PHARMACOKINETIC ANALYSIS USING SAS®: A BOON FOR CLINICAL RESEARCH INDUSTRY

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ABSTRACT

Pharmacokinetics (PK) is the study of fate of drug after its administration to the subject which involves studies of the absorption, distribution, metabolism and elimination (ADME) in human or animal though their body fluids (blood or urine). A single pharmacokinetic profile encompasses C_{max}, T_{max}, $t_{1/2}$, AUC, etc. In a clinical research study, a large number of data are collected from the subjects during clinical trial. The data may be from different sources and it may be in different format. Hence, their retrieval, storage and analysis is a major concern in a Clinical Research Organization (CRO). To deal with those data so as to determine the pharmacokinetic parameters an authentic, validated, reliable and suitable system is required and as per the prevailing reviews SAS® proves to be the best example. In this paper an attempt has been made to present the use of SAS® software for pharmacokinetic analysis.

KEYWORDS: SAS®, Pharmacokinetic analysis, clinical research, clinical trial.

INTRODUCTION

Pharmacokinetic is the branch of medical science which involves the study of ADME pattern of a drug after its administration to the subject. Absorption and distribution refers to the path followed by the drug from the site of administration to the blood and subsequently to the tissue from the blood respectively. Then its biotransformation occurs by various body mechanisms which involves the metabolism step. It is then followed by the elimination process which may occur through various routes for e.g. urine, bile or other routes. [1] Pharmacokinetic studies are conducted on volunteer subjects employing suitable study design in which blood samples are collected at a definite interval of time as per the study protocol.

Pharmacokinetic models are used after measuring the drug and metabolite concentration in blood samples after the administration of drug for calculating the parameters viz. C_{max}, T_{max}, elimination $t_{1/2}$, volume of distribution, clearance, etc. In the course of new drug development process, a series of pharmacokinetic profiling is done. [2] A huge number of data is generated which is collected by the clinical trial staffs on the case report form (CRF) and is sent for the analysis by biostatistician after being review and approved by the investigator. To deal with the big data is cumbersome task where SAS® software plays an important role for the retrieval of data from different sources which may exist in different file format. This is one of the major advantages of the SAS® software. Along with that it can present the data as per our convenience, can great graphs, calculate various parameters. All these tasks can be easily performed using the SAS® software by writing SAS® programs.

According to Jim Goodnight, CEO of SAS *"The amount of data pouring in is so vast, it's impossible to analyze quickly enough to make a difference in day-to-day decisions without a high-performance analytics infrastructure. Over the last two years, we've delivered groundbreaking analytics technology that unlocks the value in all this data"*. SAS® software turns clinical data in to meaningful information. It solves today's problem and maximizes the opportunity for tomorrow. With the advent of SAS® software people no longer have to wait for processing the data. It can be analyzed in minutes or seconds. [3]

CASE REPORT

MAJARO InfoSystems, Inc had been managing the data relevant to ADJUNT Study of Silicone Gel- Filled Breast Implants for MENTOR Co. (Santa Barbara, California, USA) for over five years. It was among the largest clinical trials ever conducted. It involved 670,000 pages from 90,000 patients and 2,000 investigators. The collected data were handled employing ClinAccess/PowerServer™, 21 CFR Part 11 compliant clinical data management system (CDMS) powered by SAS®.

In 2005, the recommendation for approval of implant was given by US-FDA. The efficiency was of prime concern due to the size of study. The handling of huge number of pages having data was a difficult job. For that various innovative techniques were used. [4]

Casebook Imaging: The images of CRF were employed for data management related activities in lieu of entering data from paper CRFs. TIFF files were used, which is an industry standard for graphical image storage. The image files were copied to MAJARO's network to

avoid loss. Then they were indexed using ClinAccess/CaseBook™ which links with the ClinAccess/PowerServer™ database. [4]

Forms Control: Practically, it is next to impossible to track 670,000 pages manually. With the use of ClinAccess/PowerServer™ Form Control it became possible to track all the pages in real time and computer generated reports could be created to ensure the data entry of each page. [4]

SAS/SHARE Database Server: This could bring about requests from multiple users for accessing and updating the data stored in database. SAS/SHARE allowed any number of users to write or read access to SAS tables.

