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Programming Approaching for PK Analysis

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ABSTRACT

PK analysis is one of important part in clinical trials' work. In this paper, we will discuss the category of PK trials; the object of the PK analysis and what will be included in; the statistical programming methods will be used for PK analysis; and how to approach the PK results from programmers' view. In this paper, we will use some example and code to illustrate below topics.

INTRODUCTION

I would like to introduce my paper from below points:

- Category of PK Studies
- Object of PK Analysis
- Overview of Object and Statistical method
- Programming approaches and methods
    - descriptive statistics
    - BE study
    - Exposure-response study
- Summary

CATEGORIES OF PK STUDIES

There are various PK studies in our clinical trials, but from the aspect of study's type, I think we can have two general types:

One, first time in humans PK analysis, we call it FTIH for short.

This kind of study usual small in population, and with dose-escalation process. And the propose is to evaluate the safety, tolerability of the drug. Based on the results we want to build the PK profile on each dose level and aiming to determine the dose in consequent studies.

Two, bioavailability or bioequivalence study.

This kind of study should after the first-time-in-humans study and to further exploring the drug characters. We usually use crossover or parallel-controlled design to compare the effect in different phase. Some studies in our daily work, e.g., FOOD-effect (FE) study, or Drug-Drug Interaction (DDI) study, are belonging to this kind of.

OBJECT OF PK ANALYSIS

The objective of PK trials usually including:

One, concentration-time profile data per subject. The example shows like in the Figure 1. And red box shows the concentration results for each timepoint for one subject.

Subject	Nominal Day	Nominal Time	Concentration (μg/mL)	LLOQ	ULOQ
05-404	C1D1	给药前30min内	BQL	25ng/mL	2400ng/mL
05-404	C1D1	给药后0.5h	25.5	25ng/mL	2400ng/mL
05-404	C1D1	给药结束即刻	84.3	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后2h	77.9	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后6h	67.2	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后24h	49.5	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后48h	29.3	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后72h	23.7	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后168h	8.47	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后240h	2.86	25ng/mL	2400ng/mL
05-404	C1D1	给药结束后336h	0.965	25ng/mL	2400ng/mL
05-404	C2D1	给药前30min内	BQL	25ng/mL	2400ng/mL
05-404	C3D1	给药前30min内	0.329	25ng/mL	2400ng/mL
05-404	C3D1	给药后#0.5h	62.0	25ng/mL	2400ng/mL
05-404	C3D1	给药结束即刻	18.5	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后2h	50.6	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后6h	57.6	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后24h	204	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后48h	39.7	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后72h	28.0	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后168h	12.0	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后240h	6.94	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后336h	3.07	25ng/mL	2400ng/mL
05-404	C3D1	给药结束后504h	0.581	25ng/mL	2400ng/mL

Figure 1 Concentration-time Profile Data

Two, the parameters' value for per subject and we can have simpler statistical analysis base on population. This picture shows the parameters we get from *WinNonlin* software.

