

Automating table production using an S-Plus[®] module

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ABSTRACT

This presentation focuses on the development and deployment of an S-Plus[®] module to support PK/PD (Pharmacokinetics/Pharmacodynamics) table production. Following an evaluation of customer requirements, skill set and knowledge base the business elected to use S-Plus as its preferred technology in Clinical Pharmacology (Modelling and Simulations). From concept to delivery, Pfizer partnered with Mango Solutions to realise the automation of components in PK/PD Reporting. The solution that was developed was fully validated and extended S-Plus functionality to integrate with the industry standard PK/PD analysis application, NONMEM (NON-Linear Mixed Effects Modelling).

INTRODUCTION

Pharmacokinetics (PK) is the study of absorption, distribution, metabolism and excretion of a drug in the body over time. Pharmacodynamics (PD) is the study of the body's pharmacological response to a drug over time (AE and/or efficacy).

PK/PD is the study of the relationship between dose, concentration and response (measured by adverse event incidence and efficacy). Additional covariates are included and together these data are analysed to explain both within subject and between subject variability. Analysts perform PK/PD Modelling and Simulations (M&S) to contribute to project decisions, dosing/labelling decisions and support regulatory filings.

Models are constructed to provide description of data and predictions from data ("what if scenarios") using an industry standard program called NONMEM. NONMEM is an application for performing analyses of population PK/PD data using general nonlinear regression techniques to fit models to data.

Within Pfizer, the Clin PK/PD analyst provides a data requirements/specification document detailing variables required for the derived dataset(s). The PK/PD support developer uses the data requirements/specification in conjunction with modular template SAS[®] macros, to read and combine a variety of raw input datasets to meet the derived dataset request (NONMEM Input dataset). To help facilitate the creation of models and simulations, the xPose[®] library is already in use within Sandwich. Written and supported by the University of Uppsala, xPose is an add-on library for S-PLUS which imports, analyses and plots information from NONMEM table files.

DRIVERS FOR CHANGE

The use of PK/PD within the pharmaceutical industry has become increasingly important over recent years. Regulatory agencies such as the FDA now require all drug filings to contain a PK/PD analysis of the drug being filed. Additionally, with costs for drug development continuing to rise, it makes commercial sense to use PK/PD Modelling and Simulation (M&S) to better understand a drug throughout a drug's development. With these increasing demands on PK/PD analysts, there is a need for more sophisticated tools to quickly deliver PK/PD tables and figures to users.

Before embarking on the development and delivery of a new tool for PK/PD tables and figures, Pfizer reviewed its requirements and highlighted its major drivers for change in its current process for PK/PD table and figure production:

- Little standardisation – different analysts produced different tables and figures;
- Resource limitation;
- Not efficient use of PK/PD analyst time;
- QC is difficult (e.g. use of Excel, non-standard scripting) and time consuming due to lack of standardisation;
- Not 21CFR Part 11 compliant;
- Difficult to move to QC (auditable process) as not all analysts had sufficient scripting skills.

SCOPE OF TOOL

In reviewing this list of drivers, the scope of the tool should:

- Deliver efficient optimal production of regulatory standard PK/PD, POP PK/PD tables/figures for reports;
- Cover any tables/figures produced directly or indirectly from input/final dataset and NONMEM table files;
- Deliver 21CFR Part 11 compliance;
- Have a scripting and GUI Interface;
- Integrate with NONMEM files - produce any tables directly or indirectly from input or final dataset(s) and NONMEM table files.

To ensure flexibility, it was also agreed primary responsibility for the production of PK/PD Tables and Figures should remain with the PK/PD analysts as they were best placed to understand the data and the NONMEM model files. Close support would be provided by the PK/PD Support group.

