	232
09	Increased perspiration	123
09	Fatigue	83
09	Impairment of short memory	75

Multiple dose study of CNS-active drug, two groups of nine subjects each (total 18)

What is – or might be – wrong here?

Study Performance

- Standardization (Confinement)
  - In-house administration, even for outpatient multiple dose studies!



Pitfalls

- Unrealistic expections of the sponsor about the properties of a new formulation
- Inappropriate sample size
- Too low sample density in the area of C_{max}
- Too short sampling period
- Insufficient number of blood samples (λ_z = ?)
- Poor standardization
- Non-compliance of volunteers and/or study personell (!)

Conclusions

Guidelines are guidelines are guidelines

- Knowledge of the PK of the drug is essential
- Collect as many information on the drug / formulation prior to designing the study
- Standard approaches sufficient in most cases
- Try to minimize variability
- Select the highest feasible sample size

Conclusions

- Failure to demonstrate BE may be caused by true differences (β = 1 – power); do not ignore existing data!
- Don't repeat a failed study without reformulation (to be submitted according to BE-GL!)
- Go for a scientific advice with the respective regulatory body whenever in doubt about a design issue (don't read tea leaves)

Guidelines are guidelines are guidelines (neither laws – nor carved in stone)

Thank You!

Part II: Study Types, Planning, and Protocol

Open Questions?

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