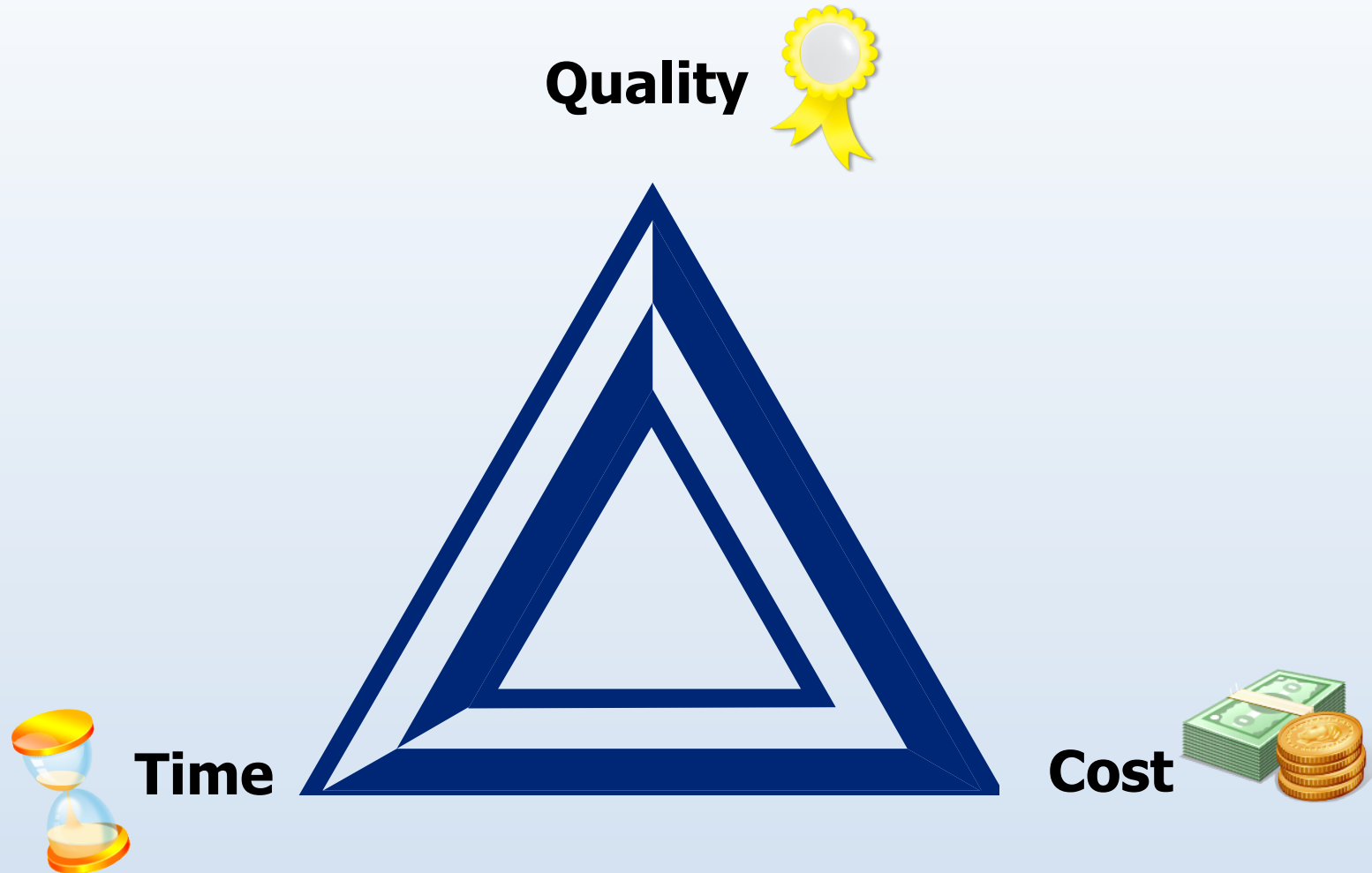


BeST – Bioequivalence Study Template

Pekka Heikkilä, CEO
StatFinn Oy

Introduction

Project Triangle



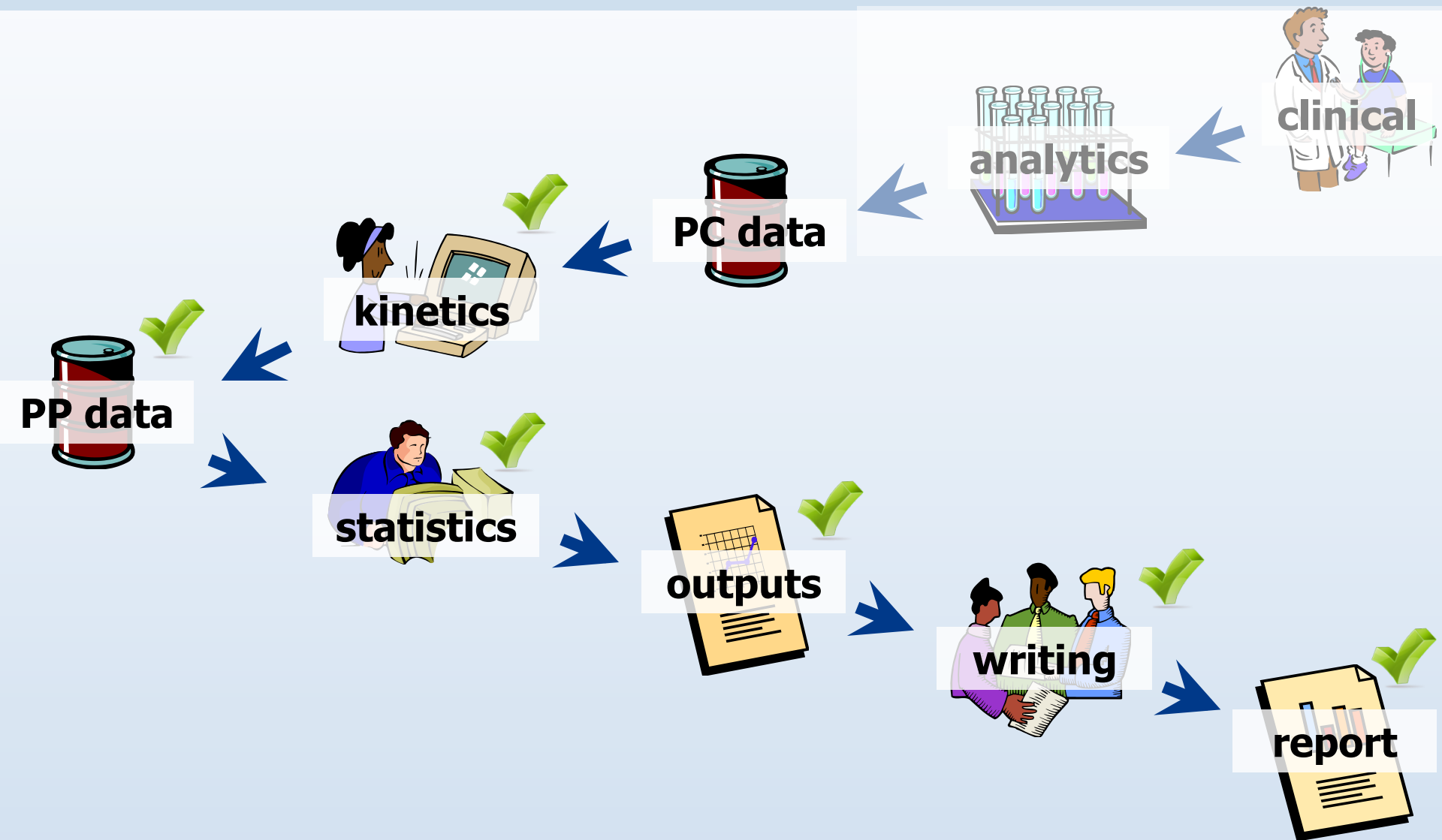
Introduction

Bioequivalence Study

- **Pharmacokinetic** two-by-two cross-over study is frequently used in drug development to evaluate **bioequivalence** of two products.
- The bioequivalence studies are strictly **regulated** and are therefore repeated in similar and **standardized** manner.

