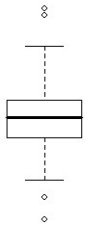
BBS Spring Seminar “Multiplicity in Clinical Trials”

Basel, 7-März-2011



Confirmatory Statistics in PK/PD Studies

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Overview

Characteristics of PK/PD studies

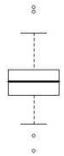
Structure in these Studies

Using the structure to devise a confirmatory analysis strategy

2 Examples

Confirmatory analysis put in context

How to select methods for the individual steps



Pharmacodynamic Studies

When

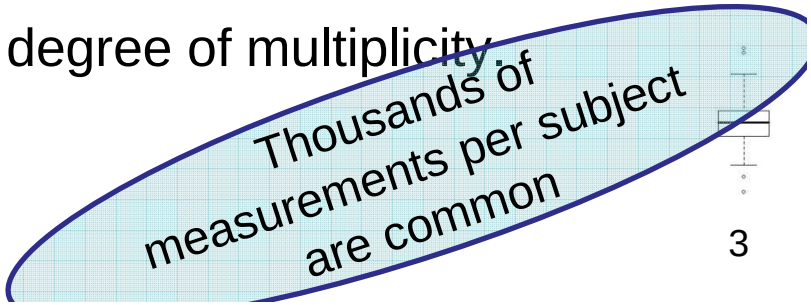
- In phase I or early phase II, but also as post marketing studies.

Why

- To contribute to proof of concept.
- To understand if a drug does what it is expected to do.

How

- They are often performed in a small sample of healthy volunteers.
- They often use one or several biomarkers as endpoint.
- They nearly always have a PK component.
- They nearly always show a very high degree of multiplicity.



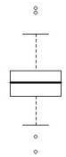
Can we Perform a Confirmatory Analysis in these Studies?

Conventional methods to address multiplicity like Bonferroni-Holm or Hochberg cannot cope with 10 000 p-values.

"Although techniques for controlling experimental error are available, CPT does not usually recommend their use;"

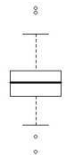
Statistical guide for Clinical Pharmacology & Therapeutics 2010

However, there is a strong structure in these studies.
This can be used to address multiplicity more efficiently.



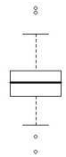
Elements to Build a Confirmatory Strategy

- **Conventional methods to address multiplicity**
- **Structure of PK/PD studies**
- **Steps in the analysis of PK/PD studies**



Conventional Methods to Address Multiplicity

- **Selection**
  - concentrate on a few endpoints
- **Summary measures**
  - mean, AUC, extreme values, but also slopes or other contrasts
- **Correction for multiplicity**
  - Bonferroni-Holm, gatekeeping procedures, Hochberg, ...



Pharmacodynamic Studies are Highly Structured

PD studies can be described as taking measurements at a

"hyper-grid"

Informal definition:

D = { δ_i; i=1,..,p}

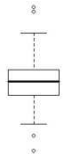
with "dimensions" $\delta_i = (d_{i1},..., d_{in_i})^T$

G = {(d_{1i_1}, ..., d_{pi_p}); $i_j = 1,..., n_j$ } is a hyper-grid or crossproduct of D

A PD-study can be seen as a random variable

(Ω, G) -> X

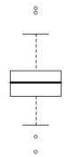
for some result space X.



Pharmacodynamic studies are highly structured (2)

Typical dimensions are

- **Time, e.g. (pre-dose, 30 min, 1 h, 1.5 h, ..., 24 h)**
- **Dose**
- **Parameter e.g. (SBP, DBP, pulse, ...)**
- **Condition e.g. (supine, standing after 3 min, ...)**

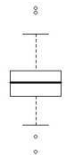


Example pharmacodynamic study

This is a study to investigate the central effect of a drug with the EEG. It has 5 dimensions:

- **5 doses: placebo, 0.3 mg, 0.6 mg, 0.9 mg, 2.0 mg**
- **13 time points: 2 predose, 11 post-dose**
- **2 conditions: Vigilance controlled, Resting EEG**
- **The EEG is recorded on 28 derivations on the scalp.**
- **It is parametrised using 4 (+ 5) frequency bands**
  - ("delta", "theta", "alpha", "beta")

This results in 14560 measurements per subject or at least 9856 comparisons of interest.



