

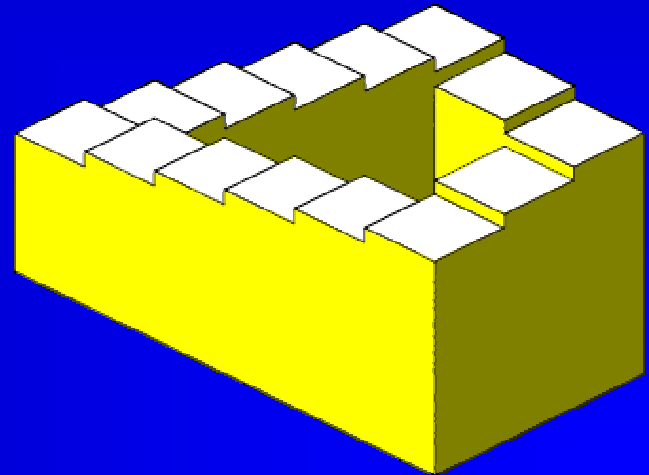
# Clinical part of BA/BE studies

Helmut Schütz  
BEBAC

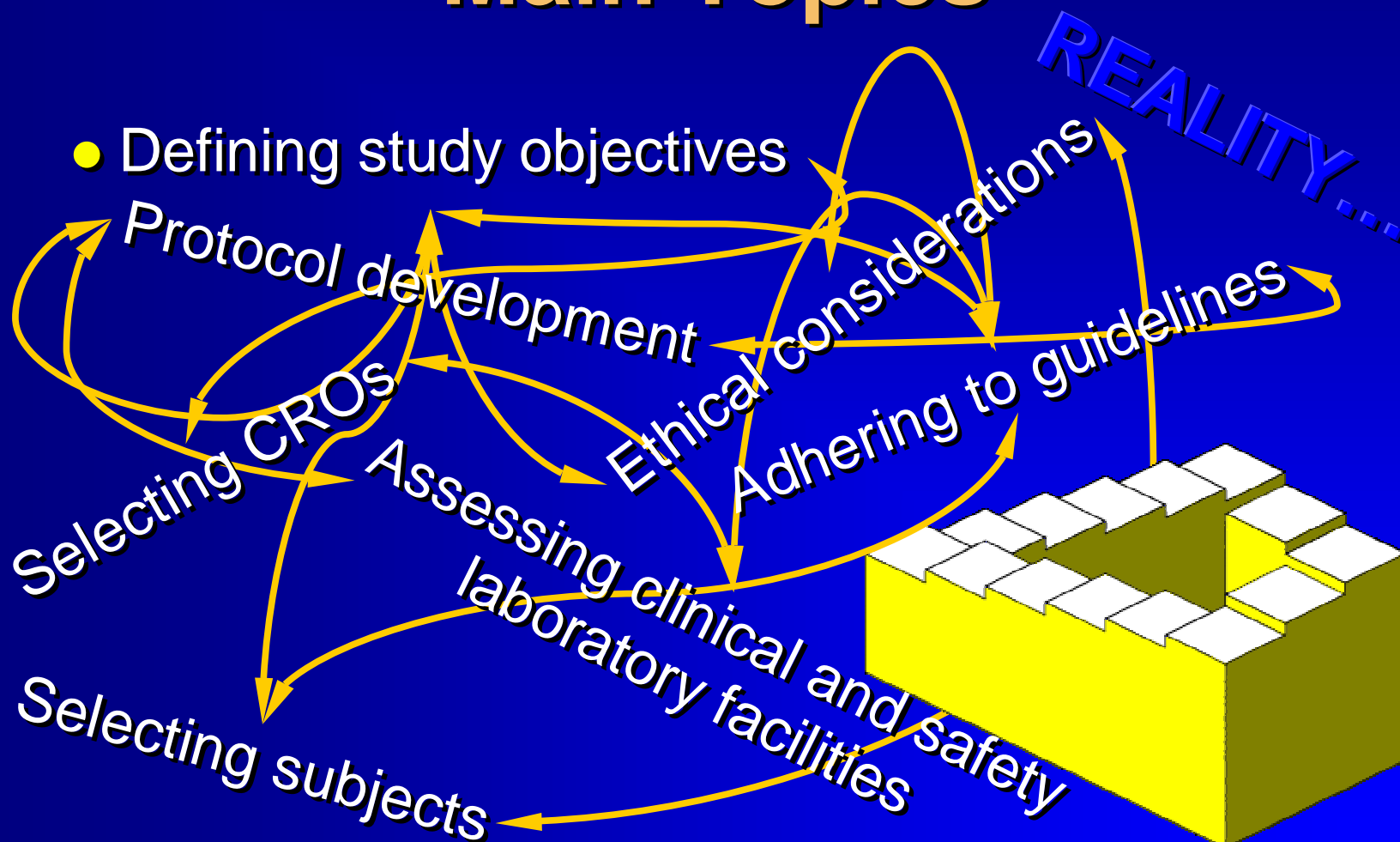
# Main Topics

DREAM...

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



# Main Topics



# Defining Study Objectives

- Types of Phase I Studies

- First in Man
- Pharmacokinetic (LADME)
- Proof of Concept
- Pilot Studies
- Bioavailability
- (Studies to support Marketing)
- (Dose Proportionality)
- Bioequivalence
- Food Studies / PK Interaction

exploratory

confirmatory

# Defining Study Objectives

- An Excursion into ICH GCP E6 (Section 6.4 Trial Design)
  - The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:
    - Primary endpoints (and secondary endpoints, if any).
    - Description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) [...].
    - Measures taken to minimize/avoid bias, including:
      - Randomization.
      - Blinding.

# Defining Study Objectives

- An Excursion into ICH GCP E6 (6.4 cont'd)
  - Trial treatment(s) and the dosage and dosage regimen of the investigational product(s).
  - Description of the dosage form, packaging, and labelling of the investigational product(s).
  - Expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
  - Description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial.

# Defining Study Objectives

- An Excursion into ICH GCP E6 (6.4 cont'd)
  - Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
  - Maintenance of trial treatment randomization codes and procedures for breaking codes.
  - The identification of any data to be recorded directly on the CRFs (*i.e.* no prior written or electronic record of data), and to be considered to be source data.

