Fit-for-purpose limits and Tolerance intervals: connecting the assay performance to the clinical trial

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Exploratory Statistics

Pharmacometrics

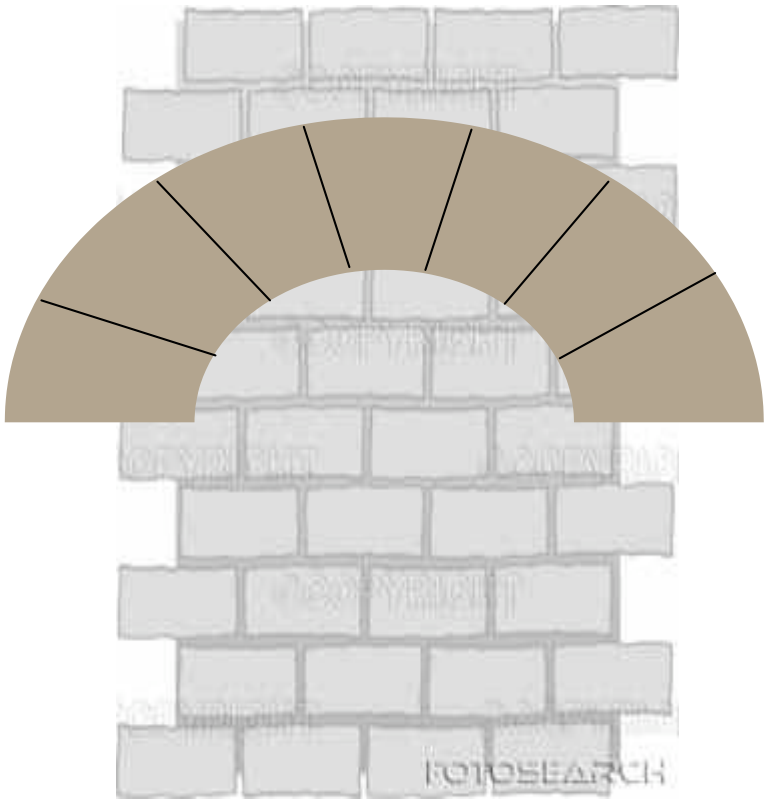
Lou, living with epilepsy

13 octobre 08

Objective

Make a bridge between :

Laboratory Performances



Clinical study Results/ Decision

Agenda

1. Validation of analytical methods
2. Use of Tolerance intervals
3. Two examples:
    1. Link between a bioanalytical method and PK study results (bioequivalence)
    2. Link between a biomarker assay and the results of an adaptive dose-ranging study
4. Conclusions

1. Validation of analytical methods

1.1 Objective of analytical procedure

- The objective of an analytical procedure is to be able to determine **accurately** **each** of the unknown quantity that the laboratory will have to quantify.

$$X \leftrightarrow \mu_T$$

X = measured value or result

μ_T = true unknown value

1. Validation of analytical methods

1.2 Objective of validation

- The **objective of validation** is to give to the laboratory as well as to the regulatory bodies **guarantees** that every single measure that will be performed in routine will be **accurate enough**.

1. Validation of analytical methods
1.2 Objective of validation

- The objective of the validation phase is to evaluate
  - if at least a minimal expected proportion, (say 80%),
  - of future results will fall within the acceptance limits $[-\lambda, +\lambda]$ i.e. accurate result.
  - given the estimated bias and precision of the analytical method:

$$E_{\hat{\mu}_M,\hat{\sigma}_M}\left\{P\left[\left|X-\mu_T\right|<\lambda\right]\middle|\hat{\mu}_M,\hat{\sigma}_M\right\}\geq 80\%$$

Expected accuracy of **results** in future

The "missing link" Between Method And Results

Estimated **method** performance in validation

2. Use of tolerance intervals

- Definition:

To make a consistent decision, we compute the β-expectation tolerance interval (Mee, 1984):

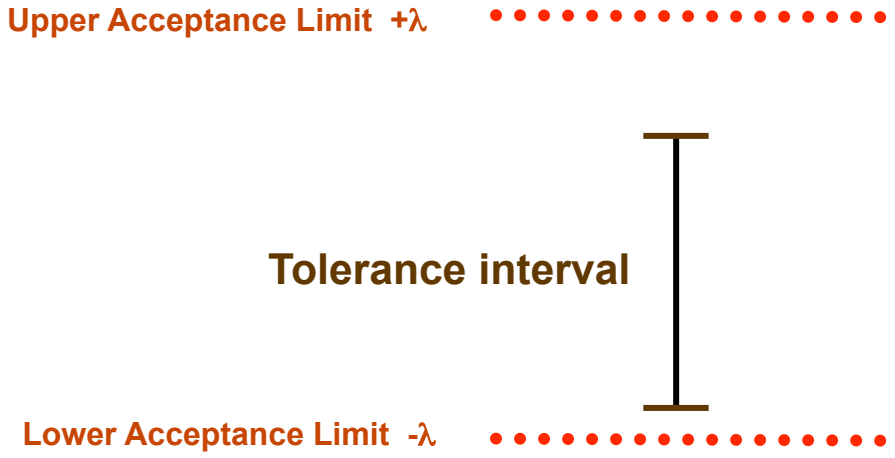
$$E_{\hat{\mu}_M,\hat{\sigma}_M}\left\{P_X\left[\hat{\mu}_M - k_E\hat{\sigma}_M < X < \hat{\mu}_M + k_E\hat{\sigma}_M \middle| \hat{\mu}_M, \hat{\sigma}_M\right]\right\} = \beta$$

the expected proportion of values falling inside the β-expectation tolerance interval is β