Analysis of a PK study is a stepwise process

Pre-processing

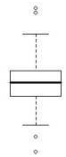
Parameter extraction and selection

Model fit

Hypothesis test

p-value-based multiplicity adjustment

Each step offers an opportunity to address multiplicity for one or more dimensions.



Example: Addressing Multiplicity

The structure of Study 1 is characterised by 5 dimensions:

- **5 doses: placebo, 0.3 mg, 0.6 mg, 0.9 mg, 2.0 mg**
- **13 time points: 2 predose, 11 post-dose**
- **2 conditions: Vigilance controlled, Resting EEG**
- **4 (+ 5) frequency bands**
- **28 derivations.**

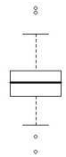
Test linear contrasts in dose.

Select only two timepoints near t_{max}

Select only VC condition, since it is less variable.

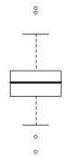
Select beta frequency band, since it is most promising for the drug class.

Assuming a positive correlation between the derivations, use a Hochberg procedure to correct for this multiplicity.

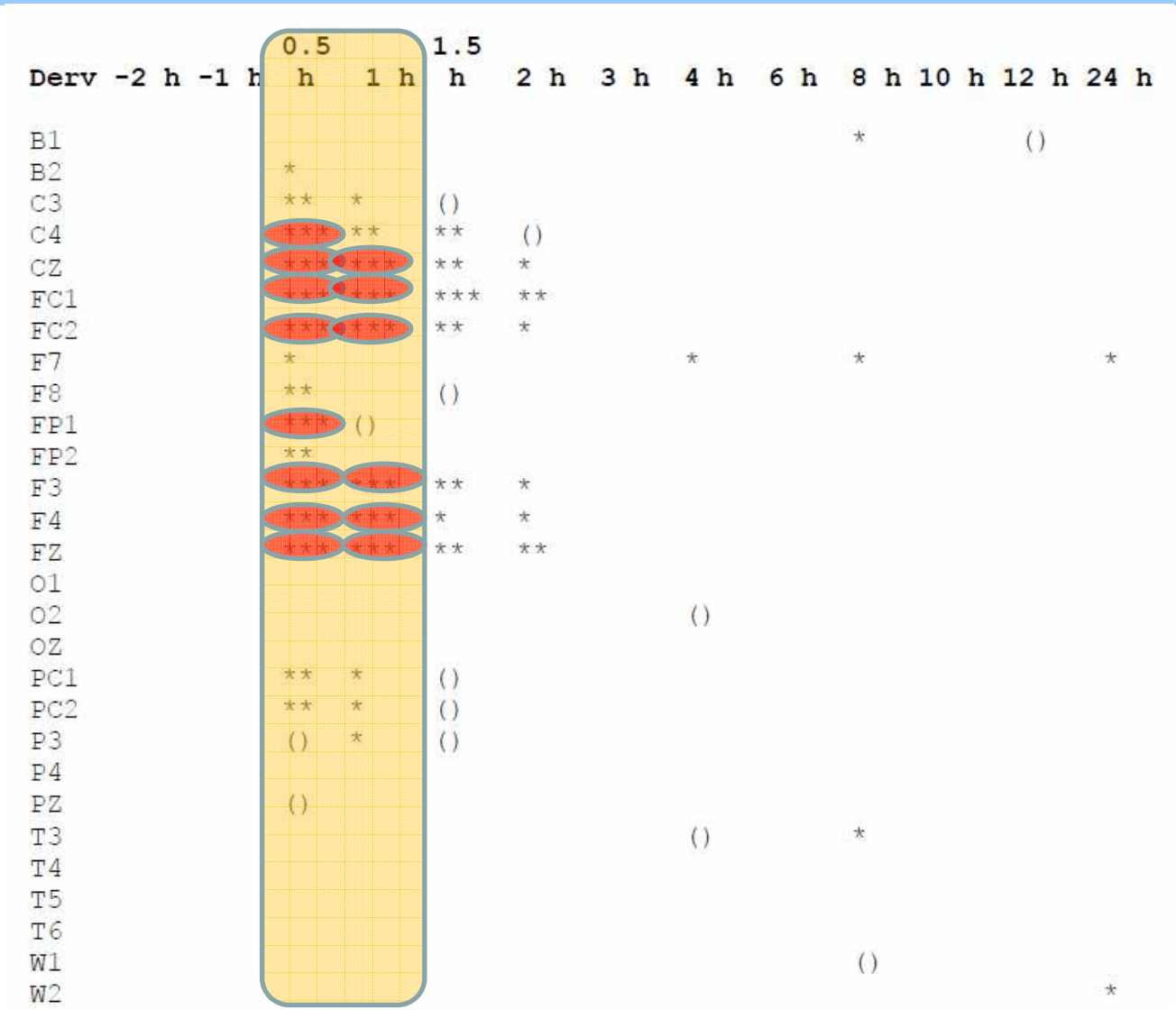


Statistical Statement

- **For each derivation**
- **a linear mixed effects model will be fitted**
  - with *beta magnitude* under *VC conditions* as dependent variable
  - time and time by treatment interaction as fixed effects
  - subject as random effect
  - baseline as covariate.
- **Linear contrasts in *dose* will be estimated for each timepoint.**
- **The p-values for *all derivations* and *times 0.5 and 1 h* will be submitted to a Hochberg procedure to keep the familywise error rate at the 0.05 level (56 p-values).**



Result: Linear contrasts in Dose for Beta magnitude



Example: Alternative Proposal

The structure of Study 1 is characterised by 5 dimensions:

- **5 doses: placebo, 0.3 mg, 0.6 mg, 0.9 mg, 2.0 mg**
- **13 time points: 2 predose, 11 post-dose**
- **2 conditions: Vigilance controlled, Resting EEG**
- **4 (+ 5) frequency bands**
- **28 derivations.**

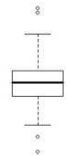
Test linear contrasts in dose.

Select only two timepoints near t_{max}, split α between timepoints.