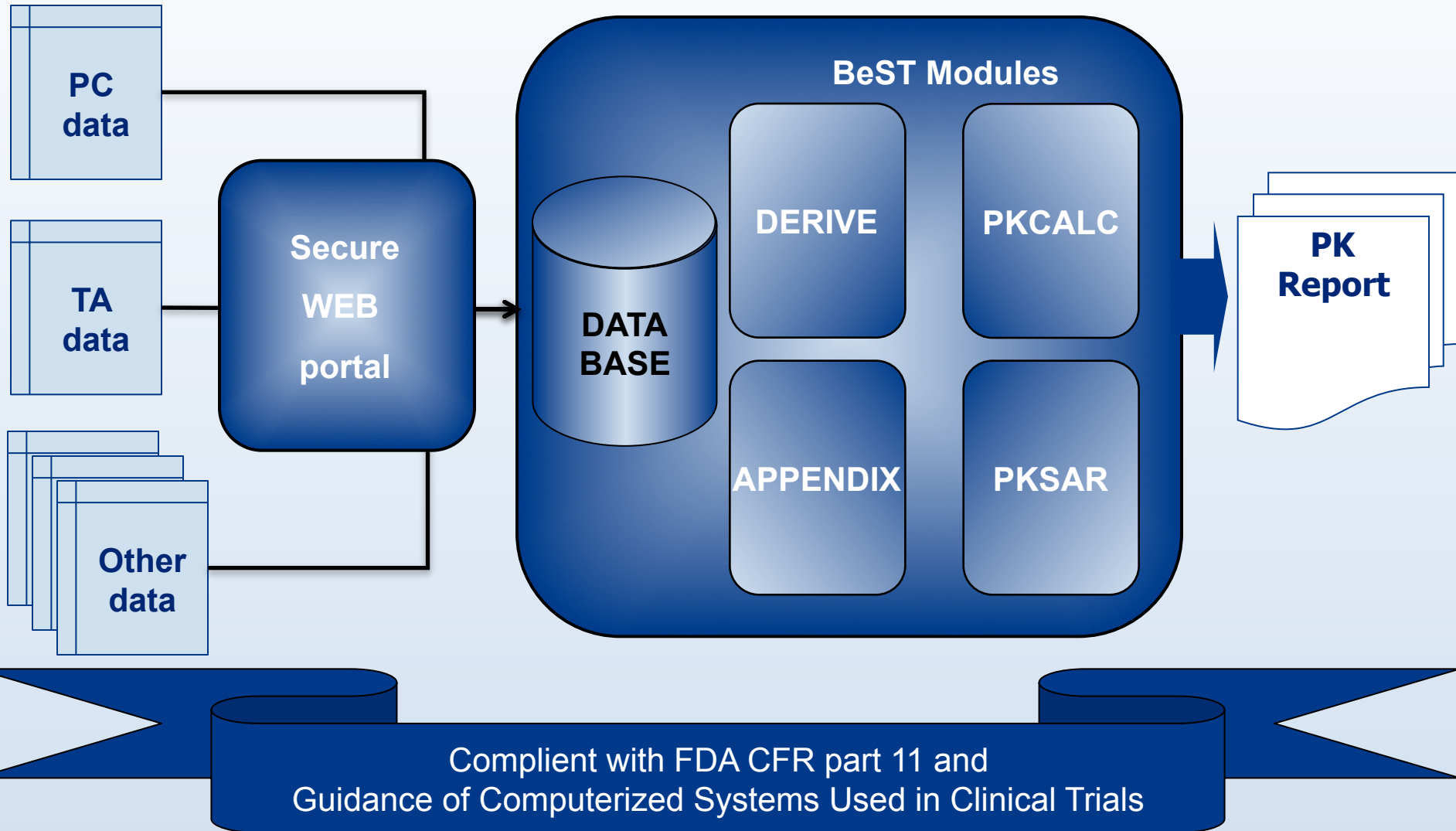
Introduction

Study Process



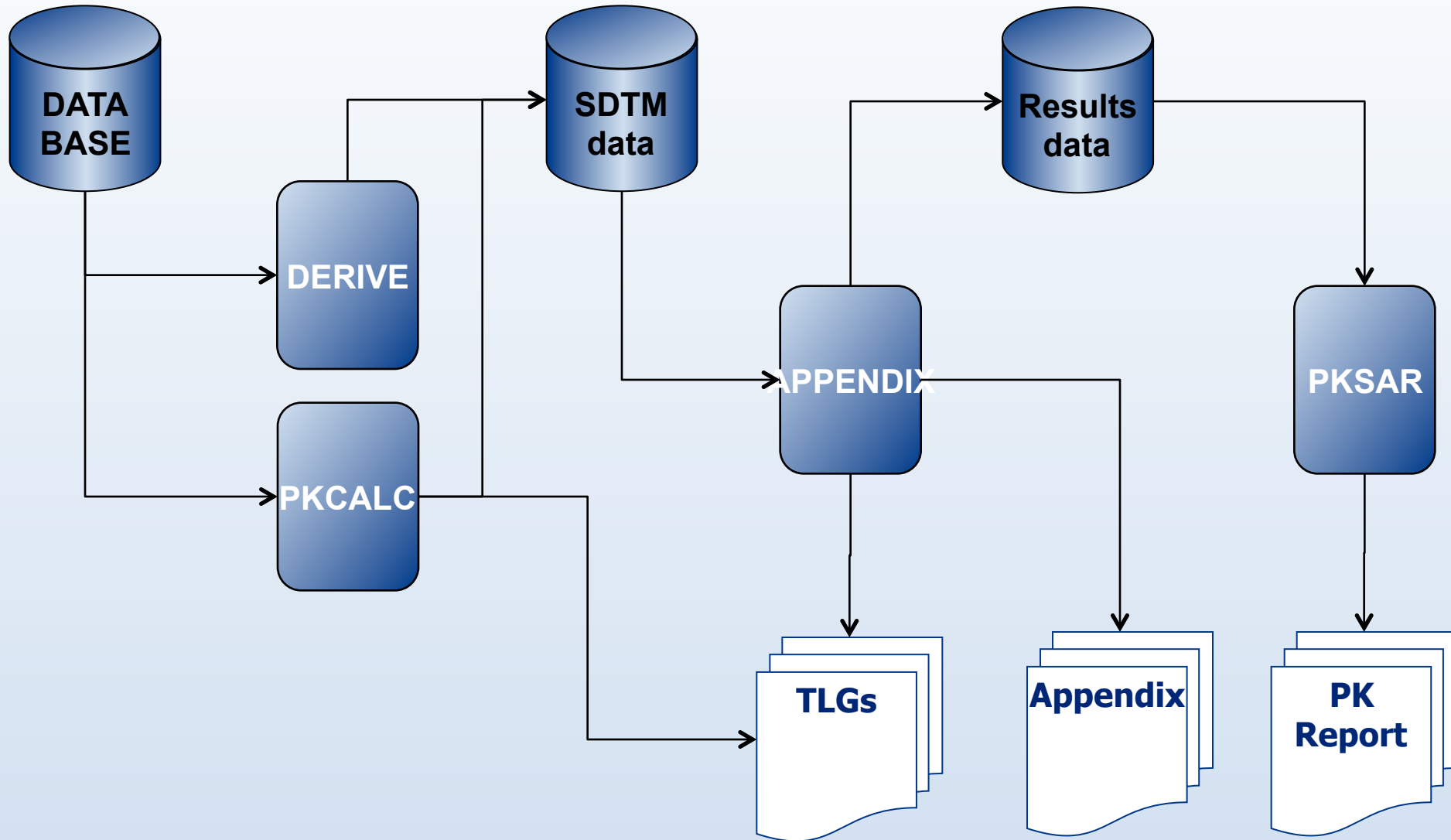
eBeST Process

Overview



BeST Process

SAS Modules



Input Data

Concentration Data (PC)

- The main source data is concentration data with the following required variables
 - ⌚ unique identifier for each subject (USUBJID),
 - ⌚ description of the sample (ETCD, PCTEST),
 - ⌚ collection time of the sample (PCDTC),
 - ⌚ obtained result (PCORRES) and
 - ⌚ reference time (PCRFTDTC).
- Rest of the variables and format to meet SDTM specifications are derived.

Input Data

Study Design Data (TA)

- In the study design data we are collecting information regarding
 - periods (VISITNUM),
 - treatments (ETCD) and
 - treatment sequences (ARMCD).
- This is the information needed to analyze the data according design of the study.

Input Data

Additional Data

- In addition to the minimum required data PC and TA additional information is collected from the web portal and used as meta information for the report.
- The BeST tool can also be used to report other datasets (DM, VS, PE, AE etc...) or use calculated PK parameters as its input.