2. Use of tolerance intervals

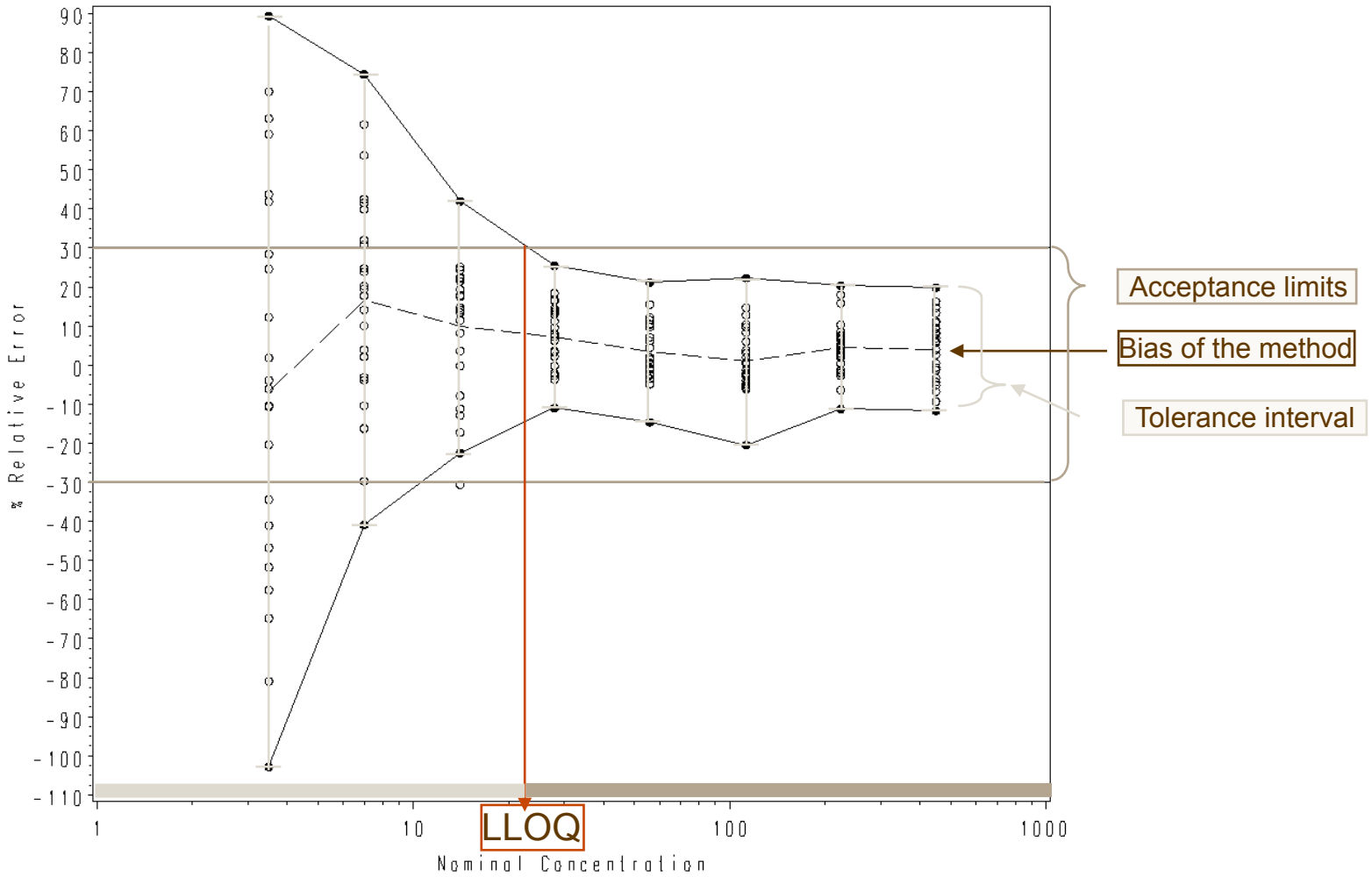
- Link beween acceptance limits and β-expectation tolerance interval

If the β-expectation **tolerance** interval is included within the acceptance limits, then the expected proportion of future results within the acceptance limits is larger or equal to β, e.g. 80%.



2. Use of tolerance intervals

Accuracy Profile as decision tools: Tolerance interval as function of quantity



3. Defining acceptance limits

3.1 How to fix them?

- What value for Acceptance Limits ?