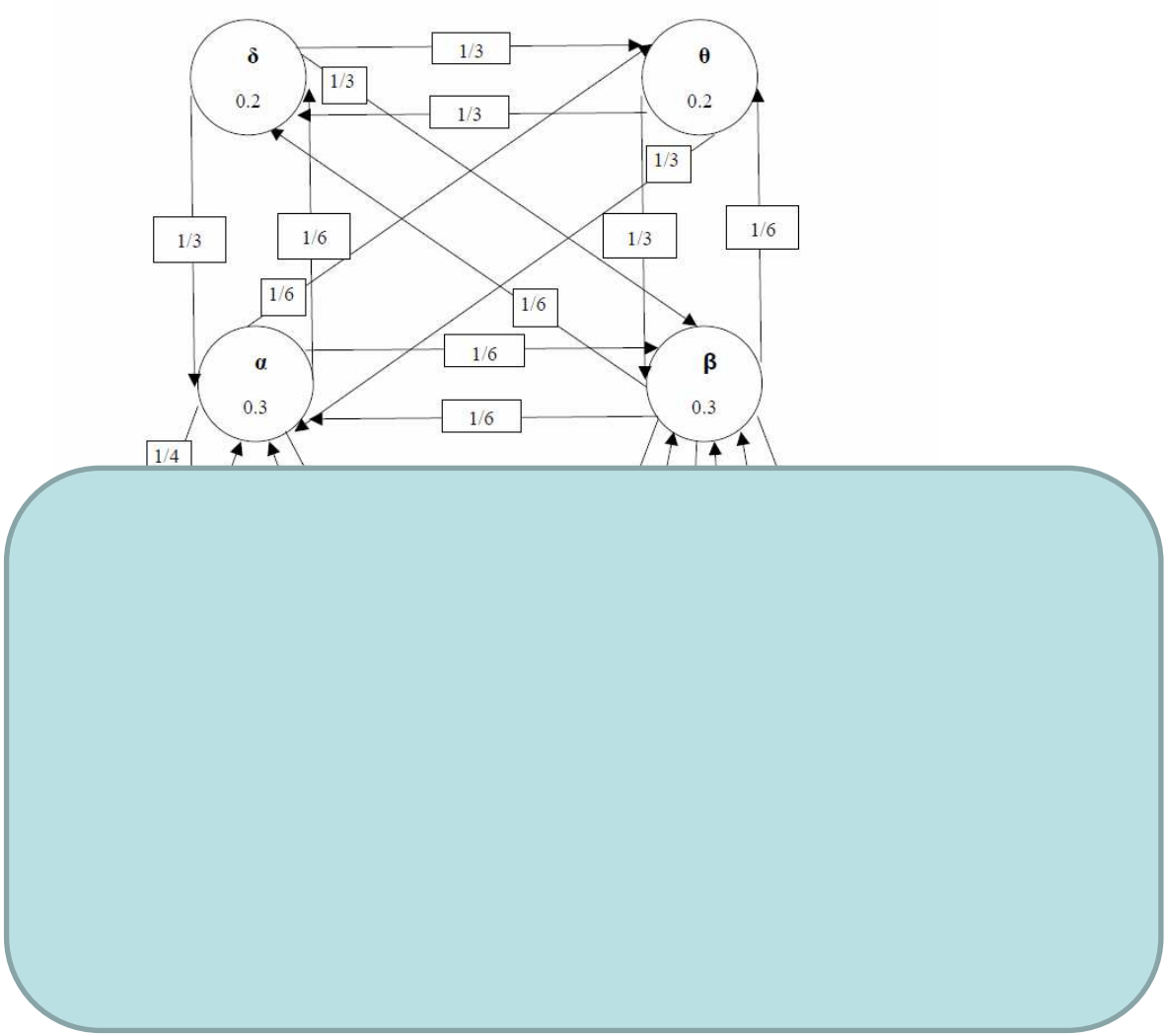
Select only VC condition, since it is less variable.

Apply a weighted sequentially rejective test procedure across all frequency bands.

Summarise over all locations with O'Brien's Rank Sum or OLS method.



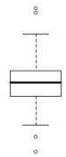
The Weighted Sequentially Rejective Test Procedure



Statistical Statement – Rank Sums

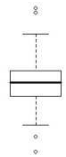
- **For each frequency band and timepoint**
  - the sum over *derivations* of ranks across subjecs
  - of change from baseline of the magnitudes in the respective frequency band under vigilance controlled conditions

will be computed.