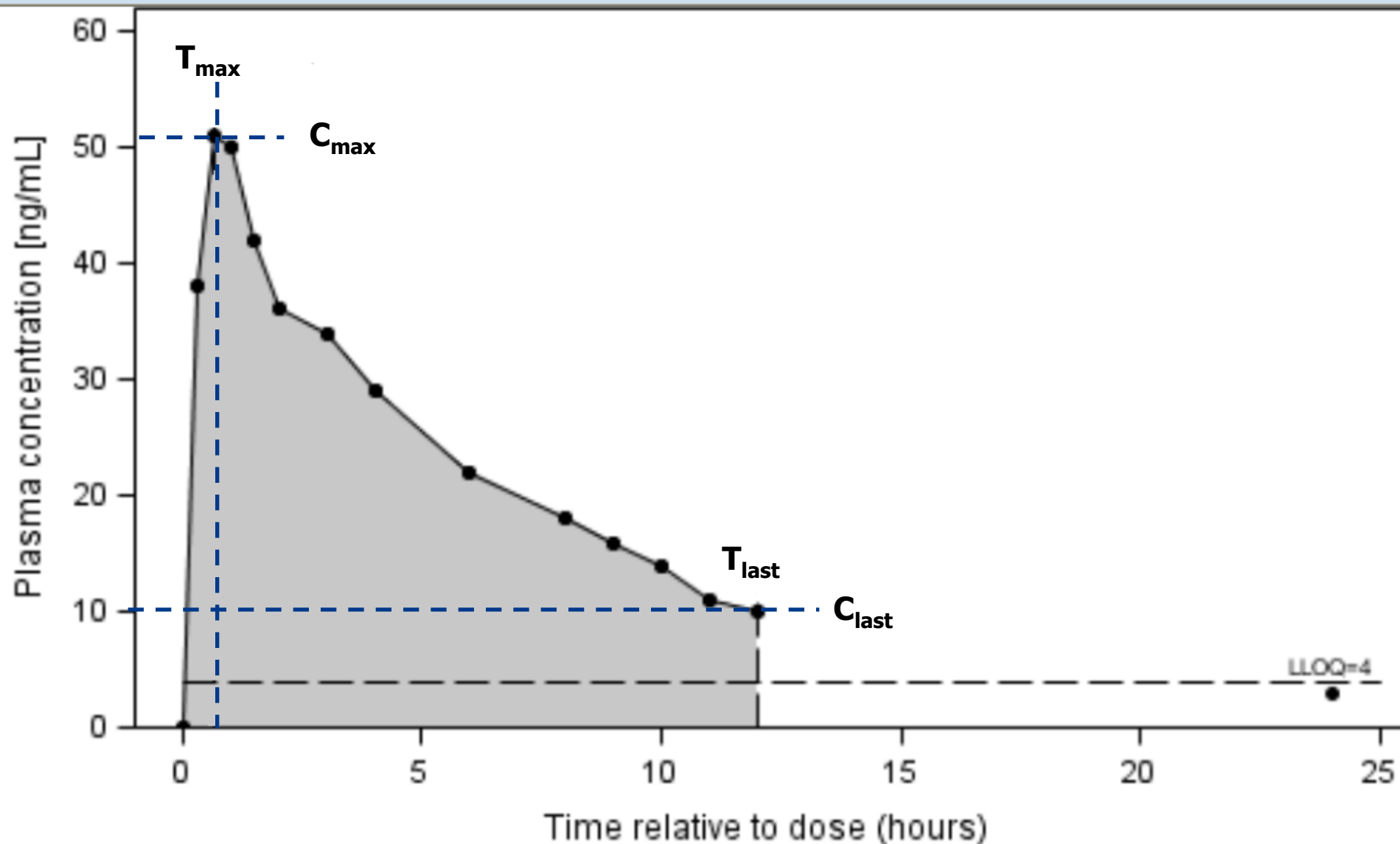
Calculation of Pharmacokinetic Parameters

C_{max}-T_{max}-C_{last}-T_{last}-AUC_t

- The pharmacokinetic parameters are calculated based on non-compartmental analysis.
- The following parameters are collected directly from concentration data
 - ⌚ Maximum concentration in the plasma (**C_{max}**) as the highest plasma concentration value,
 - ⌚ The time when C_{max} is reached (**T_{max}**),
 - ⌚ The last observed concentration above limit of quantification (**C_{last}**) and
 - ⌚ the time when C_{last} is reached (**T_{last}**).
- The area under the plasma concentration curve (**AUC_t**) is calculated using the linear trapezoidal rule.

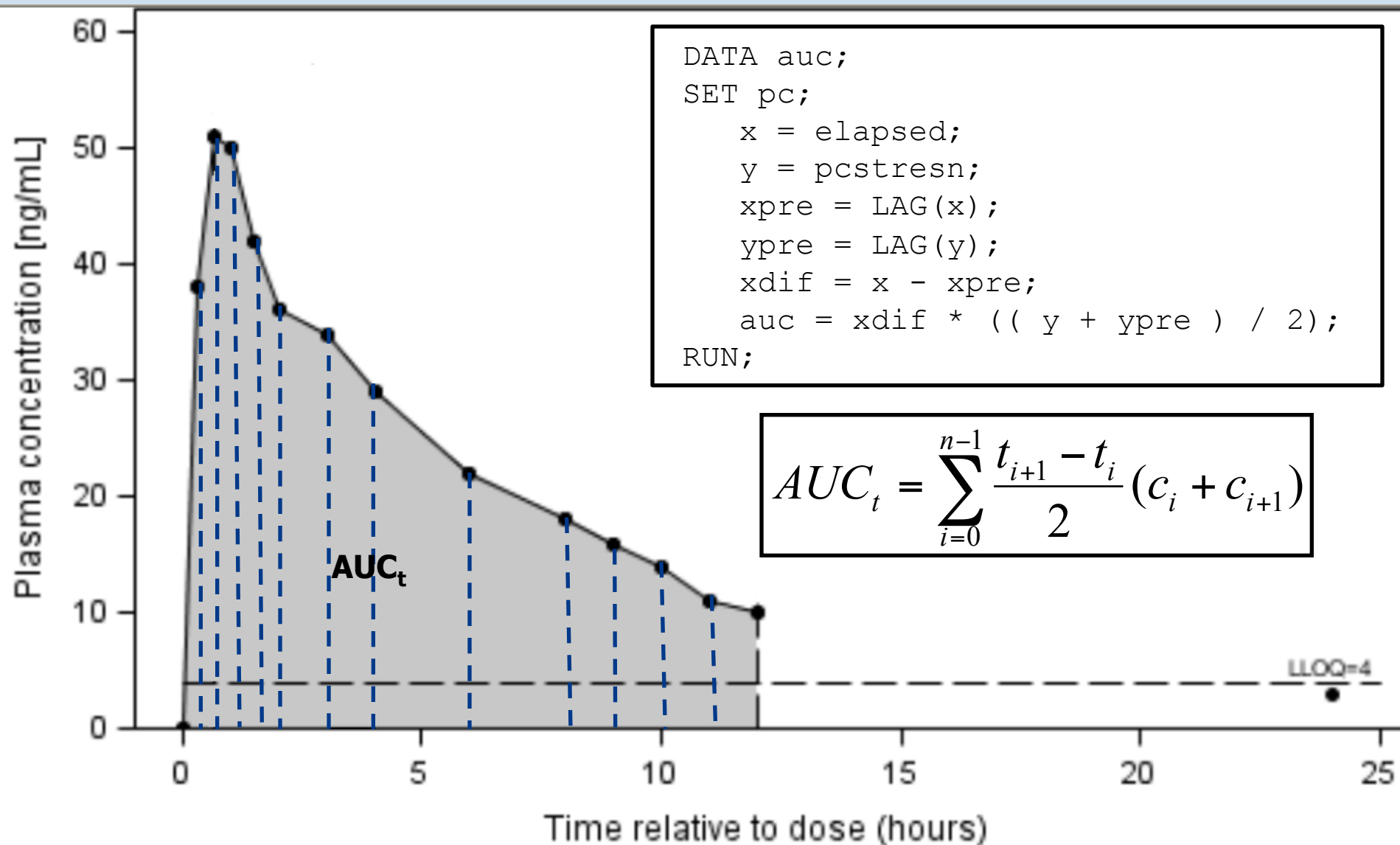
Calculation of Pharmacokinetic Parameters