# Selection of CROs

- General Suitability of the CRO
  - Pre-study facility audit mandatory (ICH-GCP)
  - How many years in Business
  - Scientific / Medical / Statistical Expertise
  - Study Personell (Experience, Continuing Education, Fluctuation)
  - Number of beds, equipment,...
  - Safety Laboratory (inhouse / external)
  - Location (Accessability, Duration of getting IEC/IRB and Regulatory Approval, Catchment Area, Sample Shipment)



# Selection of CROs

- Adherence to GxP (GCP, GMP)
  - QAU System in Operation
  - Successful Audits?
  - Regulatory Inspections?
  - Percentage of 'failed' studies?
  - Current Certificates (e.g., ISO9001)
  - GMP compliant (packaging of IMPs)
- Volunteer Data Base
  - Electronic / paper-based
  - Large, up-to-date, no nominal members

# Selection of CROs

- Volunteer Data Base (cont'd)
  - Measures to prevent 'volunteer tourism' in place
  - Special Populations (e.g., post-menopausal women, aged subjects,...)
  - Pheno-/genotyped subjects
- Scientific / Medical / Statistical Expertise
  - Set-up of Protocol
  - Evaluation of Study
  - Handling of subsequent questions (deficiency letters, addenda to reports)

# Selection of CROs

- Timelines

- Should be set *realistically*
- Should be agreed upon *and adhered to (!)*
- Timelines

- Financial Issues

- Anticipate the unexpected (e.g., repeated subjects, additional bioanalytics or biostatistical evaluations, publications).
- Investing in quality is often worth the money!
- *The bigger is not essentially the better!*