  - based on the **intended use** of the results
  - **not** based on the **performance** of procedure
  - The results are used, not the method…..
  - on the risk it may constitutes for customers/ patients and laboratory

Note:

> [-15%,15%] is clearly the intend of the FDA text for bioanalytical methods (May2001).

- [-20%,20%] has been suggested for Ligand-Binding Assays (DeSilva, 2003).
- Recent paper issued by AAPS ('07) proposes [-30%,30%] for Ligand-Binding Assays.

These limits are determined regardless of the use of the results.

Examples

- Example 1

  Acceptance limits of a bioanalytical assay to estimate the PK parameters, in support of a Bioequivalence analysis

- Example 2

  Performances of an efficacy Biomarker assay to find the optimal dose in a clinical trial using an **adaptive design**

3. Defining acceptance limits

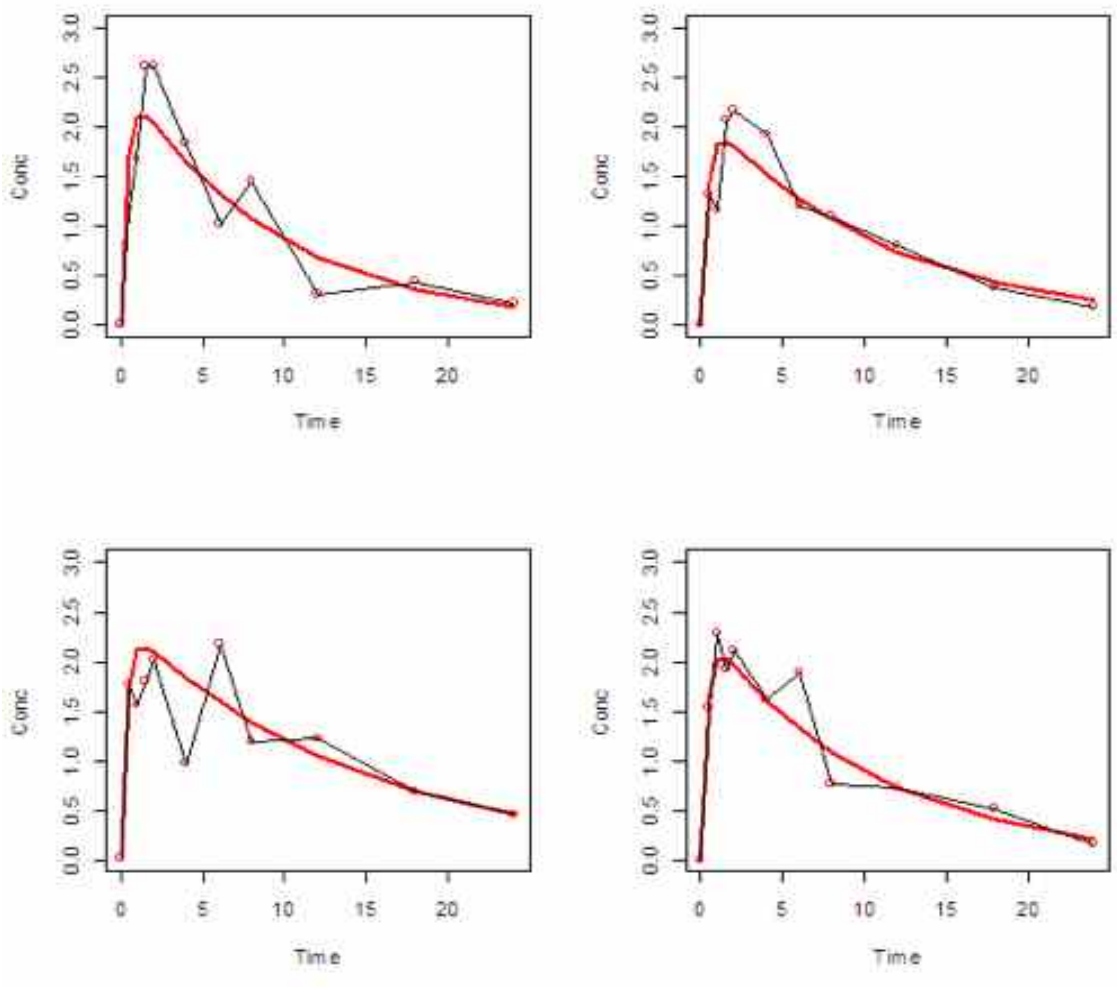
Bioequivalence study

- The objective:
  - an analytical procedure has to support a bioequivalence study.
  - The "new formulation" is anticipated to be equivalent.
- The experiments:
  - 6 to 30 volunteers could be considered
  - A non-compartmental analysis will be performed (AUC, Cmax and T1/2)
  - Confidence intervals on the ratio must be within [80% - 120%] to claim "equivalence"
- The question:
  - What acceptance limits should be used to ensure success for the trial.

3. Defining acceptance limits

Bioequivalence study

- Observations and errors



Example of observations obtained with an analytical method having **20**% total error

The red line represent the true (unknown) profile.

