

# About OMICS Group

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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, round table discussions, poster presentations, workshops, symposia and exhibitions.

# OMICS International

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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.



6th World Congress on Bioavailability & Bioequivalence:  
BA/BE Studies Summit Aug 17-19, 2015 Chicago, USA

# ~~POSSIBLE MISTAKES AND~~ MANIPULATIONS IN BIOEQUIVALENCY TRIALS

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# WHAT IS THE PROBLEM?

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

# BE TRIALS PURPOSE

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Similar plasma concentration



Similar concentration on target place



Similar effect



# DESIGN

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





# DESIGN

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

# DESIGN

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- 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?

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



# IMPORTANT TIPS

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



# FREQUENT MISTAKES 1

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- 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

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



## FREQUENT MISTAKES 3

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



## FREQUENT MISTAKES 4

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





# The Iceberg Illusion

Success is an iceberg

SUCCESS!

WHAT PEOPLE SEE

Persistence



Failure



Sacrifice



Disappointment



WHAT PEOPLE DON'T SEE

Dedication



Hard work



Good habits



@sylviaaduckworth

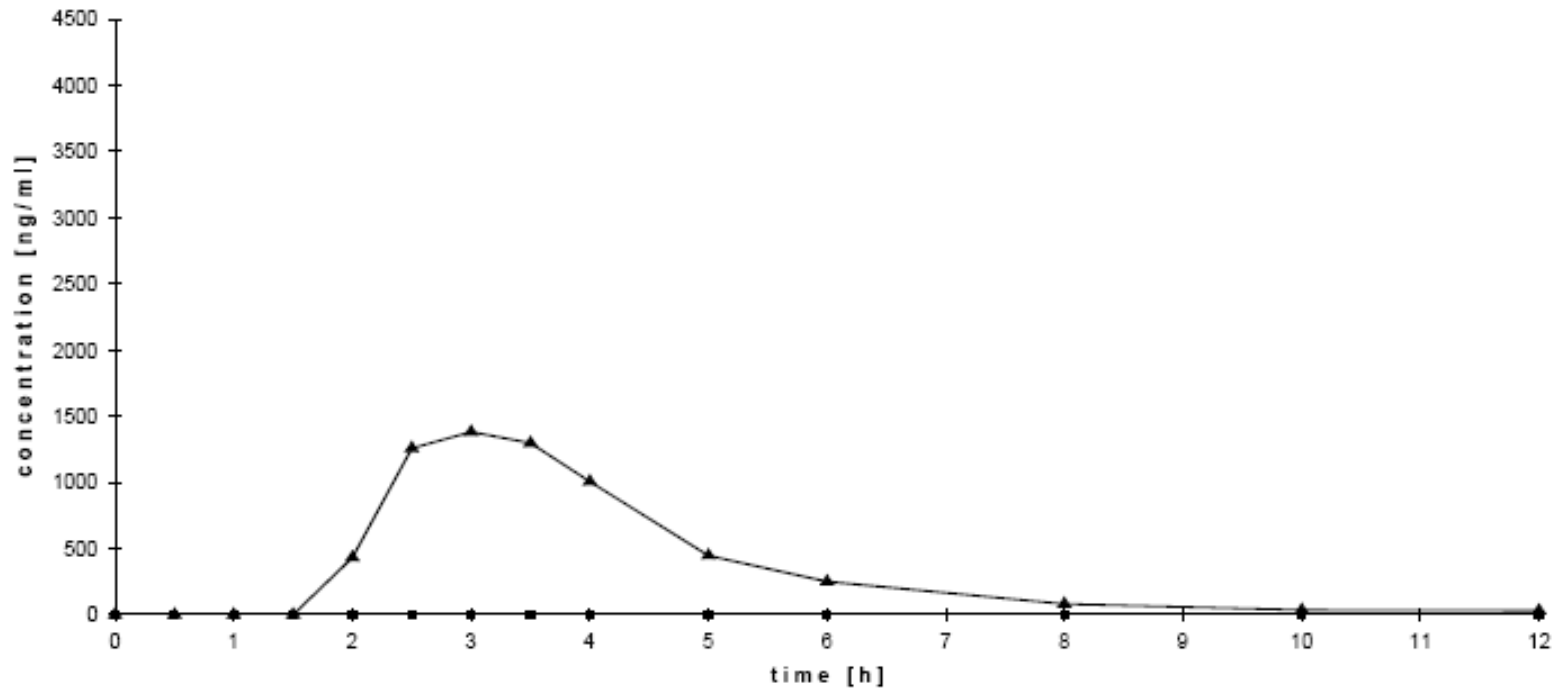


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**WHAT CAN BE MORE  
POSSIBLE REASONS?**

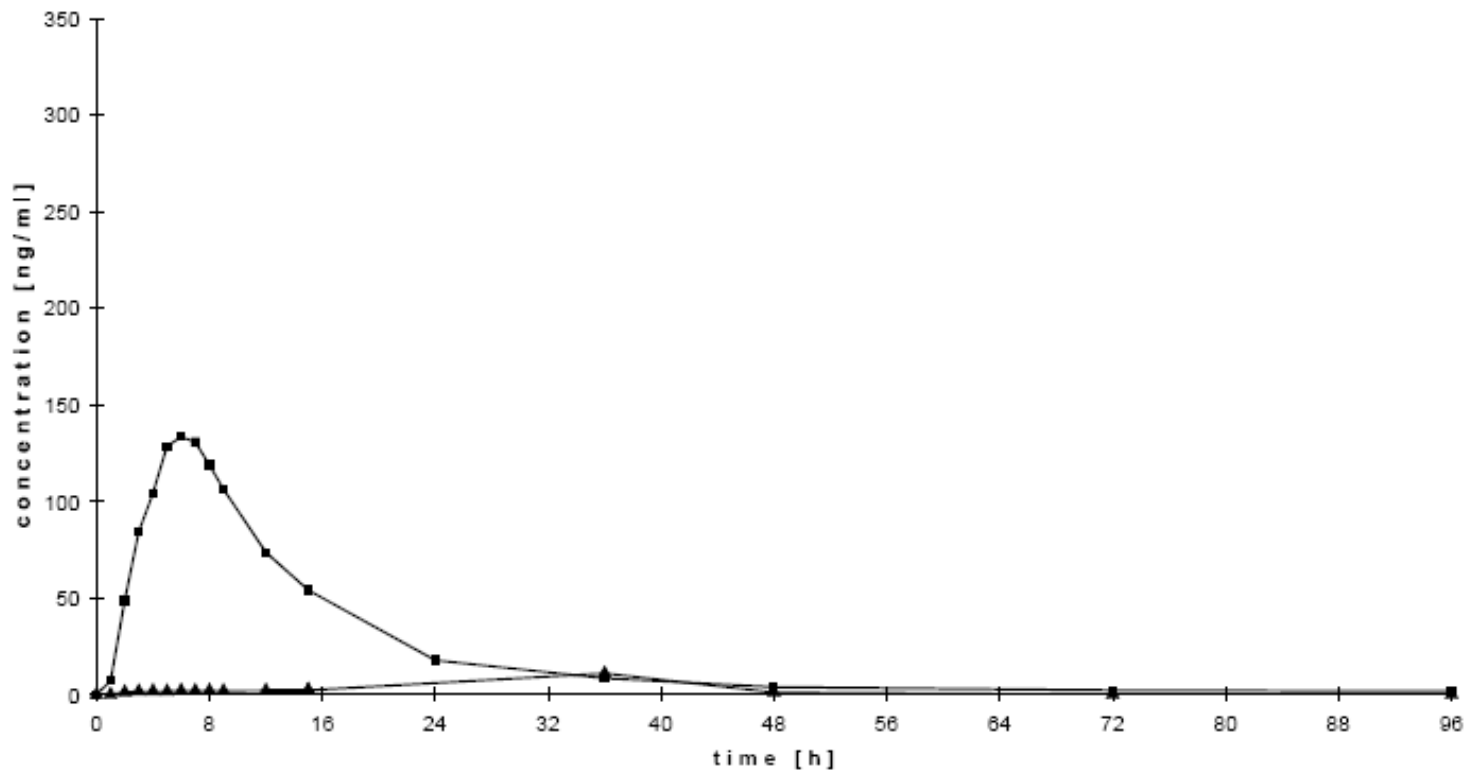
# Pantoprazole project (volunteer didn't swallow it)