C_{max} - T_{max} - C_{last} - T_{last}



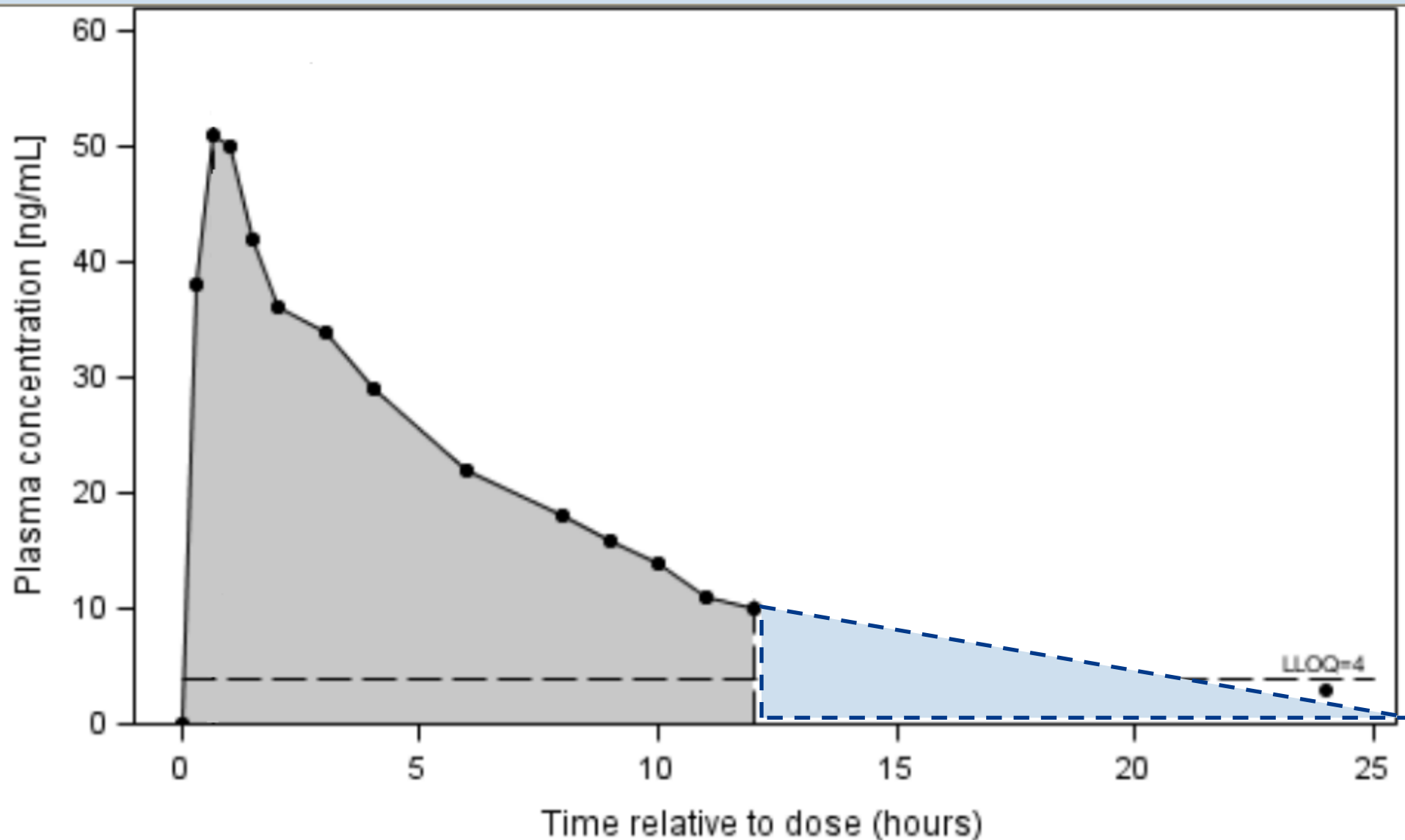
Calculation of Pharmacokinetic Parameters

AUC_t



Calculation of Pharmacokinetic Parameters

AUCinf



Calculation of Pharmacokinetic Parameters

Kel

- The elimination rate constant (K_{el})
 - ⌚ describes the rate of decrease in concentration per time.
 - ⌚ is estimated from the log-linear terminal part of the concentration-time curve, as the slope of natural logarithm of concentration against time.
 - ⌚ Data points that belong to the terminal log-linear phase are evaluated based on coefficient of determination, which is calculated with Huber's M robust regression.
 - ⌚ For each patient the highest coefficient is selected and the corresponding regression model is used in the estimation of K_{el} .

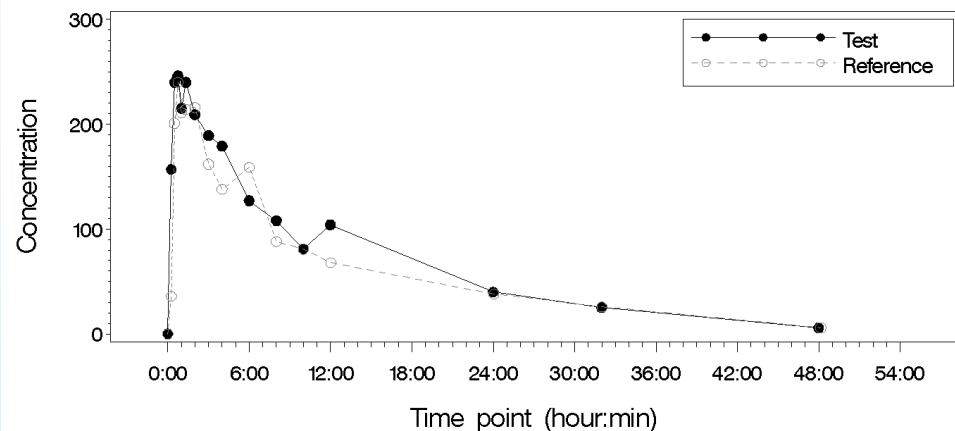
$$Y = \beta_0 + \beta_1 X + \varepsilon$$

```
PROC ROBUSTREG DATA=pc  
    METHOD=M(CONVERGENCE=COEF(EPS=0.0001) MAXITER=999999);  
MODEL log_conc = elapsed;  
RUN;
```