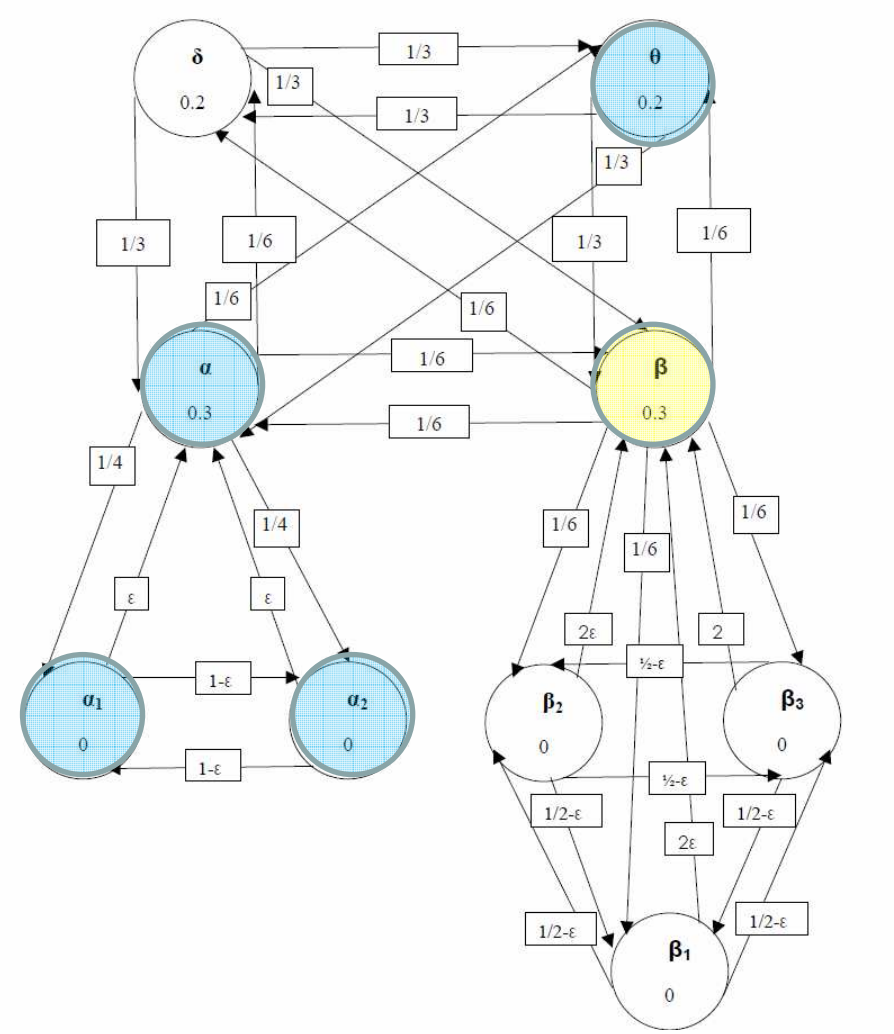


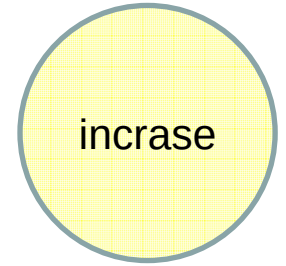
Statistical Statement – Linear Modelling

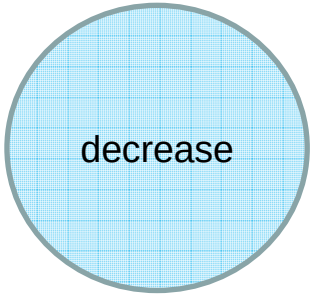
- **A linear mixed effects model will be fitted for these rank-sums**
  - separately for each frequency band
  - with time and time by treatment interaction as fixed effects
  - subject as random effect.
- **Linear contrasts in *dose* will be estimated for each timepoint.**
- **For *0.5 h and 1 h***
- **the p-values for all *frequency* bands will be submitted to a weighted sequentially rejective test procedure**
- **at an α-level of *0.025* separately for each *timepoint.***