# Selection of CROs

- Standardization of the Conduct of the Study
  - Adherence to SOPs / Working Instructions
  - Working QAU-System
  - Handling of Deviations to Protocol/SOPs
  - Sufficient space in the Ward (Catchment Area, Bedrooms, Recreation Rooms)
  - Kitchen Facilities / Catering
  - Technical Equipment (State-of-the-Art, Maintenance)

# Evaluation of CROs

- What are Inspectors looking for? (Example EMEA Inspectors Group: Investigator Site, Phase I Units)
  - Ethics and Regulatory Approval
    - Independence of the Ethics Committee
    - What documents does the Committee review
      - Approval of a generic screening consent forms
    - Approval of advertising
    - Documentation of approvals
    - Process for submission for Ethics Committee approvals
    - Updating and maintenance of ethics committee documentation
    - ICH GCP compliance statement of the Ethics Committee
    - List of members of the Ethics Committee

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Ethics and Regulatory Approval (cont'd)
    - Process for for submission regulatory approval I, updating and maintenance of regulatory documentation
    - Annual reporting to the Ethics Committee
  - Quality Assurance and SOPs
    - Written procedures for every aspect of the study process (SOPs)
    - Organisation of the QA group
    - Training on SOPs, GCP and also specific protocols
    - Audits on vendors and suppliers (mandatory according to ICH)

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Investigator Master File
    - Source documents (patient's charts, X-ray...)
    - Storage of medical records, Informed Consent Forms, CRFs
    - Long-term archive arrangements
    - Documentation of meetings
    - Delegation log in place and signed
    - Use of Direct Electronic Data Capture methods
  - Personell
    - Relationship of the Investigator with the Sponsor company
    - Organisation charts (facility management and scientific organisation charts)

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)

- Personell (cont'd)

- Documentation of delegation of responsibilities by the principal investigator
    - Qualifications of the Investigators
    - Adequate staff resources (qualification, responsibilities, experience, availability, training programmes, training records, CV.
    - Basic life support and advanced life support training
    - Qualification of Bank/Agency staff (?)
    - Management of Agency/Bank staff (?)

- Facilities

- Emergency Procedures and Equipment
      - Availability and maintenance of emergency medicines and equipment



# Evaluation of CROs

## ● What are Inspectors looking for? (cont'd)

### ■ Facilities (cont'd)

#### ■ Emergency Procedures and Equipment (cont'd)

- Emergency contact numbers provided to the volunteers
- Procedures in case of an emergency
- Agreement with the local hospital(s) for any services provided
- Fire evacuation procedures

#### ■ General Facilities

- Security of the facility with respect to unauthorised or limited access.
- Back-up power supply
- Storage of samples  
Monitoring of the fridges and freezers
- Maintenance, service and calibration of instruments/equipment
- Facilities for archiving, laboratory and pharmacy

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)

- Facilities (cont'd)

- Volunteer Care

- Procedures for testing for use of illegal drugs (drugs of abuse)
      - Measures in place to ensure compliance of the volunteers with the protocol.
      - Monitoring of subjects
      - Facilities for meals. Documentation of meals.
      - Leisure facilities for lengthy stays/overnight stays
      - Identification of subjects during their stay

- Sampling

- Processing of samples within the unit prior to shipment to the laboratory.

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)

- Sampling (cont'd)

- Facilities equipped and resourced to handle the capacity of samples.
- Procedures for collection of urine samples.
- Procedures for sample management e.g. person in charge of this tasks, collection, processing, consideration for missed and late samples, aliquoting, labelling, storage and shipment.
- Clocks – easily visible and synchronised.

- Investigational Medicinal Products

- Authorisation/Licence(s)
- Blinding, if applicable
- Storage

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Investigational Medicinal Products (cont'd)
    - Packaging and labeling
    - Instructions for handling of IMP(s) and trial related materials (if not included in protocol or investigator's brochure).
    - IMP administration

FORM 003

**DRUG USAGE RECORD**

STUDY #...184189... DRUG. XXXXXXXXXXXX

TEST FORM. "A" / TEST FORM. "B" / REFERENCE FORMULATION AD 15.4.01

CONTAINER...80774E..... INITIAL QUANTITY...50.....