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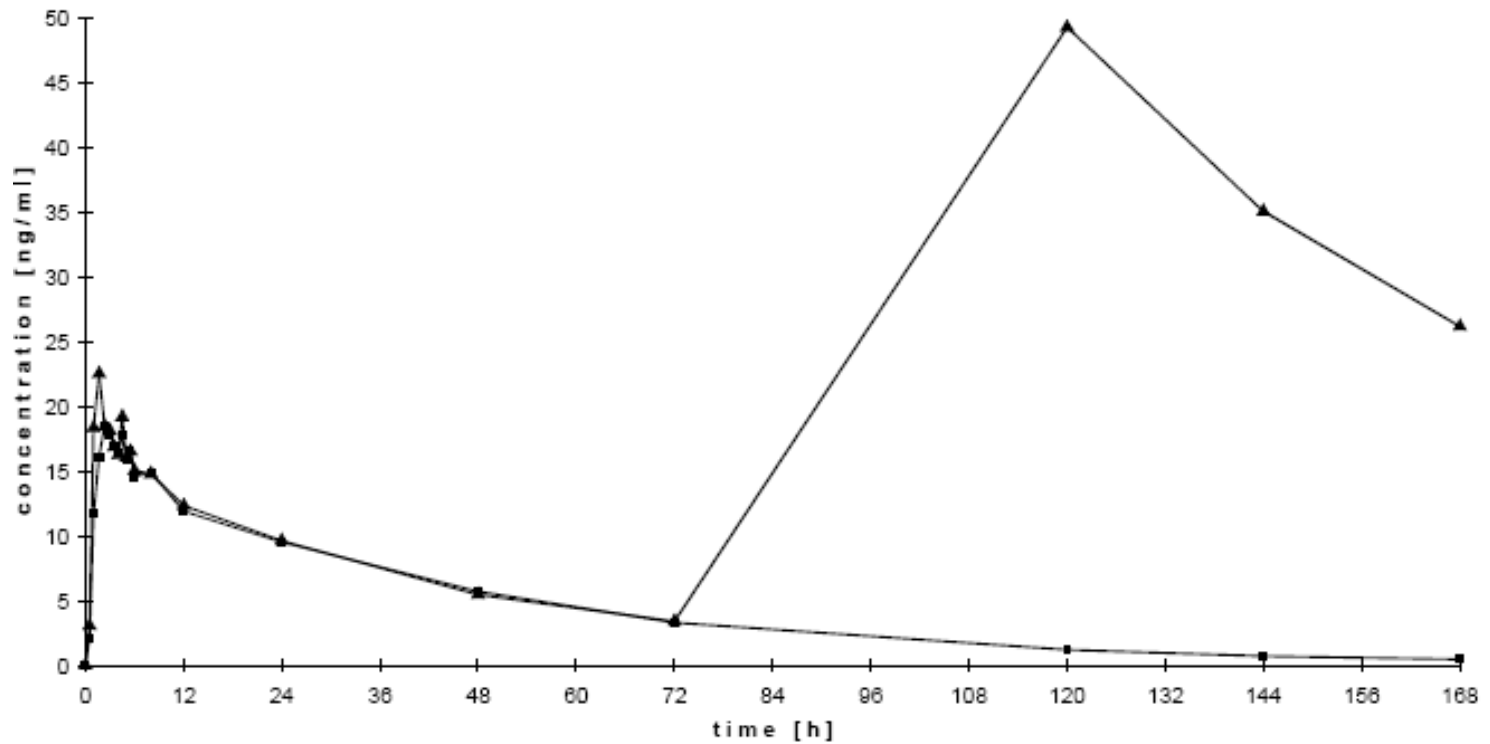


# Lisinopril tablet project vomiting 1h17min after dosing (AE record available)

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# Escitalopram project most probably volunteer has taken escitalopram 72 h after dosing



## DIFFERENT CASES

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- 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

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- Everybody in front of TV and excited.
- Abnormal analytical result: for the 2<sup>nd</sup> period plasma levels of both products are variable and decreased significantly by comparing the 1<sup>st</sup> period after 6 h dosing



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- 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.

