Noncompartmental Pharmacokinetics and Bioequivalence Analysis

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ABSTRACT
This paper provides a tested SAS® program that performs the following tasks: 1) calculates noncompartmental pharmacokinetic parameters AUCinf (Area Under the Curve from time 0 to infinite), Cmax (maximum concentration), Tmax (time at the Cmax) and the derived parameters clearance/F, volume of distribution/F and half-life; 2) performs the statistical bioequivalence analysis based on the FDA and EMEA guidelines and 3) reports the results in tables and individual plots.

INTRODUCTION
Bioequivalence studies are designed to examine whether the systemic bioavailability of a test product and those of the reference product differ significantly.

In the classical approach, a "test" formulation is compared with the standard/innovator “reference” formulation in a group of normal, healthy subjects. Each of the subjects receives both treatments alternately in a crossover fashion (two-period, two-treatment crossover design), with a “washout period” of at least 5 half-lives between them. The sequence is assigned to each subject randomly, but an equal number of subjects receive each treatment in each phase.

Following the relevant FDA and EMEA Guidelines, the statistical analysis should be based on the noncompartmental parameters AUCinf and Cmax, derived from the drug concentration-time curve (although plasma is the preferred matrix, sometimes whole blood or free concentration are used). These parameters are compared by means of an ANOVA in which the variance is partitioned into components due to subjects, periods and treatments. To conclude bioequivalence between the test and reference formulations, the 90% confidence intervals for the mean difference of the parameters after logarithmic transformation should fall in the acceptance interval 0.8-1.25.

INPUT DATASET
The input data file is a text file with the following variables separated by spaces: Subject, Period, Treatment, (1 Test, 2 Reference), Time, Concentration and Dose. Sequence of treatment is derived by the program in the ANOVA step. Sequence 1 is assigned if the subject receives the test formulation during period 1 and after the washout period the reference formulation and sequence 2 if the order of administration is the opposite. An 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
1 2 1 6 0 40
1 1 2 0 0 40
1 1 2 0.5 0 40
1 1 2 1 8.88 40
1 1 2 2 11.14 40
1 1 2 3 8.67 40
1 1 2 4 2.25 40
1 1 2 6 0 40
...```
NONCOMPARTMENTAL ANALYSIS

Noncompartmental analysis is preferred over compartmental analysis in bioequivalence evaluation due to several reasons. The main reason is that noncompartmental analysis is less prone to data manipulation. Calculation of pharmacokinetic parameters should be made with a minimum of intervention by the investigator and the rules of calculus should be defined prior to the analysis. Two steps are crucial in the process: calculation of AUC from time 0 to the last point with quantifiable concentration and calculation of terminal elimination constant. Both quantities will be used to compute one of the parameters to evaluate bioequivalence: AUCinf. Cmax is obtained directly from the data.

Prior to the calculations, individual profiles and its total number are extracted from input data. There are several ways to do this. The proposed in this paper is to create a variable named order with an ascending value for each profile as follows:

```plaintext
proc sort data = inputdata out = temp nodupkey ; by subject period;run;
data 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;
```

**AUC**

The following macro calculates AUClast (from time 0 to the last with quantifiable concentration) using the log-linear trapezoidal rule that means linear trapezoidal rule up to Tmax, and log trapezoidal rule for the remainder of the curve.

```plaintext
%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;
```

Linear rule is utilized for the ascending part of the curve, in calculations involving a concentration value equal to zero, or if the same concentration is measured in two consecutive sampling points. Otherwise, the log-linear trapezoidal...
rule is used. Note that at this point, Tlast (time of the last point with quantifiable concentration) and Tmax must have been already obtained.