DATE RECEIVED...APR 15, 2001

DATE	QUANTITY USED*	QUANTITY LEFT	COMMENTS	SIGNATURE
15.4.01	12	38		AD
22.4.01	12	26		AD
		22.4.01		

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Recruitment and Consent
    - Recruitment strategies
    - Volunteer database
    - Collection and verification of volunteer histories
    - Contact with the subject's primary physician/family doctor
    - Procedures to prevent 'over-volunteering'
    - Routine screening procedure
    - Subject records
    - Procedures taken to verify the identity of the volunteers
    - Procedures for payment

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)

- Recruitment and Consent (cont'd)

- Procedures for taking consent:

- Signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC.
- The information sheet actually used and approved by the IEC, in order to determine whether it includes all the elements required by GCP and any current regulations.
- The centre practice for giving a copy of the informed consent to the patient.
- Consent for access to medical records by the authorities.

- Training of the recruitment staff

- Recruitment of staff from the facility/institution

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Contracts
    - Contracts in place prior to study start
    - Management and documentation of collaborations with other departments/organisations
  - Insurance and Indemnity
    - Provisions in place for insurance and indemnity
    - Indemnification of the investigator
    - Professional indemnity insurance for nurses, if applicable

# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Confidentiality
    - Confidentiality agreements for Agency staff, consultants etc.
  - Adverse Events
    - Follow-up and counselling
    - Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to Ethics Committee/Regulatory Authorities
    - SUSARs information provided to investigator(s)



# Evaluation of CROs

- What are Inspectors looking for? (cont'd)
  - Implementation of the study at the site
    - Contracts between the sponsor and the investigator.
    - Qualifications and experience of the investigator's team in the considered clinical area.
    - Documentation describing the distribution of duties and functions for the conduct of the trial.
    - Compatibility of the workload of the investigator and the staff with the requirements of the study.
    - Organisation of the site for the study: organisation chart, specific training, specific equipment, specific procedures.
    - Compliance with the planned time schedule for the study.
    - Correct implementation of the correct versions of the protocol and its amendments.

# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 6.5 Selection and Withdrawal of Subjects)
  - Subject inclusion / exclusion criteria.
  - Subject withdrawal criteria (*i.e.* terminating investigational product treatment/trial treatment) and procedures:
    - When and how to withdraw subjects from the trial/ investigational product treatment.
    - Type and timing of the data to be collected for withdrawn subjects.
    - Whether and how subjects are to be replaced.
    - The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 6.6 Treatment of Subjects)
  - Treatment(s) to be administered
    - Name(s) of all the product(s)
    - Dose(s)
    - Dosing schedule(s)
    - Route/mode(s) of administration
  - Treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
  - Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 6.6 Treatment of Subjects)
  - Procedures for monitoring subject compliance.

*E.g., check of  
oral cavity...*

...but 'Gold standard'  
are drug concentrations  
in matrix!

# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 6.9 Statistics)
  - A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
  - The number of subjects planned to be enrolled. [...] Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
  - The level of significance to be used.
  - Criteria for the termination of the trial.
  - Procedure for accounting for missing, unused, and spurious data.

# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 6.9 Statistics)
  - Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
  - The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

BA/BE: safety  
population

BA/BE: BE  
Assessment

BA/BE: PK  
population

# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 7 Investigator's Brochure)
  - The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.



# Protocol Development (ICH)

- An Excursion into ICH GCP E6 (Section 7 Investigator's Brochure)
  - The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.



# Protocol Development (ICH)

## ● An Excursion into ICH GCP E9 (Section 2.1 Trial Context)

### ■ Exploratory Trial

- First in Man
- Pharmacokinetic (LADME)
- Proof of Concept
- Pilot Studies
- Bioavailability
- (Studies to support Marketing)

The rationale and design of confirmatory trials nearly always rests on earlier clinical work carried out in a series of exploratory studies. Like all clinical trials, these exploratory studies should have clear and precise objectives. However, in contrast to confirmatory trials, their objectives may not always lead to simple tests of predefined hypotheses.