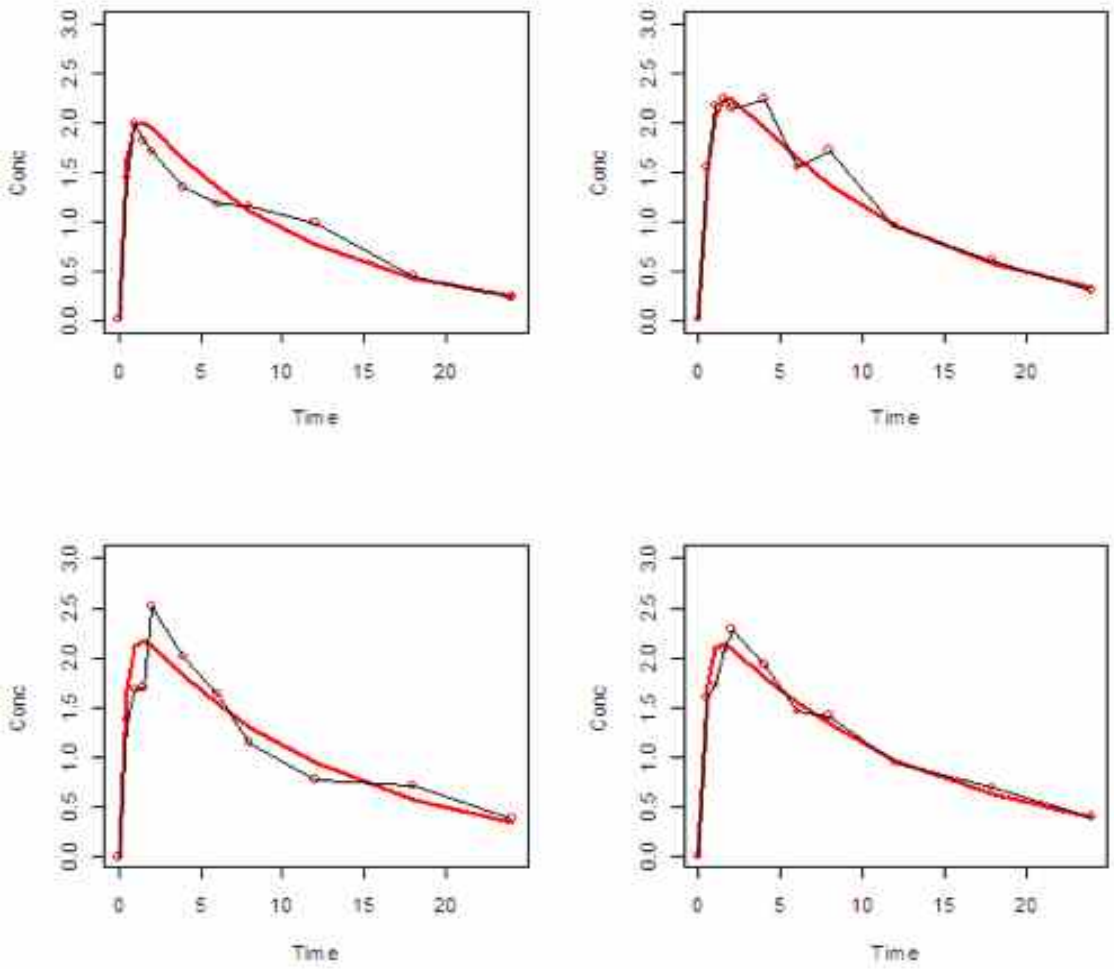
The black lines and dot represent the observations.

How will NCA PK parameters be estimated?

3. Defining acceptance limits

Bioequivalence study

- Observations and errors



Example of observations obtained with an analytical method having **10%** total error.

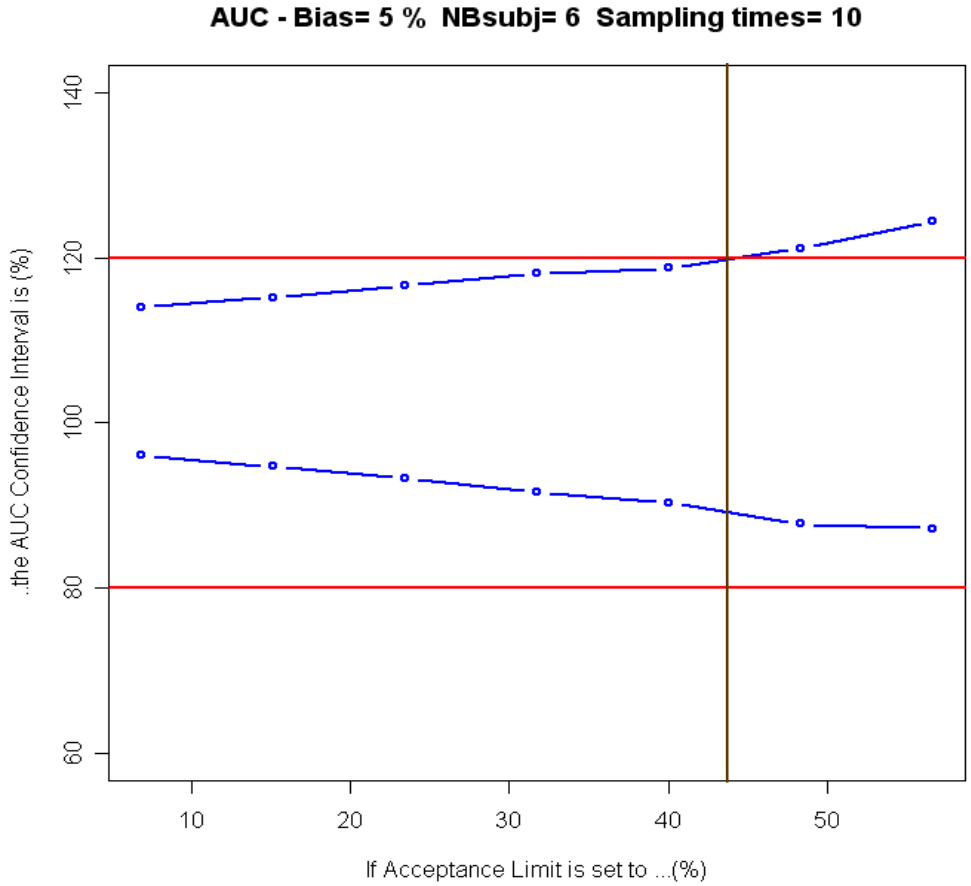
The red line represent the true (unknown) profile.