ubject	N_Sample	Dose	Rsq_adjusted	Lambda_z	HL_Lambda_z	Tmax	Cmax	Tlast	AUClast	AUCINF_obs	AUC_%Extrap_	Vz_F_obs	Cl_F_obs	MRT
		mg/kg		1/h	h	h	ng/ml	h	h*ng/ml	h*ng/ml	%	ml/kg	ml/h/kg	h
01-101	9	0.6	0.988982427	0.024839853	27.90464083	1.5	12.5	239.73	481.7768817	483.3630424	0.328151018	49972.23629	1241.303011	39
01-201	11	1.2	0.98238942	0.013981272	49.57683125	1.53	26.4	502.72	1674.815076	1677.010871	0.130935015	51179.81034	715.5588679	72
01-301	11	2.4	0.990397692	0.010870243	63.7655646	1.57	57.8	527.28	4666.442934	4694.501184	0.597683319	47030.81851	511.2364244	12
01-302	11	2.4	0.989251636	0.009738921	71.17289557	7.58	77.6	504.3	4879.113388	4933.328841	1.0989629	49952.85907	486.4869295	12
03-303	11	2.4	0.996206829	0.008682451	79.83312084	3.3	89.4	503.6	5921.698617	6003.587934	1.364006283	46042.40616	399.7609474	10
04-401	11	3.6	0.98657637	0.007624697	90.90816138	1.62	79.2	503.47	8315.59037	8501.82728	2.19055156	55535.10997	423.4383835	12
04-402	11	3.6	0.989316038	0.009201415	75.33050144	3.62	85.9	503.33	9959.738122	10141.23195	1.789662558	38579.55215	354.9864569	13
03-403	11	3.6	0.98864425	0.008800605	78.76130807	25.67	96.8	503.55	9351.992062	9512.208316	1.68432238	43003.97565	378.4610135	12
05-404	11	3.6	0.999847391	0.013517836	51.27648895	1.62	96	506.33	6522.970768	6531.773952	0.134774781	40772.20258	551.1519576	80
03-406	11	3.6	0.986122247	0.007301529	94.93177905	3.58	86	505.2	9503.99888	9721.761475	2.239949987	50715.84877	370.3032634	12

Figure 2 Parameters' Value for per Subject

Three, exploring the dose-response based on selected parameters among results from WinNonlin, and the typical measures like Cmax, AUC and tmax. By log transformation Power model, we can get linear model like shows in Figure3.

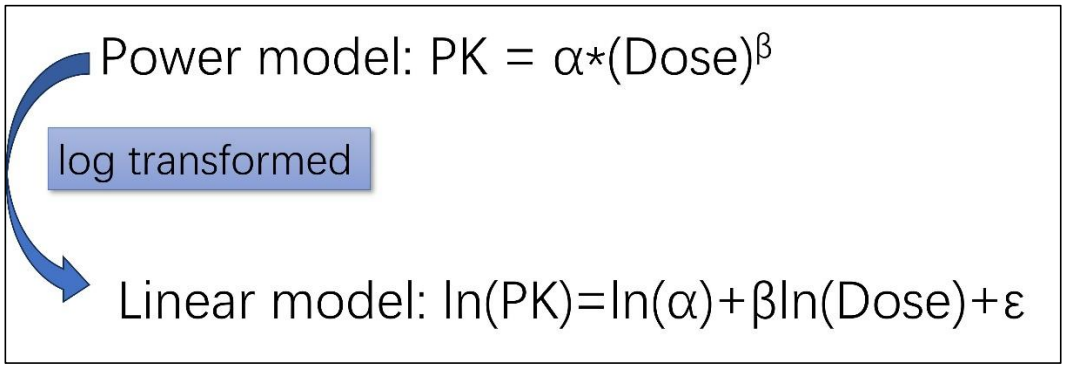

Figure 3 Power Medel Log Transformation

OVERVIEW OF OBJECT AND STATISTICAL METHOD

Before getting into PK analysis methods, firstly introduces three common parameters.

C_{max} indicates the maximum concentration. The peak in Y- axis, which you can see in the Figure 4.

t_{max} indicates the amount of time that a drug is present as the maximum concentration. You can see the vertical line shows in the Figure 4.

AUC indicates the area under the plasma drug concentration versus time cure. You can see the shadow in the Figure 4.