Employing the SAS, the performance was increased for clinical data management. SAS Indexing was used which is defined by DATA step, PROC step, PROC DATASETS, or the SCL ICREATE function. WHERE clauses are used in conjunction with indexed variables which results in increased response time. [4] This shows that how SAS proves to be the useful software for handling with the large number of data created in clinical research industry.

SAS® SOFTWARE

According to Stefan Driessen, Directorof Global Biometrics Solvay Pharmaceuticals *"The power to get to know your compound better by using SAS Drug Development will translate into improved earnings through shorter time to market and decreased development costs"*.[5] Compared to other statistical software, SAS is more useful. This can be attributed to the fact that data from various sources irrespective of the file format such as excel, access, text formats can be imported and exported very easily.

SAS® Drug Development

It is the only solution for easy project management for analysis and reporting. Apart from that it has many benefits as well such as truthful single version can be accessed globally, more confident decisions can be taken in clinical research, existing regulatory requirements can be met (for e.g., 21 CFR Part 11), for all data analysis tasks automated integrity, traceability, and transparency can be accomplished, streamlined process, reduced costs and accelerate time for marketing [5]

SAS[®] PROGRAMMING MADE PK ANALYSIS EASIER

Here the examples of SAS programs [6] have been presented to determine various PK parameters.

Input dataset

Variables viz. Subject, Period, Treatment (1-Test, 2-Reference), Time, Concentration and Dose are present in a text data file. In the ANOVA step, sequence is determined as follows.

Sequence 1: Test product in period 1 and after washout period reference product in period 2

Sequence 2: Reference product in period 1 and after washout period test product in period 2

Example of input data is given below.

Subject Period Treatment Time Concentration Dose

1 2 1 0 0 40

1 2 1 0.5 11.31 40

1 2 1 1 22.29 40

1 2 1 2 11.91 40

1 2 1 3 8.19 40

1 2 1 4 3.03 40

Noncompartmental analysis

SAS program for creating a variable named order with an ascendent value for each profile as follows:

```
proc sort data = inputdata out = temp nodupkey ;
by subject period;
run;
data temp;
set temp;
order = _n_;
run;
proc sort data = temp;
by subject period;
run;
proc sort data = inputdata;
by subject period time;
run;
```

```
data temp2;

merge inputdata temp;

by subject period;

run;

proc sql;

create table max as

select max(order) as max

from temp2;

quit;

data max;

set max;

call symput('max',max);

run;
```

Calculation of AUC using SAS program

```
%macro auc (dsn);

data auctree;

 set &dsn;

 if concentration = 0 and time > tlast then delete;

 x = time;

 y = concentration;

 xpre = lag(x);

 ypre = lag(y);

 xdif = x - xpre;

 if x <= tmax or y = ypre or y = 0 or ypre = 0 then do;

 auc = xdif * (( y + ypre ) / 2);

*linear rule;

 end;

 else do;

 auc = xdif * ((y - ypre) / log (y / ypre));*log-linear rule

 end;

 run;

 proc summary data = auctree noprint;

 var auc;
```

```
output out = aucest sum = aucL;

run;


proc sort data = auctree out = part1 nodupkey ;

by subject;

run;

data AUCs&i (keep = subject period aucL);

merge part1 aucest;

run;

%mend auc;
```