The black lines and dot represent the observations.

How will NCA PK parameters be estimated?

3. Defining acceptance limits Bioequivalence study

- AUC



Assuming a bias of 5% and a range of precision, here are the Confidence Intervals on AUC estimates as a function of the Acceptance limits, assuming the procedure reaches those limits.

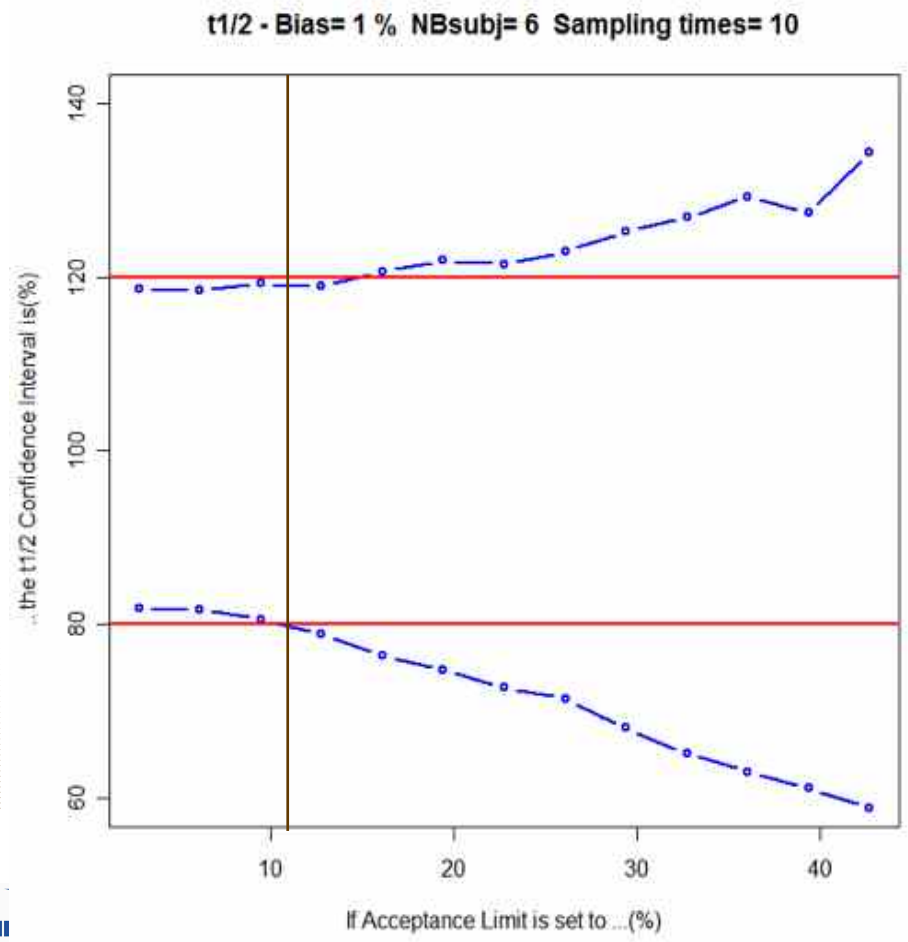
➔Using Acceptance limits of [-30%,30%] is sufficient to achieve the objective wrt AUC, with 6 subjects and 10 sampling times per subject.

➔Make sense because AUC is a sum of many measurements.

3. Defining acceptance limits

Bioequivalence study

- t1/2



➔However using Acceptance limits of [-30%,30%] is NOT sufficient to achieve the objective wrt t1/2, for 6 subjects and 10 sampling times per subject.

➔Indeed less points are used for t1/2.