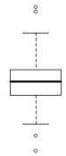


Results of Alternative Strategy







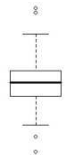


Georg Ferber

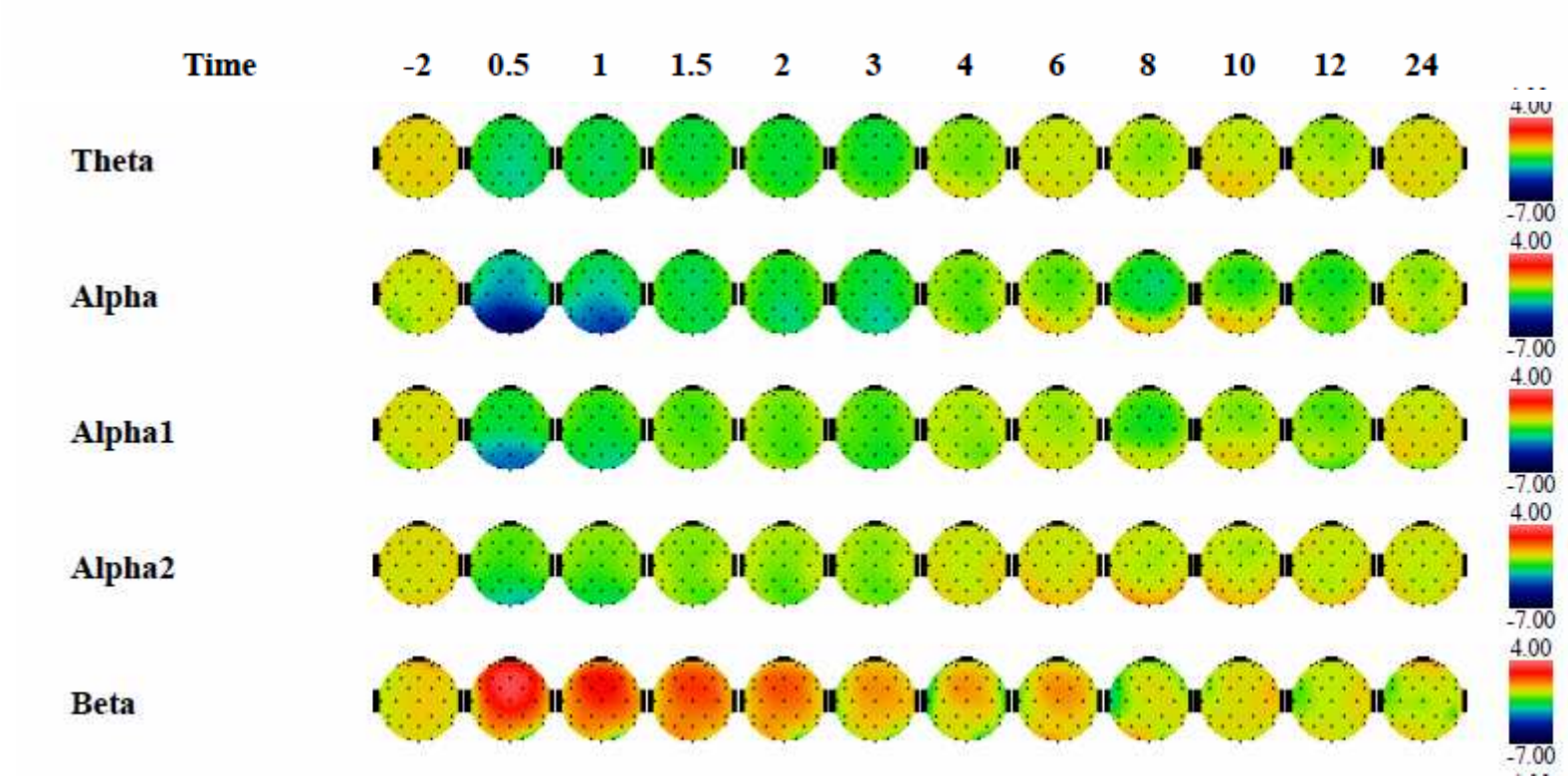
Confirmation versus Exploration

In many PK/P studies, descriptive or exploratory analysis will remain of primary interest

- **A full and careful descriptive analysis is indispensable.**
- **A predefined confirmatory component is an added value**
- **A more detailed analysis of the structure of significant effects will be of particular interest.**

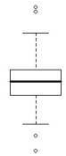


Descriptive Follow up



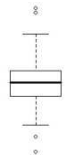
How to Select Methods to Address Multiplicity?

- **Selection:**
  - if we have expectations on where to find the maximum (e.g. t_{max})
- **Summary:**
  - if the measures at different levels are positively correlated
  - and if the question where the effect is located is not so important
- **Linear contrast:**
  - This is not restricted to linear relationships, but we should expect strict monotonicity.
- **Multiplicity Correction:**
  - Of interest if we need to know where (at what levels) the effect is in fact located.



Other Methods

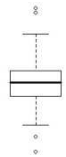
- **Extreme values:**
  - These are used e.g. in TQT studies.
  - May need special tests, e.g. permutation tests.
  - Bootstrapping has been shown to be inappropriate.
- **Eigenvectors and discriminant functions**
  - Of interest, if a learning set is available.
  - Often difficult to explain to scientists.



Power

Power is not a straightforward concept in case of multiplicity anyway since many alternatives are possible.

- **If our guesses were right, we are fine**
- **If some of them were wrong**
  - e.g. the effect occurred later than anticipated
- **the hypergrid-structure can still be used as a guide for a descriptive analysis.**



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