

Using SAS graphics to help with decision making in Early Clinical Development

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ABSTRACT

The Early Clinical Biometrics department (ECB) at AstraZeneca (AZ) is part of Early Clinical Development (ECD). ECD is a stand-alone, dedicated resource for the early stage portfolio. The role of programming group within ECB is to provide our ECD colleagues with access to clinical analyses which supports decision-making on important strategies and projects, part of the work we do in programming is around providing quick, clear and informative graphical representations to help make these key decision. The intention of this poster is to present three examples of decision making plots. The poster will illustrate the **MDI** (Medicines Differentiation Index) plot, **eDISH** plot (Evaluation of Drug-Induced Serious Hepatotoxicity) and **Pharmacokinetic Profile plot**. A brief description of the purpose of plots within ECD will be made and any special features used in the coding of the plots within Graph Template Language and the ODS Graphics procedures.

INTRODUCTION

The intention of this poster is to present three examples of decision supportive plots: MDI plot, eDISH plot and Pharmacokinetic Profile plot produced by SAS/GRAPH®
Visual data interpretation will facilitate early decision making process in drug projects.

MDI PLOT

- A tool that will aid in the setting and evaluation of the TPP (Target Product Profile) targets in an efficient way and is used as an efficient visual description of current data, modeled data and competitors data.
- MDI Display Elements:
 - Observed performance
 - Simulated performance
 - Standard of care performance
 - Product Profile Range
 - Competitive Program Performance
- Using SAS to produce MDI plot is an improvement in the flexibility and user friendliness
- SAS program reads data from a comma delimited spreadsheet (.csv) and plots those data in the standard format.

```
• SAS code snippets:
proc template;
define statgraph sgplot;
begingraph / pad=(left=40%);
layout lattice / rows=5 columns=1 ROWGUTTER=10;
layout overlay /
xaxisopts=( display=none type=linear linearopts=( tickvaluelist=( 0 2 4 6 8 10 )
viewmin=0 viewmax=10 ) )
yaxisopts=( display=none type=linear linearopts=( tickvaluelist=( 1 2 3 4 5 6 )
viewmin=1 viewmax=6 ) );
HighLowPlot Y=yvarn High=up0 Low=lo0 / primary=true Group=LABEL LegendLabel="yvarn"
NAME="HIGHLOW";
DrawText textAttrs=( COLOR=black FAMILY="Arial" size=8) "Compound and
Indication: xxx" / X=0 Y=94 DRAWSPACE=graphpercent ANCHOR=left WIDTH=100;
```

PhUSE 2015

```
DrawRectangle height=10 width=15 x=20 y=75 / DRAWSPACE=graphpercent display=all
fillattrs=( COLOR=blue transparency=0.4) outlineattrs=( COLOR=white)
cornerradius=0.5;
.
.
```

EDISH PLOT

- eDISH plot is a simple but very informative tool for medical reviewers that enables them to view individual lab patient data, study data or pooled data over time.
- eDISH plot allows the project teams to see the lab data trends clearly, quickly to help make informed decision
- A tool used for evaluation of DILI (Drug induced liver injury)
- DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years
- Hy's Law – a rule of thumb named after Hy Zimmerman which states: "A drug is at high risk of causing a fatal drug-induced liver injury when given to a large population, if it caused cases of liver injury that satisfied certain criteria when given to a smaller population."
- Components of Hy's law:
 - 1.) The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the upper limits of normal (ULN) of ALT or AST than the (nonhepatotoxic) control agent or placebo.
 - 2.) Among subjects showing such elevations, often much greater than 3xULN, some subjects also show elevation of serum total bilirubin to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).
 - 3.) No alternative cause for elevations

- SAS code snippets:

```
ods html close;
ods pdf file='M\edish.pdf' style=edish bookmarklist=none;

proc sgplot data=lft2;
    scatter x=mult_alt y=mult_bili / markerattrs=(size=8px);
    xaxis label='Peak ALT (x ULN)' grid type=log logbase=10 min=0.01 max=100;
    yaxis label='Peak TB (x ULN)' grid type=log logbase=10 min=0.01 max=100;
    refline 3 / axis=x label=('3 x ULN') lineattrs=(color=black pattern=1);
    refline 2 / axis=y label=('2 x ULN') lineattrs=(color=black pattern=1);
    inset "Hy's Law Quadrant" / position=topright;
    inset "Temple's Corollary Quadrant" / position=bottomright;
    inset 'Cholestasis Quadrant' / position=topleft;
run;
.
.
```

PK PROFILE PLOT

- Play an important role in interpreting drug concentration-time data as they provide a quick view of the general trend of the drug concentrations over time.
- Normally contains PK profiles of geometric mean concentration with STD bars vs. time
- PROC SGRENDER procedure in SAS 9.3 was used to create a plot:

```
proc sgrender data=stat template=sgplot;
```
- PROC TEMPLATE is efficient tool used for layout control (figures of linear scale and log scale are displayed on the same page; there are options to display side-by-side or top-bottom.):

```
proc template;
define statgraph sgplot;
```

PhUSE 2015

```
beginningraph / pad=(left=0%);

layout lattice / rows=2 columns=1 ROWGUTTER=5;
layout overlay / xaxisopts=( Label="Time Post-Dose (Hours)" type=linear
linearopts=( tickvaluelist=( 0 10 20 30 ) viewmin=0 viewmax=30 ) )
              yaxisopts=( griddisplay=on Label="Linear Scale" type=linear
linearopts=( tickvaluelist=( 0 5000 10000 15000 ) viewmin=0 viewmax=15000 ) );
              ScatterPlot X=PCTPTNUM Y=GMEAN / primary=true Group=TRT
Markerattrs=( Size=8px) YErrorUpper=UPPER YErrorLower=LOWER LegendLabel="GMEAN"
NAME="f1" groupdisplay=cluster clusterwidth=1;
              SeriesPlot X=PCTPTNUM Y=GMEAN / Group=TRT LegendLabel="GMEAN"
NAME="SERIES" groupdisplay=cluster clusterwidth=1;
              DiscreteLegend "f1" / Location=Inside across=1 halign=right valign=top
Title="" Border=false;
endlayout;

.
```

CONCLUSION

One of ECBs key objective is to deliver the standard data structures to generate recognizable graphical output in order to promote effective internal decision making , e. g. Go/No-go criteria as presented above. Members of the statistical programming group has been tasked with promoting the usage and awareness of ODS functionality. ECB is managing a area of template and code library together with other useful graphics information for easy re-use purposes. SAS ® is one of the standard tool that is used for graphical presentation of the data, following the SAS/GRAPH® improvement with the release of the ODS procedures. Present in the code library are example code and output for MDI , eDISH, PK profile plot, Scatter plot, Patient Exposure over time plot, Waterfall plots produced by the SAS/GRAPH®

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