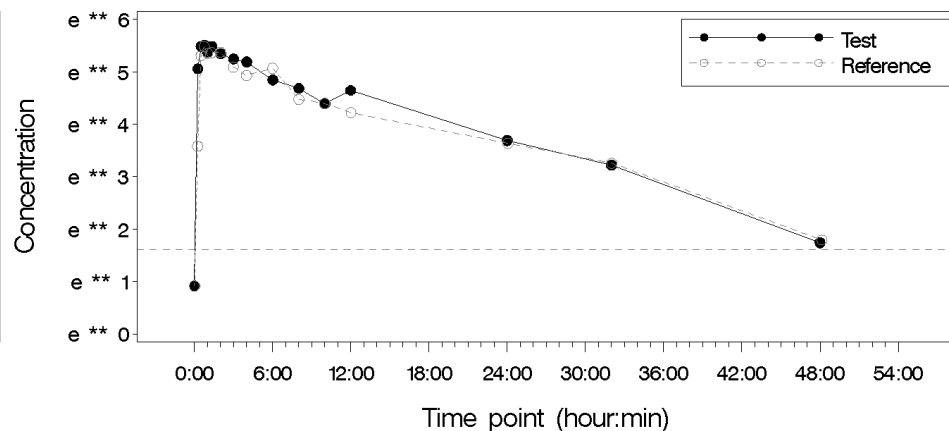
Calculation of Pharmacokinetic Parameters

Kel

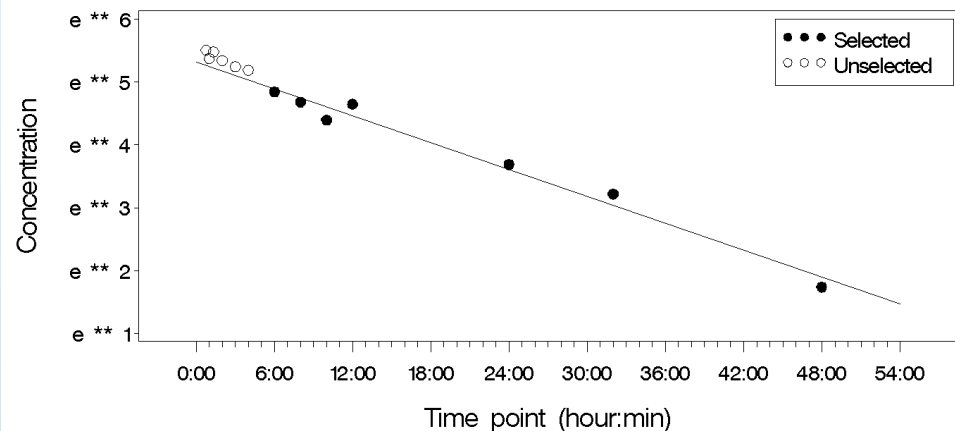
Concentration curve by Formulation



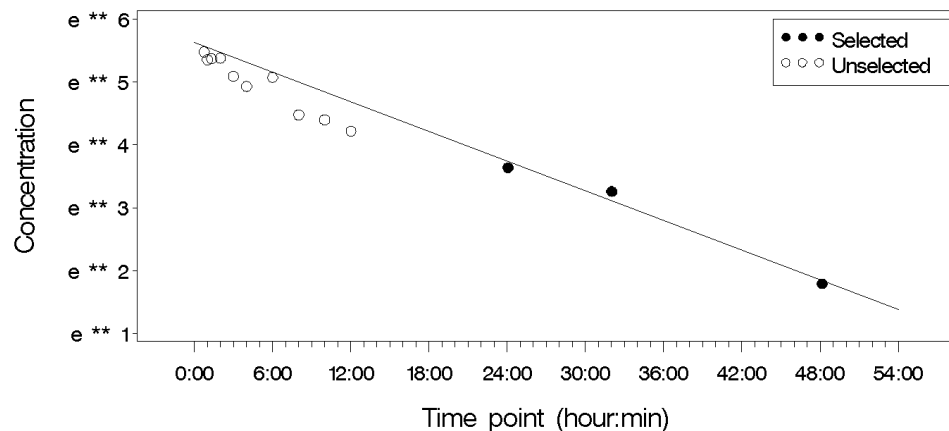
Concentration curve by Formulation (log-scale)