Terminal elimination constant

```
%MACRO Lambda (DSN);

data &dsn;

set &dsn;

where concentration > 0 and time >= tmax;

lny = log (concentration);

run;

proc sort data = &dsn out=&dsn;

by descending time;

run;

%global npoints;

%let opendsn = %sysfunc(open (&dsn) );

%let npoints = %sysfunc(attrn(&opendsn,NOBS));

%let rc = %sysfunc(close(&opendsn) );

%put _user_;

%if (%eval (&npoints > 2)) %then %do;

%do j = 3 %to &npoints;

 data point&j;

 set &dsn( obs = &j );

 orderreg = &j;

 run;

 data point&j ;

 set point&j;
```

```
rename time = x;

rename lny = y;

x2 = time ** 2;

y2 = lny ** 2;

xy = time * lny;

run;

proc sql;

create table operats as

select

sum(x) as sumX,

sum(Y) as sumY,

sum(x2) as sumX2,

sum(Y2) as sumY2,

sum(xy) as sumXY

from point&j;

quit;

data _null_;

set operats;

call symput('sumX',sumX);

call symput('sumY',sumY);

call symput('sumX2',sumX2);

call symput('sumY2',sumY2);

call symput('sumXY',sumXY);

run;

data point&j;

set point&j;

m = ((&sumX * &sumY) - (orderreg * &sumXY)) / ((&sumX**2)-(orderreg * &sumX2));

r = (&sumXY - ((&sumX * &sumY) / orderreg)) / (sqrt((&sumX2 -
((&sumX*&sumX)/orderreg))*(&sumY2 - ((&sumY *&sumY)/orderreg))));

r2 = r * r;

adjr2 = 1 - ((1 - r2) * (orderreg - 1)) / (orderreg - 2);

run;

proc sort data = point&j nodupkey;

by subject;
```

```
run;
%end;
data allestimates;
set %do k = 3 %to &npoints;
point&k
%end;
run;
proc sort data = allestimates out = estimatecomp ;
by descending adjr2 descending orderreg;
run;
data estimatecomp;
set estimatecomp;
regnum = _n_;
where m < 0;
run;

proc sql;
create table maxi as
select max(regnum) as maxi from estimatecomp;
quit;
data _null_;
set maxi;
call symput('maxi',maxi);
run;
%if &maxi = . %then %goto skip;
%if &maxi = 1 %then %do;
data best_estimate;
set estimatecomp (obs = 1);
run;
%end;
%else %do;
data estimate2 ;
set estimatecomp (firstobs = 2);
run;
```

```
data estimate2;
set estimate2 (obs = 1);
adjr2 = adjr2 *1;
call symput ('estimate2' , adjr2);
call symput ('oderreg2' , orderreg);
run;
data estimate1;
set estimatecomp (obs = 1);
adjr2 = adjr2 *1;
call symput ('estimate1' , adjr2);
call symput ('oderreg1' , orderreg);
run;
data _null_;
dif1 = &estimate1;
dif2 = &estimate2;
dif = (dif1 - dif2);
call symput('dif',dif);
run;
%let difer = %SYSFUNC(PUTN(&dif,15.10));
%if &difer < 0.0001 and &oderreg2 > &oderreg1 %then %do;
data best_estimate;
set estimatecomp;
where regnum = 2;
%end;
%else %do;
data best_estimate;
set estimatecomp;
where regnum = 1;
run;
%end;
%end;
data lambda&i (keep=m r2 adjr2 subject period orderreg);
set best_estimate;
m=m*-1;
```

```
run;

proc datasets library = work nodetails nolist;

delete %do iii=1 %to &npoints; point&iii %end;;

run;

quit;

%end;

%else %do;

%put Warning, Less than 3 points, lambda is not estimable;

%skip:;

proc sort data=profileno&i out=id data nodupkey;by subject;

run;

data lambda&i (keep=m r2 adjr2 subject period orderreg);

set iddata;

m=.;

r2=.;

adjr2=.;

orderreg=.;

run;

%end;

%MEND lambda;
```

Call for macros [6]

```
%macro indcalc;

%do i = 1 %to &max;

data ProfileNo&i;

set temp2 (where = (order = &i));

run;


/***********************************************************

i) Cmax , Tmax

***********************************************************/


proc sort data=profileno&i out=profilenoinvCmax&i;

by descending concentration;run;

data Cmax&i;
```

```
set profilenoinvCmax&i (obs = 1);

rename concentration = Cmax time = Tmax;

run;


/************************************************************

ii) Clast

************************************************************/


proc sort data=profileno&i (where =(concentration > 0)) out = profilenoinv&i;

by descending time;

run;


data Clast&i (keep = subject period clast order tlast);

set profilenoinv&i (obs = 1);

rename concentration=Clast time=Tlast ;

run;


proc sort data = profileNo&i; by subject period time;

proc sort data = Cmax&i; by subject period;

proc sort data = Clast&i; by subject period;

data profileNo&i;

merge profileNo&i Cmax&i Clast&i;

by subject period;

run;


%auc (profileno&i);

%lambda (profileno&i);

data Pkparam&i;

merge cmax&i aucs&i lambda&i clast&i;

run;

%end;


/************************************************************

Joint PK Parameters of all patients

************************************************************/
```

```
data allPkParam (rename = (m = lambda orderreg = npoints));
set %do i = 1 %to &max;Pkparam&i %end;;
run;
%mend indcalc;
```