# Protocol Development (ICH)

## ● An Excursion into ICH GCP E9 (Section 2.1 Trial Context)

### ■ Exploratory Trial (cont'd)

- First in Man
- Pharmacokinetic (LADME)
- Proof of Concept
- Pilot Studies
- Bioavailability
- (Studies to support Marketing)

In addition, exploratory trials may sometimes require a more flexible approach to design so that changes can be made in response to accumulating results. Their analysis may entail data exploration; tests of hypothesis may be carried out, but the choice of hypothesis may be data dependent. Such trials cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence.

# Protocol Development (ICH)

## ● An Excursion into ICH GCP E9 (Section 2.1 Trial Context)

### ■ Exploratory Trial (cont'd)

- First in Man
- Pharmacokinetic (LADME)
- Proof of Concept
- Pilot Studies
- Bioavailability
- (Studies to support Marketing)

Any individual trial may have both confirmatory and exploratory aspects. The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis.

# Protocol Development (ICH)

## ● An Excursion into ICH GCP E9 (Section 2.1 Trial Context)

### ■ Confirmatory Trial

- (Dose Proportionality)
- Bioequivalence
- Food Studies
- PK Interaction
- Fixed-combination products

A confirmatory trial is an **adequately controlled trial** in which the **hypotheses are stated in advance and evaluated**. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety. [...] key hypothesis of interest follows directly from the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete. [...] it is equally important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance.

# Protocol Development (ICH)

## ● An Excursion into ICH GCP E9 (Section 2.1 Trial Context)

### ■ Confirmatory Trial

- (Dose Proportionality)
- Bioequivalence
- Food Studies
- PK Interaction
- Fixed-combination products

Confirmatory trials are intended to provide firm evidence in support of claims and hence adherence to protocols and standard operating procedures is particularly important; unavoidable changes should be explained and documented, and their effect examined.

A justification of the design of each such trial, and of other important statistical aspects such as the principal features of the planned analysis, should be set out in the protocol. Each trial should address only a limited number of questions.

# Protocol Development

## ● Study Design

### ■ Based on

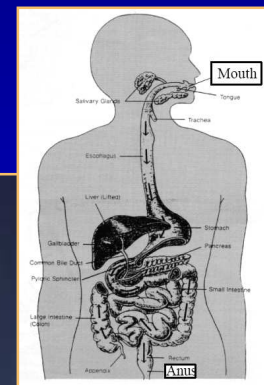
- Human pharmacokinetic data (except FIM studies)
- Parallel groups / cross-over / replicate design
- Study type (exploratory / confirmatory)
- Study target (metric, variability)
- Pharmacology of the drug (both effects *and* AE profile)
- Single dose / multiple dose
- Study Population (healthy volunteers, 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
  - 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 pass metabolism (presystemic)
    - Hepatic first pass metabolism