# DIFFERENT CASES

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## 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



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## **WHAT CAN BE POSSIBLE MANIPULATIONS?**

-Clinical

-Analytical

-Data management



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## **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**)

**CAN NOT BE DETERMINED EXCEPT STRICT  
MONITORIZATION BY SPONSOR NOT CRO**



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**Clinical:**

Manipulations on volunteer records according to analytical records

**CAN BE EXAMINED BUT DOUBTFUL**

## Analytical:

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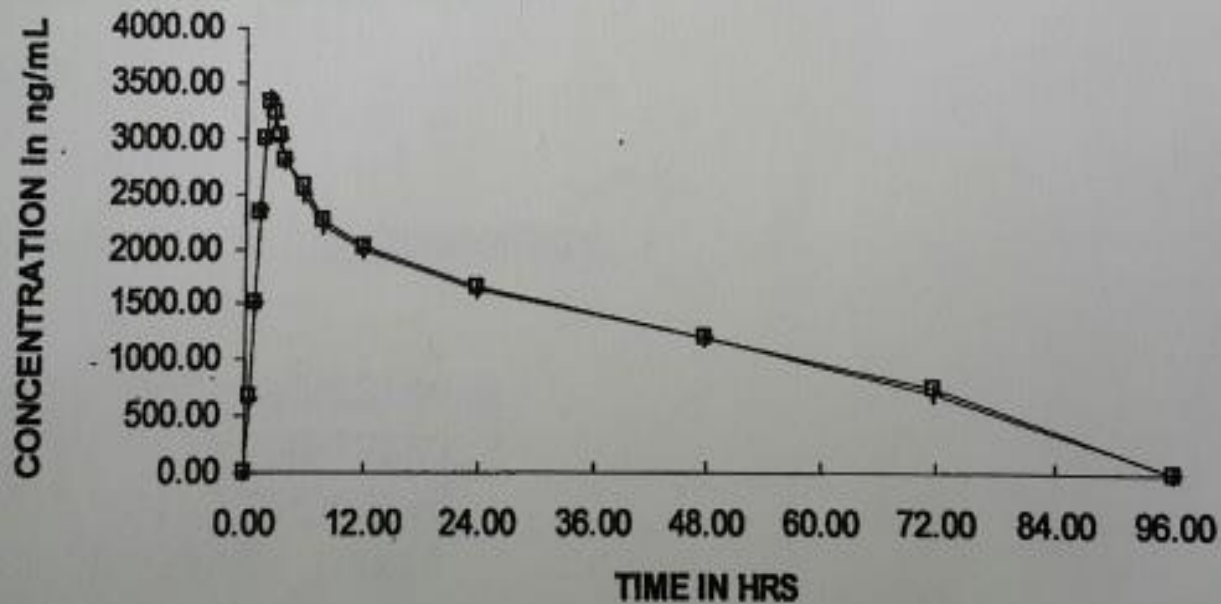
Dilution: Only some dilutions can be used for chromatographic analysis. Plasma samples are not used

**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 \_\_\_\_\_ in healthy human Volunteers;  
Concentration graph for the Reference and Test preparation - Volunteer No. 1



—□— Volunteer Concentration graph; Reference preparation    —+— Volunteer Concentration graph; Test preparation



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## **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?

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- 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



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DZIRI  
KURU-SULU

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# Let us meet again..

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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/](http://bioavailability-bioequivalence.pharmaceuticalconferences.com/)