Finally, derived parameters are calculated from previous and library work cleared:

```
data phsug.PkNCA (keep = subject period treatment r2 adjr2 npoints lambda HL tmax cmax
aucL AUCinf clearance vz clast tlast);
format r2 adjr2 lambda HL aucL AUCinf clearance vz clast tlast 10.4;
set allPkParam;
AUCinf = aucl + clast / lambda;
Clearance = dose / AUCinf;
Vz = clearance / lambda;
HL = log(2) / lambda;
run;
```

```
PROC DATASETS MEMTYPE = DATA LIB = work kill nodetails nolist;
RUN;
quit;
```

Bioequivalence analysis using SAS program[6]

Accordaning to prevailing bioequivalence guidelines such as FDA, EMEA and other authorities, 90% confidence interval (CI) is considered for testing bioequivalence. The acceptable range for CI is [0.8-1.25].

In the following program, PROC GLM has been used to obtain the estimate and the MS (residual) to construct the confidence limits using a data step:

```
%macro anova(param =);
data PkNCA;
set phsug.PkNCA;
if period = 1 and treatment = 1 then seq = 1;
if period = 2 and treatment = 2 then seq = 1;
if period = 1 and treatment = 2 then seq = 2;
if period = 2 and treatment = 1 then seq = 2;
```

```
ln&param = log (&param);
run;

ods output LSMeans = LSMeans
OverallANOVA = OverallANOVA
ClassLevels = ClassLevels;
proc glm data = PkNCA;
class subject period seq treatment;
model ln&param = seq subject (seq) period treatment ;
lsmeans treatment /;
contrast 'Treatment 1 versus 2' treatment 1 -1;
ESTIMATE 'T vs. R' treatment 1 -1;
run;

data MSerror(keep = order MS) ;
set OverallANOVA ( where = (source = 'Error'));
order = 1;
run;
proc transpose data=lsmeans out=difference name=lncmaxLSMean
prefix=ls;
id Treatment;
run;

data difference1 (keep = order ls1 ls2);
set difference;
order = 1;
run;

data ClassLevels1 (keep = order levels);
set classlevels (where = (class = 'Subject'));
order = 1;
run;

data IC;
merge MSerror difference1 ClassLevels1;
```

```
by order;

run;

data ic1;

set IC;

difference = ls1 - ls2;

SEdifference = sqrt(2 * MS/levels);

ratio = 100 * exp (difference);

lower = 100 * exp (difference - 1.761 * SEdifference);

upper = 100 * exp (difference + 1.761 * SEdifference);

interval                                                                 =
trim(left('['))||trim(left(put(lower,8.3)))||trim(left(',')||trim(left(put(upper,8.3)))||trim(left(']'));

if 80 <= lower <= 125 and 80 <= upper <= 125 then result = "Both formulations can be
considered bioequivalent in terms of &param";

else result = "Both formulations cannot be considered bioequivalent in terms of &param";

label interval = 'IC90%' ratio = 'Estimate' result = 'Conclusion';

run;

proc print noobs l;

var ratio interval result;

title h = 2 j = c "Bioequivalence analysis of &param";

run;

%mend anova;
```

CONCLUSION

In the field of clinical research where big data is major issue SAS software has proved to be a boon for pharmacokinetic analysis as it helps to retrieve, analyse and make quick decision. Moreover, irrespective of the source and file format of dataset, SAS software can handle them easily.

ACKNOWLEDGEMENT

SAS and its software are registered trademarks of SAS Institute in USA and other country. All other software names used in this paper are the trademark of their respective companies. The names used here are only for informational purpose.

All the programs have been referred from the paper entitled "Noncompartmental Pharmacokinetics and Bioequivalence Analysis" by Arturo Soto Matos-Pita, Bernardo de Miguel Lillo from PharmaMar SAU, Madrid, Spain.

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