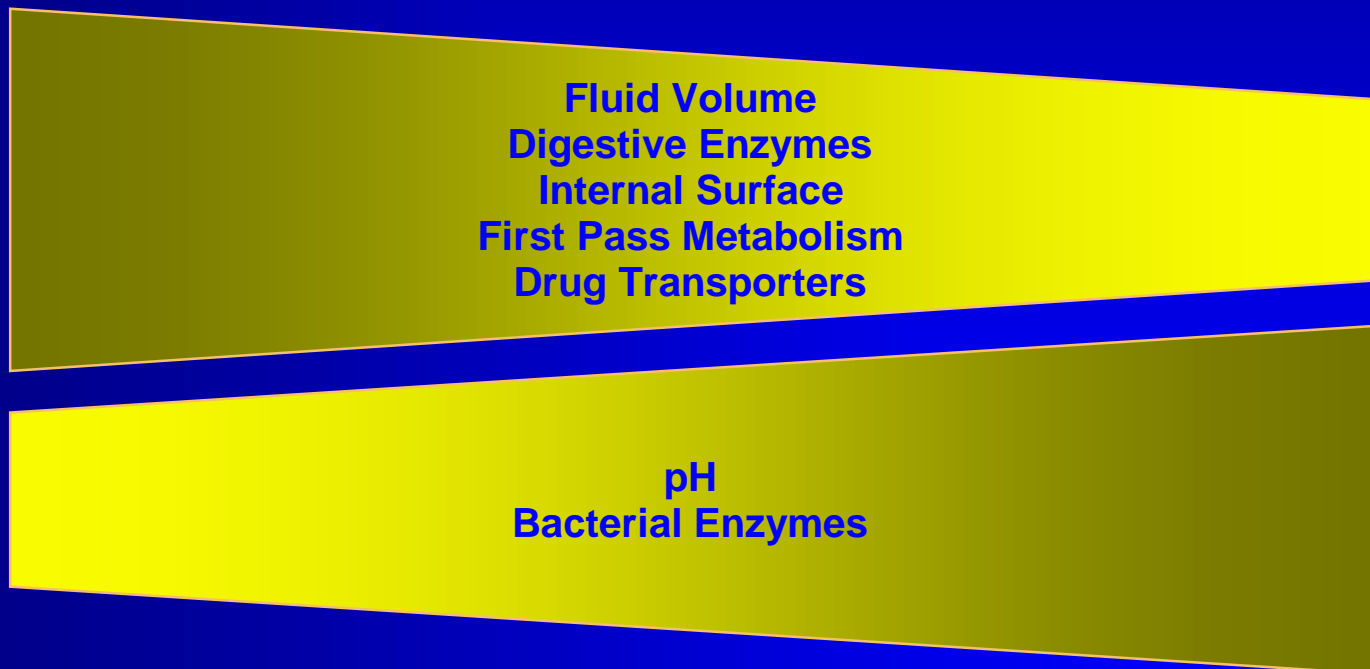
# Models vs. Reality





# Protocol Development

- Study Design based on PK (cont'd)
  - Differences in Absorption Conditions along the Gut



# 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  $\geq 30\%$ )
    - Intraindividual variability of the formulation(s) (test and/or reference, HVDP – Highly Variable Drug Product:  $CV_{intra}$  of formulation  $\geq 30\%$ )
    - 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)
  - 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)

- Frequent sampling in the area of  $C_{\max}$
- Lag-time expected?
- Spread 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, ..., 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  $\sim C_{\text{last}}$
      - ULOQ  $\sim C_{\text{max}}$
      - $AUC_t/AUC_{\infty} \geq 80\%$  (depending on the design)
      - Rule of thumb in BE-GL: LLOQ  $\sim 5\%$  of  $C_{\text{max}}$
    - Cooling prior to centrifugation
    - 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)

- 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

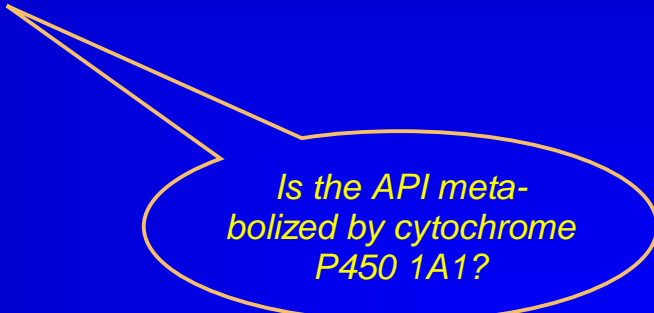
- EU GL on BE (Section 4.1.3)  
The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed 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*

EMA/CHMP/3916/2005 – ICH, London (Jan 2005)

<http://www.emea.europa.eu/pdfs/human/ich/391605en.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 (cabbage 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
    - standardised  
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<sub>2</sub>O)<sub>n</sub> 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, 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](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