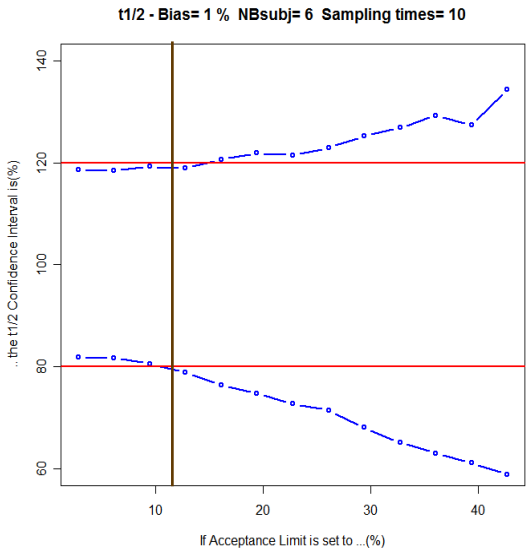
If only 6 subjects are envisaged, Acceptance Limits should not be greater than 10%

3. Defining acceptance limits

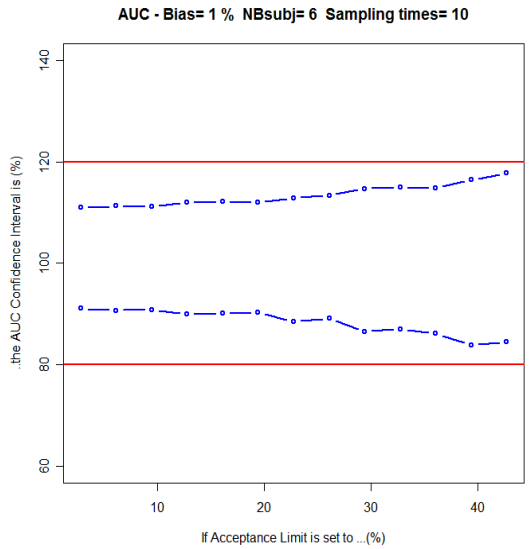
Bioequivalence study

• Accuracy of PK parameters as a function of Acceptance limits with 6 subjects in a study

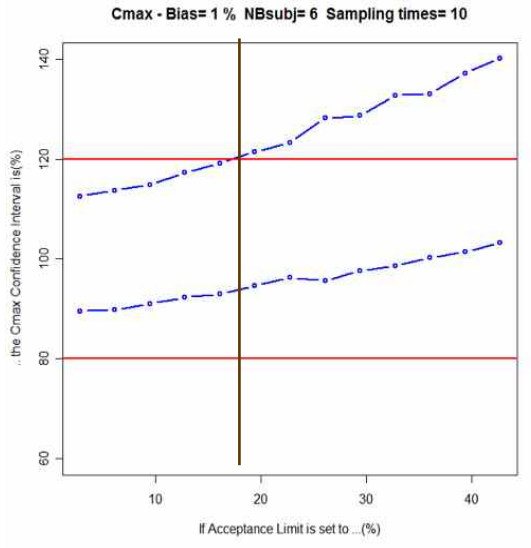
t1/2



AUC



Cmax

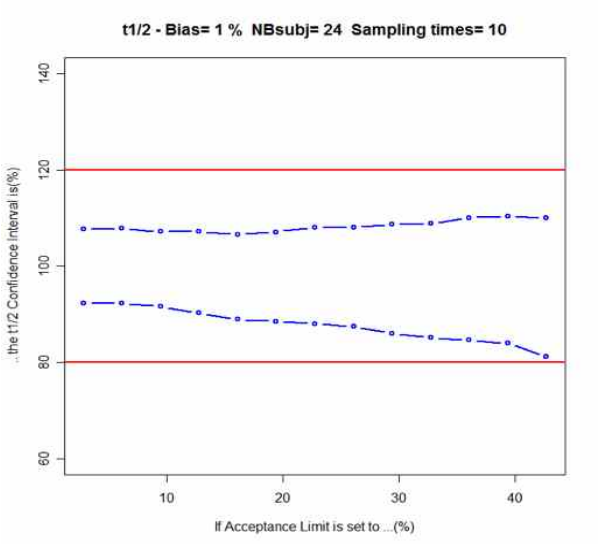


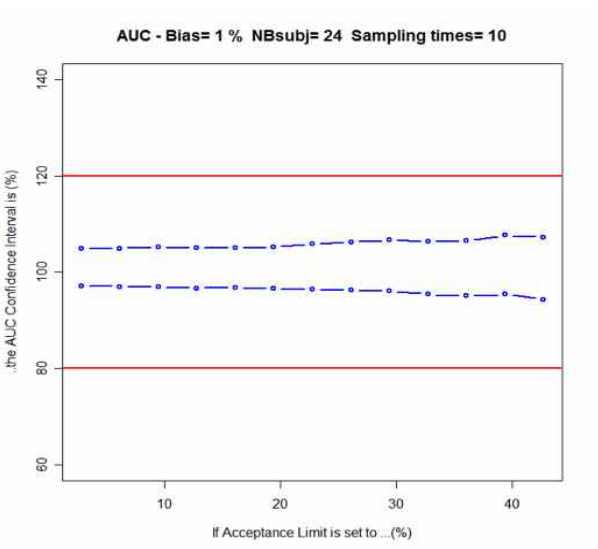
If only **6 subjects** are envisaged, Acceptance Limits should not be greater than **10%-15%** to likely demonstrate equivalence of equivalent formulations