**TERMINAL ELIMINATION CONSTANT**

The next macro calculates the first order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. The rules are that a minimum of three points is needed to define the terminal (log-linear) portion of the curve and the selection is based on the best adjusted square coefficient of regression ($r^2$). Additionally, if the adjusted $r^2$ does not improve, but is within 0.0001 of the largest adjusted $R^2$ value, the regression with the larger number of points is used.

```sas
%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))));
    %end; %end;
  %end; else %do;
    %put WARNING: Not enough data to estimate terminal constant.
  %end;
%endo_macro;
r2 = r * r;
adjr2 = 1 - ((1 - r2) * (orderreg - 1)) / (orderreg - 2);
run;
proc sort data = point&j nodupkey; by subject;run;
%

data all_estimates;
    set %do k = 3 %to &npoints;
        point&k
    %end;;
run;
proc sort data = all_estimates 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('orderreg2',orderreg);
run;
data estimate1;
    set estimatecomp (obs = 1);
    adjr2 = adjr2 * 1;
    call symput('estimate1',adjr2);
    call symput('orderreg1',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 &orderreg2 > &orderreg1 %then %do;
data best_estimate;
    set estimatecomp;
    where regnum = 2;
%end;
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=iddata nodupkey;by subject;run;
data lambda&_i (keep=m r2 adjr2 subject period orderreg);
set iddata;
m=.;
r2=.;
adjr2=.;
orderreg=.;
run;
%end;
%MEND lambda;

This is the most tedious part of the program. It could have been made easier using SAS/IML®, but was intentionally
developed in SAS base to be run by most of the SAS users. It generates different datasets (point&_i) for each group of
points beginning with 3 and finishing with all the points till the Cmax. Raw r² and r² adjusted by the number of points
are calculated for each group. Then a dataset is generated with all estimates, and the best is selected based in the
adjusted r². If there are less than three points available to calculate the slope or is not possible to calculate it, the
corresponding variables are set to missing (.).

CALL FOR MACROS
The next step is to send each individual profile to the two previous macros. As it was mentioned before, the obtention
of Tlast, Cmax and Tmax is needed at this point.

%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);
%end;
%MEND indcalc;
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

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;
The performance and validity of the program was tested against WinNonlin®, one of the most commonly used
programs for pharmacokinetic analysis in the Pharmaceutical Industry. The results of twenty bioequivalence clinical
trials were evaluated using both WinNonlin and SAS. PROC COMPARE of SAS was used to test for differences.
There was a 100% agreement in all 20 studies.

BIOEQUIVALENCE ANALYSIS
As recommended in their respective Bioequivalence Guidelines by the FDA, the EMEA and other Authorities, the
general approach to test bioequivalence is to construct a 90% confidence interval for the difference of the means
of the logarithmic transformed values of AUCinf, AUClast and Cmax. To accept bioequivalence, this confidence interval
has to be contained in the interval [0.8-1.25]. Due to the nature of normal-theory confidence intervals, this is
equivalent to carrying out two one-sided tests of hypothesis at the 5% level of significance. The antilogs of the
confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the
values for the Test and Reference products.

In our program, we use PROC GLM 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 = 1 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"
         v = 2;
  run;
%mend anova;
INDIVIDUAL PLOTS AND TABLES

Finally, results have to be reported in tables and graphs. The following figures and tables show the result of implementing the advanced tools available in SAS for these purposes. Graphs have been created using PROC GPLOT, then grouped with PROC GREPLAY and exported to cgm (Computer Graphics Metafile) format, that can be directly imported to Microsoft® Word. Again, the last process can be made at once via DDE (Dynamic Data Exchange).

Some examples of the figures and tables generated on the basis of the program results using the SAS output procedures are shown below:
**Summary of pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Subject</th>
<th>TEST AUCl</th>
<th>TEST AUCinf</th>
<th>TEST Cmax</th>
<th>TEST InAUCl</th>
<th>TEST InAUCinf</th>
<th>TEST InCmax</th>
<th>REFERENCE AUCl</th>
<th>REFERENCE AUCinf</th>
<th>REFERENCE Cmax</th>
<th>REFERENCE InAUCl</th>
<th>REFERENCE InAUCinf</th>
<th>REFERENCE InCmax</th>
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<td>158.81</td>
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<td>CV</td>
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<td>12.84</td>
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<td>36.06</td>
<td>35.32</td>
<td>17.04</td>
<td>5.84</td>
<td>3.53</td>
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**Summary of bioequivalence analysis of aucinf**

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<th>Source</th>
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<th>Mean Square</th>
<th>F Value</th>
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<table>
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<th>IC90%</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>103.628</td>
<td>[99.004,108.467]</td>
<td>Both formulations can be considered bioequivalent in terms of aucinf</td>
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**CONCLUSION**

The program described in this paper was proved to be a useful tool to obtain pharmacokinetic parameters using noncompartmental analysis. In the scenario of bioequivalence studies, the integration of all parts can automatize the whole process, from raw data to final report. Although the program was developed for the common 2x2 crossover design, it can be easily adapted for other bioequivalence designs.
CONTACT INFORMATION
Your comments and questions are valued and encouraged. Contact the author at:

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