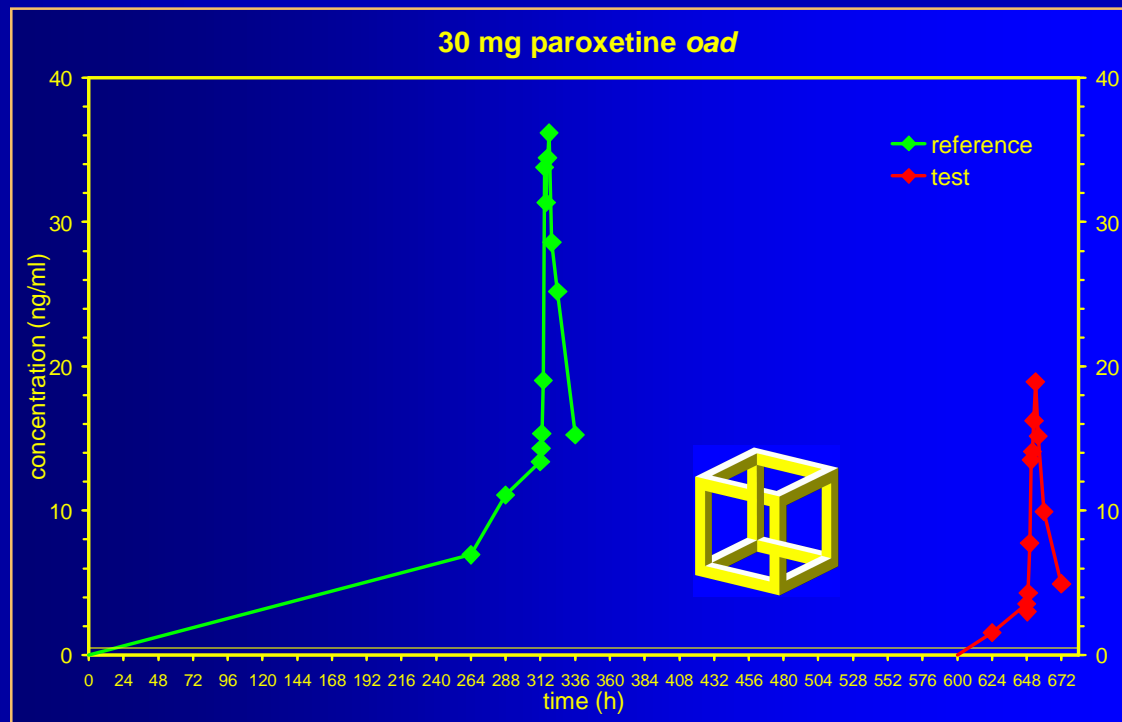
Subject	Adverse Event	Duration
01	Impairment of short memory	271
02	Obstipation	241
02	Impairment of short memory	246
02	Reduced capability of concentration	248
02	Dry mucosa of mouth	241
02	Fatigue	271
03	Obstipation	252
03	Impairment of short memory	261
03	Dry mucosa of mouth	241
03	Fatigue	95
04	Euphoria	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 expectations 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 ( $\lambda_z = ?$ )
- 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 ( $\beta=1$ -power); do not ignore existing data!
- Don't repeat a failed study without reformulation (to be submitted according to BE Draft!)
- 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!*  
**Clinical Part of  
BA/BE Studies**  
*Open Questions?*  
(References in your Handouts)

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# References

- Collection of links to global documents

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    - Model BE Data Summary Tables (2007)
    - Submission of Summary BE Data for ANDAs (2009)

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Directive 2005/28/EC: Principles and detailed Guidelines for GCP as regards IMPs for Human Use, as well as the Requirements for Authorisation of the Manufacturing or Importation of such Products (2005)

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Definition of IMPs and NIMPs (2006); Additional Information on IMPs (2007)

EMA GCP Inspector's Group

Procedure for Conducting GCP Inspections requested by the EMA

- Annex I: Investigator Site (2007)
- Annex IV: Sponsor Site and/or Contract Research Organisations (CRO) (2007)
- Annex V: Bioanalytical part, Pharmacokinetic and Statistical analyses of Bioequivalence Trials (2008)

EMA/CPMP

Pharmacokinetic Studies in Man (1988)

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PK Studies in Patients with Renal Impairment (2004)

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