Concentration curve with regression line (Tmax—Tlast) for Test



Concentration curve with regression line (Tmax—Tlast) for Reference



Calculation of Pharmacokinetic Parameters

Kel, Thalf, AUCinf, AUCextrap

$$T_{1/2} = \ln(2) / K_{el}$$

$$AUC_{\infty} = AUC_t + (C_{last} / K_{el})$$

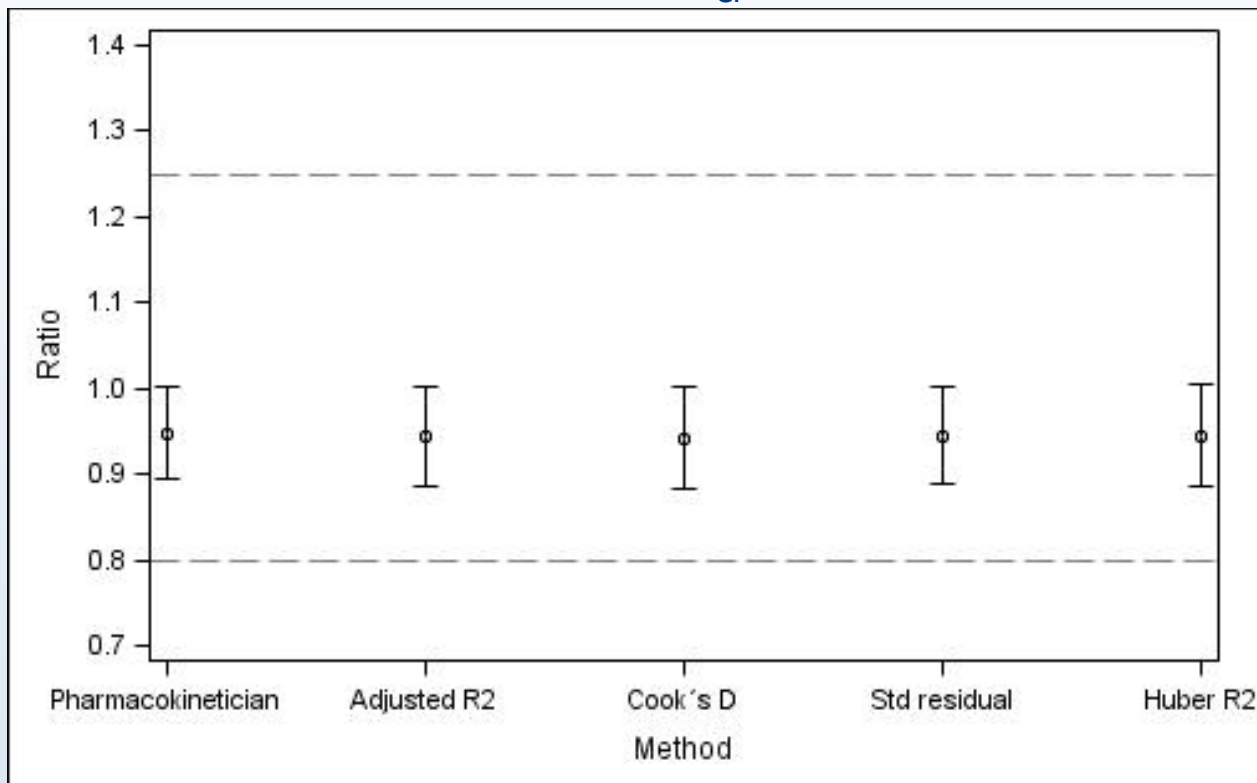
Formulation	Number of points	Selected	R square	Time range	Cmax	Tmax	AUCt	Kel	AUCinf	Thalf	AUCextrap
Test	3	No	0.9177	23.98	246	0.75	2903.6583	0.0828	2972.4795	8.37	2.3
	4	No	0.7160	36.00	246	0.75	2903.6583	0.0807	2974.2495	8.58	2.4
	5	No	0.8604	37.98	246	0.75	2903.6583	0.0736	2981.1388	9.42	2.6
	6	No	0.9173	39.98	246	0.75	2903.6583	0.0718	2983.0989	9.66	2.7
	7	Yes	0.9242	41.98	246	0.75	2903.6583	0.0712	2983.7548	9.74	2.7
	8	No	0.8915	43.98	246	0.75	2903.6583	0.0726	2982.1189	9.54	2.6
	9	No	0.8823	44.98	246	0.75	2903.6583	0.0735	2981.2259	9.43	2.6
	10	No	0.8818	45.98	246	0.75	2903.6583	0.0742	2980.4668	9.34	2.6
	11	No	0.8558	46.65	246	0.75	2903.6583	0.0752	2979.4164	9.21	2.5
	12	No	0.8486	46.98	246	0.75	2903.6583	0.0753	2979.3339	9.20	2.5
	13	No	0.8459	47.23	246	0.75	2903.6583	0.0759	2978.7549	9.13	2.5

$$AUC_{extrap} = 100 \times [(C_{last} / K_{el}) / AUC_{\infty}]$$

Calculation of Pharmacokinetic Parameters

Comparison of Methods

Ratio of AUC_{∞} with different K_{el} evaluation methods



The bioequivalence conclusion based on AUC_{∞} is the same for any of the methods presented above.

Statistical analysis

Analysis of Variance Model

- The **assessment of bioequivalence** is based upon **90% confidence intervals** for the ratio of the population geometric means for the pharmacokinetic parameter.
- A confidence interval for the difference on the log scale between formulations is obtained from **analysis of variance model** and then back-transformed to obtain the desired confidence interval for the ratio on the original scale.