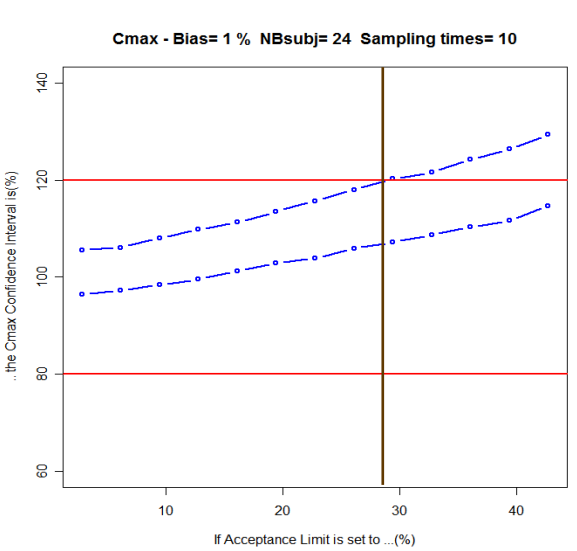
3. Defining acceptance limits

Bioequivalence study

- Accuracy of PK parameters as a function of Acceptance limits with 24 subjects in a study





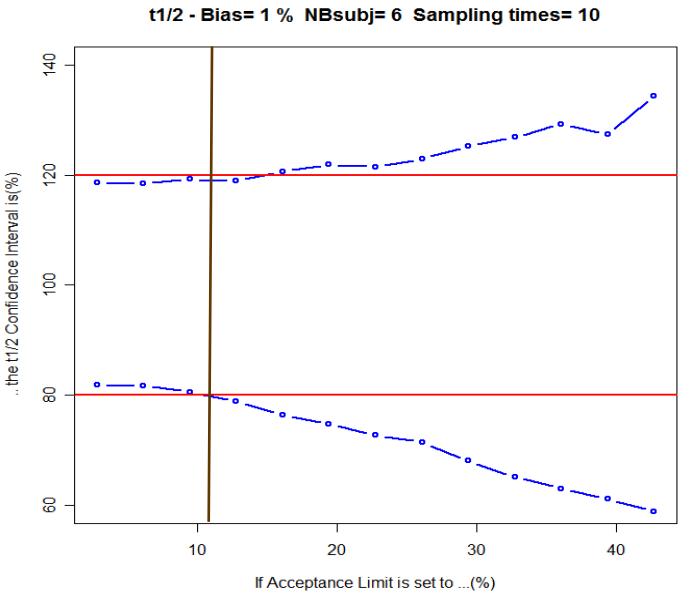


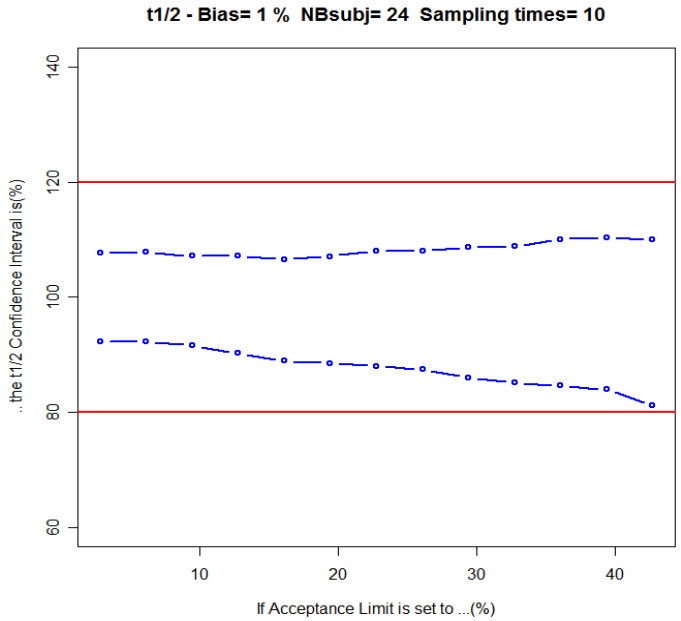
If **24 subjects** are envisaged, usual Acceptance Limits +-20% or +-30% are sufficient to demonstrate equivalence of equivalent formulations

3. Defining acceptance limits

Bioequivalence study

- Acceptance Limits, ethics and costs?





What is the most cost effective strategy?

1. Acceptance limits set to [-30,30%] and enrolling 24 subjects
2. Acceptance limits set to [-10,10%] and enrolling 6 subjects

Depends on a case by case analysis.