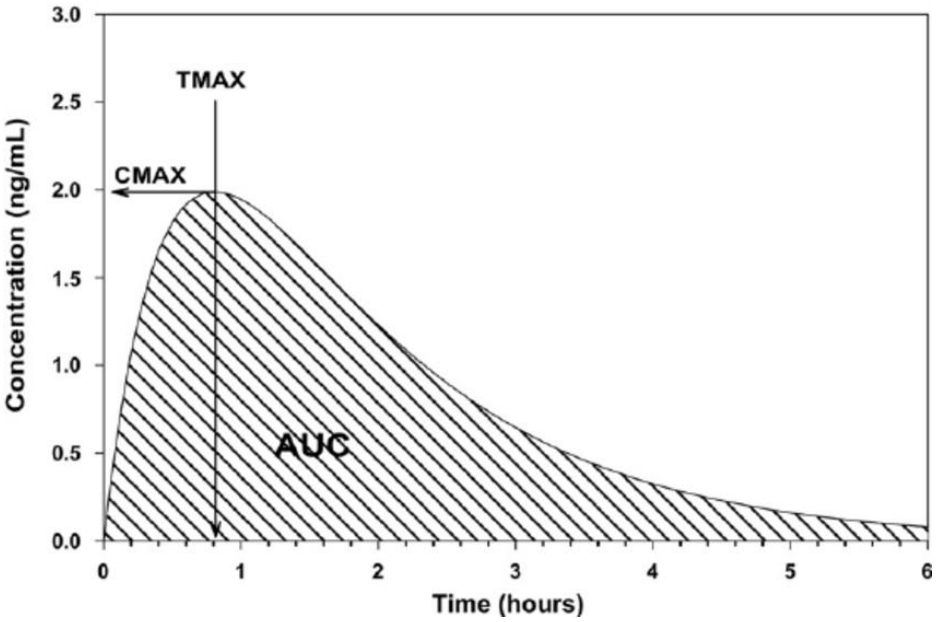

Figure 4 PK Parameters illustration

Table 1 summarized three objects and corresponding statistical methods, and the datasets will be used.

For concentration analysis, we used descriptive statistics in tables, and the listing for subjects' PK results and the mean with SD curve in figure. The datasets will be used including PC in SDTM and ADPC in ADaM.

For parameters analysis, like in BA or BE study, we used besides descriptive statistics in tables, we also used paired test or non-parametric univariate tests in table, like in FE study or DDI study. And the listing the parameters' results for each subject. The datasets will be used including PP in SDTM and ADPP in ADaM.

For dose-response analysis, we used power-law model with confidence interval criteria shows in table. And showed the relations in figure. The datasets will be used including PP in SDTM and ADPP, ADEX or ADEXSUM in ADaM.

Object	Statistical method	SDTM/ADaM datasets used
Concentration analysis	descriptive statistics in table list subjects' observed results Mean with SD curve	PC / ADPC

Parameters analysis (BA/BE study)	descriptive statistics in table paired test/Non-Parametric Univariate Tests (e.g., FE study, DDI study) list parameters' results	PP / ADPP
Exposure-response	Model results with confidence interval criteria in table display relations in figure	PP/ADPP, ADEX (ADEXSUM)

Table 1 Objects and corresponding statistical methods, and the Datasets

PROGRAMMING APPROACHES AND METHODS

First, let's look at the descriptive statistics in PK analysis. Unlike common descriptive statistics we used for continuous variables, In FDA guideline of Statistical Approaches to Establishing Bioequivalence, which recommends that the measures be log-transformed using either common logarithms to the base 10 or natural logarithms (e). Figure 5 shows 2 types of table styles which besides common results, we also displayed like co-efficient of variation (CV%), Geo-mean and Geometric CV% in table for both concentration and parameter tables.

药物浓度汇总表

PK浓度集

随机号/筛选号	分组	周期	0h C1	0.25h C2	0.5h C3	1.0h C4	1.5h C5	2.0h C6	2.5h C7	3.0h C8	3.5h C9	4.0h C10	5.0h C11	6.0h C12	8.0h C13	10.0h C14	12.0h C15	14.0h C16	24.0h C17
xxx			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xxx			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xxx			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xxx			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
…			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xxx			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
n			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean			xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x
SD			xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx
CV%			xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx
Geo-mean			xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x
CV%-GM			xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx	xx. xx
Median			xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x	xx. x
Min			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Max			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx

