Harmonised PK Analysis & Reporting

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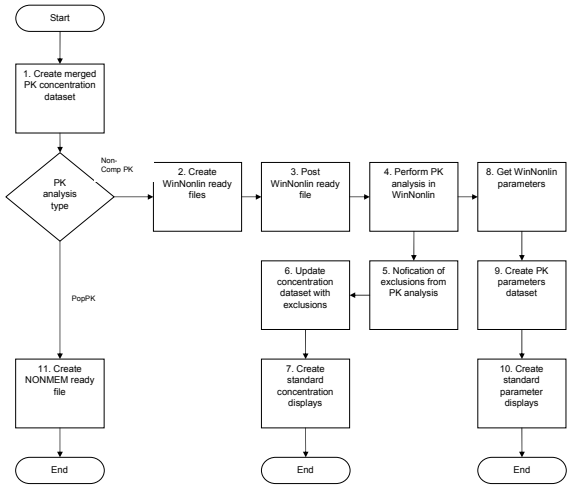
Abstract

Introduction

GSK undertook a project to harmonise the way in which PK data is analysed and reported for the majority of clinical pharmacology and late phase studies. This included developing a set of dataset and data display reporting standards, a means of joining and reconciling data sources, designing the underlying SAS macro code and finally transferring data between validated and auditable systems using the in-house analysis and reporting application (HARP).

This poster outlines the steps involved in conducting a PK analysis within GSK using standard tools.

The Business Process



PK Reporting Standards

Underlying the entire process is a set of standards that set out the scope of deliverables and expectations from the tools. Firstly, the business process was documented, secondly the Analysis and Reporting (A&R) datasets were defined, specifying required and optional variables along with algorithms for derived variables. Finally, the output was detailed indicating standard default displays that may be produced for the study report, along with output naming conventions and flexibility allowed dependent on study design. The data displays created conform to GSK reporting standards.

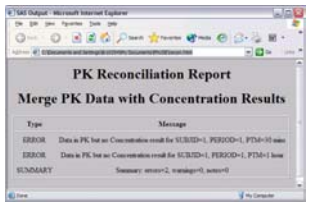
Non-Compartmental PK Analysis

The PK Analysis Dataset

Creation of the A&R concentration dataset has three main stages: the join of the laboratory assayed concentration data and CRF sampling time data, the addition of treatment and common data information, and the imputation of non-quantifiable results and inclusion of derived variables.

Dataset specifications within the reporting application control how the dataset should be created for a particular study.

The critical component of the A&R dataset creation process is the successful join of the concentration data and the sampling time data. This is achieved using a common key which all owners of the data agree to uphold. Exception reporting is performed using the key variable to reconcile the data.



WinNonlin

In order for a non-compartmental PK analysis to occur in WinNonlin, proprietary files structures of the concentration data and dosing data need to be constructed. In essence these are a comma separated values file of concentration data and a sequential dosing and modelling file.

Using the HARP reporting application all data transfer between biometrics and the kineticist (and vice versa), and WinNonlin analysis is handled in a controlled regulated environment.

After the non-comp PK analysis, the summarised PK parameter data is passed back to biometrics where it is converted to an A&R dataset using the same dataset specification and standards principles used for the concentration data. We are now ready for statistical analysis and reporting.

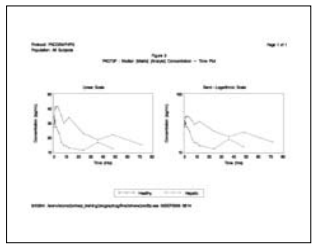
Standardised Data Displays

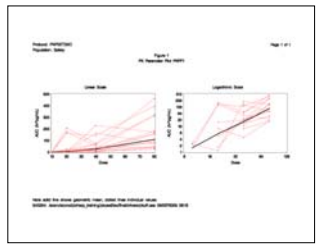
The majority of the textual data displays made good use of existing GSK utility macros. This ensures consistency over all the biometrics deliverables based on GSK A&R standards and also led to an efficient use of time and resources.

Displays covered by these are the PK concentration and PK parameter listings and summary tables. Standard driver macros are available with default parameter values for both simple parallel group and cross over designs for each display shell.

Graphical Data Displays

A first for the GSK reporting tools was the standardisation of graphical output. The underlying principals and guidelines for displays have been adhered to. Macros exist to create summary and individual concentration plots (using linear and logarithmic scales) as well as macros for PK parameter comparative and dose escalation plots.





The design of the macros, although tailored for PK data, has also enabled other data domains access to macros with easy to use parameters for both continuous and categorical data.

Population PK Analysis

For the first time GSK now has standard macros for the creation of NONMEM data files for both Population PK and PK/PD data. These are used in conjunction with a *pro-forma* which is contained within the Reporting & Analysis Plan (RAP) that defines how the file should be constructed.

The current version of the macros create a fully expanded NONMEM data file based on one record per dosing event. Other functionality allows the handling of the following:

- Multiple dependent variables
- Add compartments and indicators to dependent variables
- Multiple covariates
- Imputation of missing covariates (by using pre-data of individual, post-data of individual or mean of population)
- Importing a post-hoc NONMEM analysis file for use as a covariate
- Performing standard derivations (RTLD, RTFD)
- Provide unit information in row #1
- Provide decode information in row #2
- Utility to provide supplementary covariate NONMEM files

The next release of the NONMEM macros will enable

- Setting dummy randomisations and data scrambling for early NONMEM setup
- Imputation of Event Identification (EVID) of 2 and 4
- Creation of Additional Dose (ADDL), Interdose Interval (II), and Steady State (SS) columns
- Amalgamation of studies