$$Y_{ijk} = \mu + \xi_{ik} + \pi_j + \tau_{jk} + \gamma_k + \varepsilon_{ijk}$$

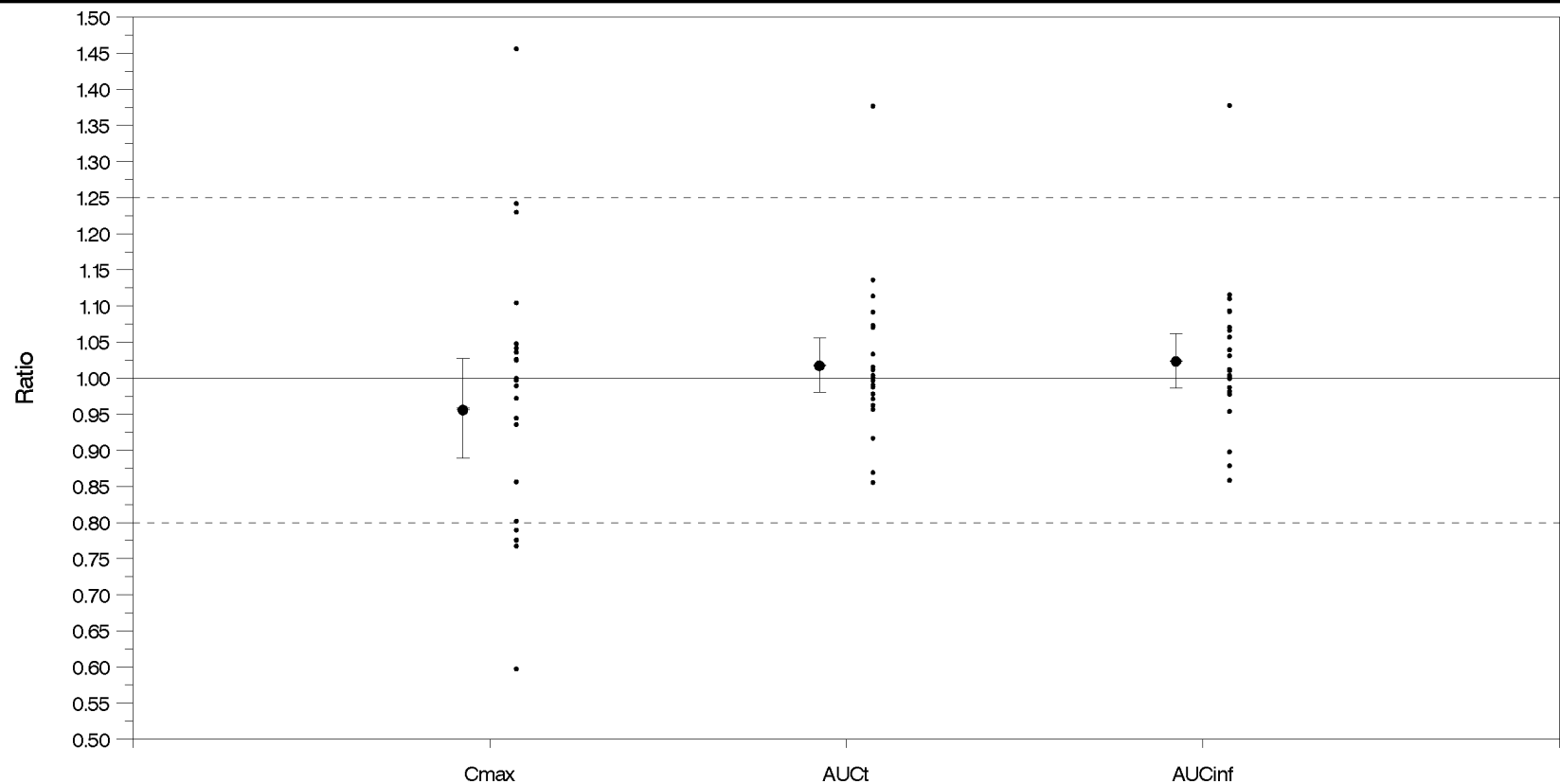
```
PROC MIXED DATA=pp ORDER=internal;  
  CLASS usubjid armcd visitnum etcd;  
  MODEL log_var=armcd visitnum etcd;  
  RANDOM usubjid/armcd;  
  ESTIMATE 'Test / Reference' etcd -1 1 / ALPHA=0.1 CL;  
  LSMEANS etcd / ALPHA=0.1 CL;  
RUN;
```

Statistical analysis

Analysis of Variance Model

Table 14.2-2.1-3 Summary statistics and statistical analysis of AUC_t (hr*g/l) for Metabolite (Page 2 of 2)

Effect	NDF	DDF	F-test	p-value
Treatment	1	20	1.394	0.2515
Sequence	1	20	0.285	0.5994
Period	1	20	0.004	0.9527



Pharmacokinetic Analysis Report

Outputs

Graphics

- Estimated geometric mean ratios
- Mean concentration-time profiles
- Overlaying individual concentration-time profiles
- Individual concentration-time profiles

Tables

- Descriptive statistics of demography
- Summary statistics of PK parameters
- Statistical analysis for PK parameters
- Summary statistics of concentrations
- Summary statistics of sampling times

Listings

- Demographical variables
- Individual subject ratios (Test/Reference)
- Listing of individual PK parameters
- Individual concentration data
- Adverse events

PK calculations

- Individual subject concentration graphs (semi-log)
- Individual subject concentration graphs (Tmax-Tlast)
- Line plot (All possibilities)
- Summary of exclusions
- Summary table with all possibilities (Points, Kel, AUCt/AUCinf, ...)

Pharmacokinetic Analysis Report

Outputs



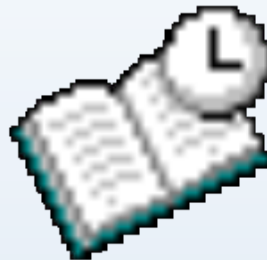
Appendix 1



Appendix 2

Pharmacokinetic Analysis Report

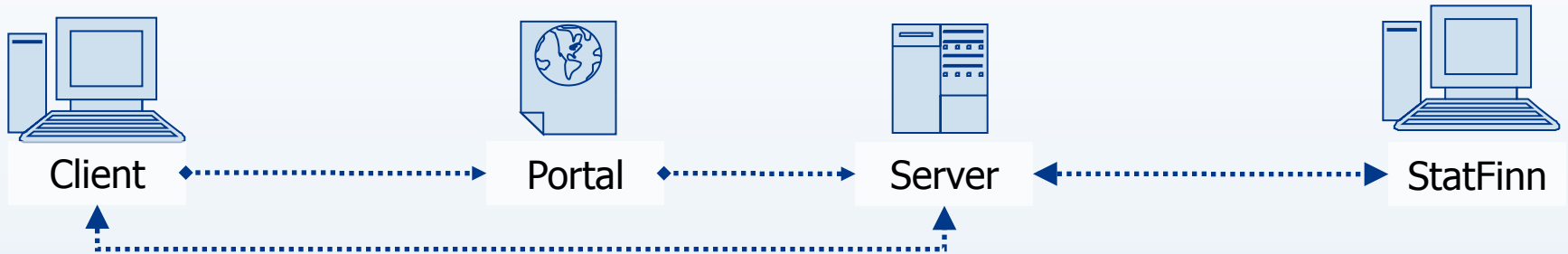
Report



Pharmacokinetic
analysis report

System Safety

Data Security

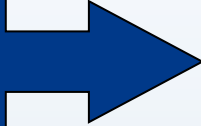


- Connections secured with the SSL encryption.
- Data stored directly to the server behind a firewall.
- Version controlled environment build on server.
- VPN connection used to access the server.

Summary

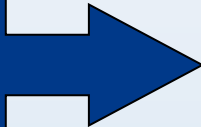
Benefits

**Keep with
Timelines**



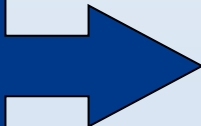
Final pharmacokinetic analysis report from a concentration data reported within a day.

**Control your
Budget**



Standardizing routine and repeated tasks to have resources in more demanding activities.

Top Quality



Validated system with automated calculation of pharmacokinetic parameters.

Kiitos !

