About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology ‘Open Access’, OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, roundtable discussions, poster presentations, workshops, symposia and exhibitions.
OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
POSSIBLE MISTAKES AND MANIPULATIONS IN BIOEQUIVALENCY TRIALS

Prof. Dr. Aydın Erenmemişoğlu
WHAT IS THE PROBLEM?

- PHARMACEUTICAL COMPANY (SPONSOR) AFTER INEQUIVALENT RESULT
- WHERE IS THE PROBLEM?
- CLINIC?
- ANALYTIC?
- DATA MANAGEMENT?
BE TRIALS PURPOSE

Similar plasma concentration

Similar concentration on target place

Similar effect
DESIGN

- Usually two period cross over
- Different a lot of design possible
- We have to consider total blood loss volume
DESIGN

- It is possible to test or reference more than one product.
- Especially valid for pilot trials.
DESIGN

- Fasting single dose.
- Under fed conditions single dose
- Multiple dose under fasting conditions
- Multiple dose under fed conditions
- Cross over or parallel
- Two stage
- Replicate/semireplicate
HOW MANY VOLUNTEERS?

- Variance, pilot trials, published results and previous trials and experience
- Statistical power
- According to the first stage results for two stage trials
IMPORTANT TIPS

- Well clarified inclusion and exclusion criteria such as all clinical trials
- Well standardization
FREQUENT MISTAKES 1

- Incorrect reference product
- Incorrect design
- Insufficient volunteer number
- Excessive amount of volunteer number
- Too short wash-out period
- Insufficient standardization of clinical procedures
- Incorrect blood sampling points
- Mistakes on sample preparation (light sensitivity, cool chain etc)
FREQUENT MISTAKES 2

- Dosing (discrepancy with randomisation)
- Blood sampling (discrepancy with protocol)
- Anticoagulant agents
- Preservatives (interference)
- Mixing-up blood samples (clinical, analytical)
- Thawed plasma samples, dissappering during shipment
- Incorrect packaging
FREQUENT MISTAKES 3

- Insufficient analytical method (LLQ etc)
- Insufficient validation
- Wrong analytes
- Wrong modelling
- Insufficient data management
FREQUENT MISTAKES 4

- Insufficient in vitro results
- Pilot trials evaluation
- Special meals
- Bias (volunteer screening, data evaluation)
Success is an iceberg

What people see:
SUCCESS!

What people don't see:
- Dedication
- Hard work
- Good habits
- Things I have to give up

Persistence
Failure
Sacrifice
Disappointment
FAIL

@sylviaduckworth
WHAT CAN BE MORE POSSIBLE REASONS?
Pantoprazole project (volunteer didn’t swallow it)
Lisinopril tablet project vomiting 1h17min after dosing (AE record available)
Escitalopram project most probably volunteer has taken escitalopram 72 h after dosing
DIFFERENT CASES

- Case I:
  - Dosing time at 08.00 the 2nd period of one BE trial.
  - World cup football organization in Korea Turkey Team was on quarter final around at 13.00
DIFFERENT CASES

- Everybody in front of TV and excited.
- Abnormal analytical result: for the 2nd period plasma levels of both products are variable and decreased significantly by comparing the 1st period after 6h dosing.
We should not permit to volunteers to watch football game on TV. We couldn’t provide the same conditions for both periods.

There was nothing to do because as you have known analytical results come after some months by following of clinical part. It was too late.
CASE II:

- A BE trial with quinolone antibiotics
- Abnormal curves.
- Everything has been checked retrospectively
- There was fish on meal
- Contaminated meal with quinolone antibiotics because of cultivated fish
- We repeated; because it was too late when we have learned the reason
WHAT CAN BE POSSIBLE MANIPULATIONS?

- Clinical
- Analytical
- Data management
Clinical:

About randomization code

In cross over design
Test product against test (correct)
Reference product against reference
T-T or R-R instead of T-R or R-T (bias)

CANT NOT BE DETERMINED EXCEPT STRICT MONITORIZATION BY SPONSOR NOT CRO
Clinical:
Manipulations on volunteer records according to analytical records

CAN BE EXAMINED BUT DOUBTFUL
Analytical:

Dilution: Only some dilutions can be used for chromographic analysis. Plasma samples are not used

**CAN NOT BE DETERMINED**

Some chromatograms can be used from previous trials *(There is one big disaster in the past)*

**CAN BE DETERMINED BUT NEEDS VERY STRICTLY INSPECTION**
Bio-equivalence of [drug name] in healthy human Volunteers;
Concentration graph for the Reference and Test preparation - Volunteer No. 1

CONCENTRATION in ng/mL

TIME IN HRS

Volunteer Concentration graph; Reference preparation

Volunteer Concentration graph; Test preparation
Data Management:

Results can be manipulated by after clinical and analytical part by some statistics tricks and management.

**CAN BE DETERMINED BUT NEEDS VERY STRICTLY INSPECTION**
SOLUTION?

- Well inspection
- Well monitoring
- Strict evaluation of dossiers by authority after submission
- There is no certification against insufficiency
- GCP and GLP are only valid on trial base not all
Let us meet again..

We welcome you all to our future conferences of OMICS International
7th World Congress on
Bioavailability & Bioequivalence: BA/BE Studies Summit
On
August 29 - 31, 2016 at Atlanta, USA
http://bioavailability-bioequivalence.pharmaceuticalconferences.com/