Figure 5 Descriptive Statistics in PK analysis style 1

7.6.2.1. 单次给药(Tab)后 PK 参数的描述性统计——PKS

参数	项目	0.6mg/kg N=1	1.2mg/kg N=1
T_{max}(h)			
	N(Nmissing)	1(0)	1(0)
	Median	1.50	1.53
	Min - Max	1.50 - 1.50	1.53 - 1.53
	Q1,Q3	1.50 , 1.50	1.53 , 1.53
C_{max}(ng/ml)			
	N(Nmissing)	1(0)	1(0)
	Median	10.40	27.20
	Min - Max	10.40 - 10.40	27.20 - 27.20
	Q1,Q3	10.40 , 10.40	27.20 , 27.20
	Mean (SD)	10.40 (-)	27.20 (-)
	CV%	-	-
	GeoMean （GeoSD）	10.40 (-)	27.20 (-)
	Geometric CV%	-	-
AUC_{0-t}(h*ng/ml)			

Figure 6 Descriptive Statistics in PK analysis style 2

In Figure 7, showing the core sentence for calculating the geometric results. The first highlighted code shows the logarithmic transformation base on natural logarithms. The second highlighted code shows calculation to the transformed results. The next one shows retransformed into the result of geomean. The last code here shows retransformed into the results of CV% based on lgsd result.

```
        .....
lgaval = log(aval) ;
        .....
proc means data = adpc n mean median std min max q1 q3 cv;
    var lgaval ;
    output out = lgmeans n=n mean=lgmean std=lgsd;
        .....
gm = exp(lgmean) ;
 gsd = exp(lgsd) ;
gcv = sqrt(exp(lgsd**2) - 1)*100 ;
```

Figure 7 Descriptive Statistics

THE BASIC CONSIDERATIONS OF BIOEQUIVALENCE ANALYSIS

Before we get into the BE study, I want to show some basic consideration of BE study.

Bioequivalence, we call it BE for short, is a study which used to consider two products to be bioequivalent in pharmaceutical ingredient.

Among parameters we got from *WinNonlin* software, recommend AUC, and C_{max} or t_{max} as PK analysis response variable.

The models we will be using including mixed-effects and two-stage linear models.

For BE study, which is a comparing tool, the criterion for testing the results is important. And the criterion is to construct a 90% confidence interval for ut – ur of the average of selected parameter. Here u indicates the average

value. T indicates test drug; R indicates reference drug. The last one, besides getting the comparing result, we also want to evaluate the sequence effects.

PROGRAM APPROACHING FOR BIOEQUIVALENCE ANALYSIS - GLM MODEL.

With these basic ideas, let's first look at GLM model. In Figure 8 shows the code for GLM model. In CLASS sentence, we list the variation of sequence, subject, period, and treatment. In MODEL sentence, the log transformation of parameter as response. From ESTIMATE sentence, we obtain the adjusted difference between treatment and the standard error of these difference.

```
proc glm data=adpp;
        ......
        class arm usubjid aperiod trt(ref='R');
        model logpk=arm usubjid(arm) aperiod trta ;
        random usubjid(arm);
        estimate 'T VS R' trta 1 -1;
        ......
```

Figure 8 GLM Model

PROGRAM APPROACHING FOR BIOEQUIVALENCE ANALYSIS - MIXED MODEL.

The next one is MIXED model (in Figure 9). Same as in GLM model, in CLASS sentence, we list the variation we want to test, and so dose in MODEL sentence. In ESTIMATE, here I used T versus R, means the ratio of test drug to reference drug, but if change to R versus T, the coefficients need change to -1 1.

```
proc mixed data=adpp;
   ......
   class arm usubjid aperiod trta(ref='R');
   model logpk=arm aperiod trt  ;
         ......
   random usubjid (arm) ;
   estimate "T VS R" trt 1 -1  /  cl alpha=0.10;
run;
```

Figure 9 MIXED Model

COMPARISON OF GLM AND MIXED.

For missing case, GLM will removes all subjects with any missing period, while MIXED model uses all observed data, even only one period in crossover design.