4. Defining laboratory performances

Adaptive Design

- The objective:
  - To determine the optimal dose (ED80) within +-10mg in a Dose-Ranging study based on a biomarker.
  - A Bio-analytical procedure measures a biomarker.
- The experiment:
  - Adaptive design, cohort of 16 patients, 4 on placebo.
  - Bayesian Emax model to optimally allocate the patients.
- The question:
  - What total error should be accepted to ensure accurate estimate of optimal dose using an Adaptive Design?

4. Defining laboratory performances

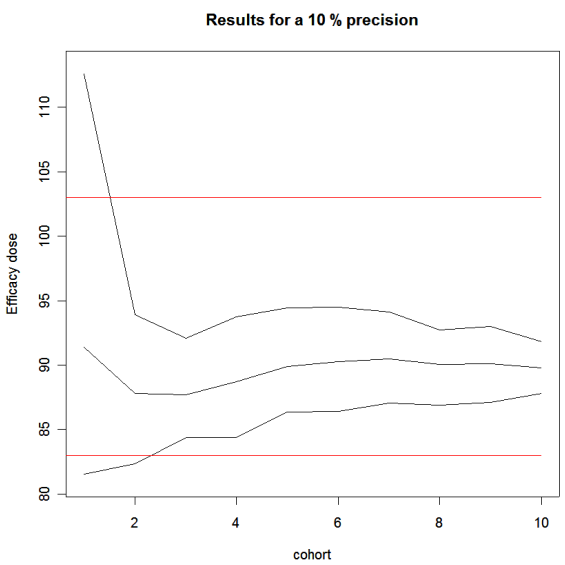
Adaptive Design

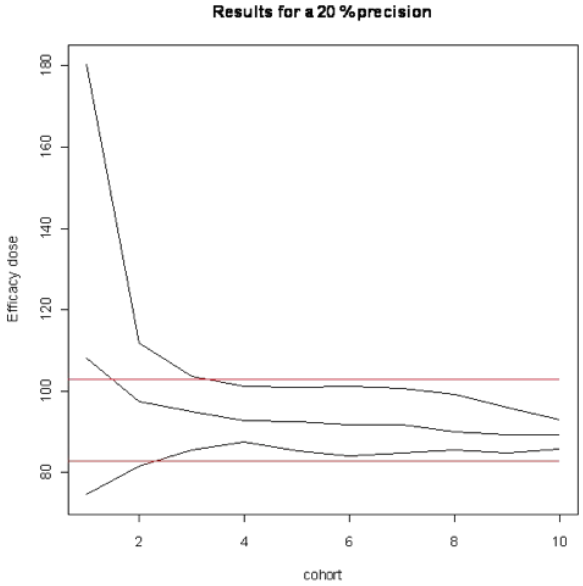
- Simulations:
  - True optimal dose : 93 mg [83mg – 103mg]
  - True Performance of the analytical method (biomarker):
    - No bias
    - CV : 10% 20% 25%

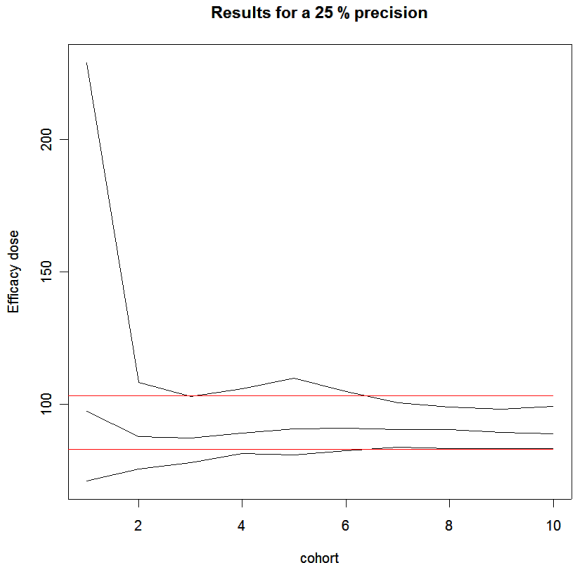
4. Defining laboratory performances

Adaptive Design

- Acceptance limits and number of cohorts/patients







True CV=10%
2 cohorts
32 patients

True CV=20%
3 cohorts
48 patients

True CV=25%
6-8 cohorts
96-128 patients

4. Defining laboratory performances

Adaptive Design

CV=20%
3 cohorts
48 patients

- Depending on the objective (ED80 vs DR) and the allocation rule, the patients are rapidly allocated at the doses of interest.
- Adaptive Designs, when logistic permits, are preferred for this type of purpose.

➔ Is it worth the tremendous efforts to set-up an adaptive design (logistic, simulations,...) ?

NB: it depends on inter-individual variability relatively to assay precision

➔ Knowing min. true performance allowed, the acceptance limits and decision rules can be derived to ensure performance will be met.

Conclusion

- Making a decision based on the predictions of future results is the very objective of validation
- The use of Tolerance Interval has been proven effective.
- The Acceptance Limits should be established as a function of the intended use of the results. Start with the end in mind.
- Derive the practical acceptance limits depending on the whole context (sample size, computation methods,...).
- Be business minded: make a cost-effectiveness analysis before locking a decision. Make simulations.

Thank you !