Which method be used in primary endpoint should be pre-specified in protocol or SAP.

PROGRAM APPROACHING FOR BIOEQUIVALENCE ANALYSIS - T_{MAX} ANALYSIS.

In prior slides, we mentioned three parameters in PK analysis, C_{max}, AUC and t_{max}, but t_{max} has some differences to other two. This page shows the difference. Please note, C_{max} and t_{max} are obtained from observational data, meaning not calculated or derived. But t_{max} variable is a categorical variable that can only take values based on the planned sampling scheme, although theoretical the result should be continuous. For example, if the planned timepoint is 0, 2,

4 and 8 hours after dose, we cannot get the 1.5-hour result. From the point of different type, for C_{max} we can use average and standard deviation for summary statistics, for t_{max} we use medians and ranges. And further, for comparison of t_{max}, we use non-parametric test.

Figure 10 shows the simple code for t_{max} analysis in BE study. In DATA step, create a difference between two related variables. e.g., in DDI study, avalt indicates the median of test drug, avalr indicates the median of refer drug. In UNIVARIATED procedure, using the variable of difference in the VAR statement.

```
data ana;
        merge indst indsr;
        by usubjid;
        if n(avalt,avalr)=2 then diff=avalt-avalr;
.....
proc univariate data=ana;
        var diff;
run;
```

Figure 10 t_{max} Analysis

There are some tips for t_{max} analysis. For related samples, like before and after meal on single group of subjects in FE study, in another way, we also call it paired samples or matched pairs test. In UNIVARIATED procedure performs a Wilcoxon signed rank test and a sign test for default.

But for two independent samples, we recommended use NPAR1WAY procedure, and for details test method, please first discuss with your statistician team or depends on data distribution.

INTRODUCTION OF EXPOSURE-RESPONSE.

Next and last section let's talk about exposure-response. The exposure -response we call it as ER for short, is a tool that estimate the pharmacokinetics characters or saturability on modeling selected parameters (like C_{max}, AUC) and expose level.

For Power model, which describe the PK and dose relationship, after log transformed, if the hypothesis is linear relation.

There are different types of ER analysis models:

1. the linear regression models using the procedure of REG or GLM
2. simpler linear regression with estimate statement using GLM
3. simpler nonlinear regression models (without multiple variance components) using procedure NLIN
4. nonlinear regression with estimate random effects (same as MIXED procedure in BE study) using PROC NLMIXED

Figure 11 shows the REG procedure. In MODEL sentence, log transformed PK value as response variable, and log transformed dose value as test variable, CLB option here computes 100(1-α)% confidence limits for the parameter estimates.

```
proc reg data = adpp alpha= 0.1 plots=none ;

   model lgaval = lgdose/clb ;

   ods output parameterestimates = parameterestimates ;

run;
```

Figure 11 REG Procedure

In GLM procedure, similar like in REG, and the SOLUTION option produces a solution to the normal equations for the parameter estimates. And CLPARM option produces confidence limits for the parameter estimates.

```
proc glm ;

 model lgaval = lgdose/ solution clparm alpha = 0.1 ;

run;
```

Figure 12 GLM Procedure

Results are showing in this page. The criteria is usual $1+\ln(\theta_L)/\ln(r) \sim 1+\ln(\theta_H)/\ln(r)$. If the 90% CI full fall into the CI, like showing in the axis, the conclusion is having linear relationship between exposure and the PK parameter (and here is Cmax). Else the conclusion will be not linear relationship but can be further research other relation.

CONCLUSION <HEADING 1>

PK analysis is part of clinical trial, and also one mainly works for SAS programmers. This paper just introduced some points we used. The model and options used can be discussed more further and deeper. But the statistical methods can be used by the analysis propose. We recommend that discuss the method and model with team members, especially with medicine and statistician.

REFERENCES

SAS® Help Center

https://documentation.sas.com/doc/en/helpcenterwlcm/1.0/home.htm

CONTACT INFORMATION <HEADING 1>

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