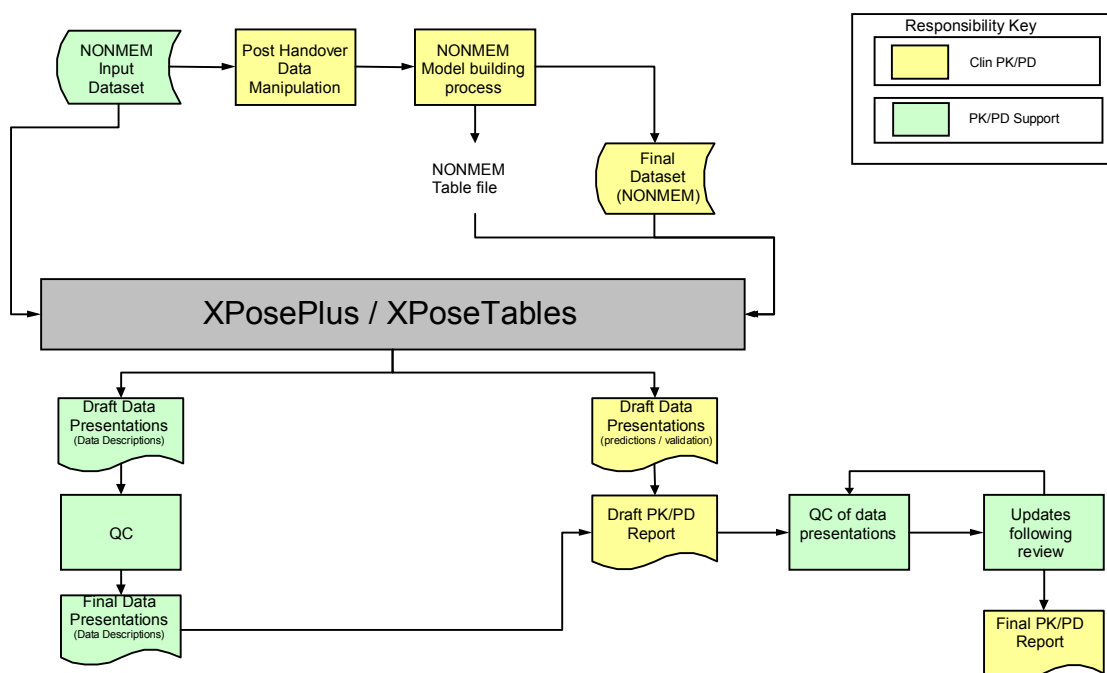


Figure 1: Tables and Figures delivery process and responsibilities

DEVELOPMENT CONSIDERATIONS

Having determined the basic scope of the tool, the next question was what would be the best technology to deliver these requirements? There were two main technologies available: SAS or S-Plus, and both had their advantages and disadvantages.

SAS

- ✓ Existing knowledge and support from PK/PD support developer.
- ✗ High overhead on PK/PD analyst. The majority of PK/PD analysts are not familiar with SAS and it would take some considerable time and effort to train them.
- ✗ Would need to pass data to/from S-Plus.
- ✗ Currently no "off-the-shelf" validated technical solution.
- ✗ Lack of flexibility for analysts. Require 'real-time' assistance from PK/PD support developer to change tables.
- ✗ Conclusion:
SAS Does not fit with proposed working model and therefore not progressed.

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S-Plus

- ✓ Familiar platform to Clin PK/PD (GUI and scripting). It is the tool of choice for production of PK/PD outputs (tables / graphs).
- ✓ xPose[®]: Written and supported by the University of Uppsala, xPose is an add-on library for S-PLUS which imports, analyses and plots information from NONMEM table files. It is widely used by PK/PD analysts at Pfizer in Sandwich. A proposed upgrade to xPose would offer direct access to NONMEM outputs within S-Plus for report production.
- ✓ Identified growth area – the use of S-Plus is becoming more accepted in Reporting and Analysis, in part due to the ease with which graphics can be produced.
- ✗ Currently no “off-the-shelf” validated technical solution.
- ✗ Current lack of familiarity of S-Plus within PK/PD Support. However, this could be addressed through appropriate training.
- ✓ Conclusion: S-Plus was selected as:
simpler implementation (modules easily incorporated in to the main application)
level of skills within Clinical are medium to high (whereas SAS skills are limited)

VENDOR SELECTION

Having selected the preferred technology platform, Pfizer met with several vendors to discuss the brief, and to invite tender proposals. From these, Mango Solutions was selected to partner with Pfizer on the development of the PK/PD Figures and Table tool.

The benefits of selecting Mango Solutions:

- ✓ Utilises a current collaboration between Uppsala and Mango Solutions.
- ✓ Vendors familiar with PK/PD data, and the proposal to expand xPose functionality to cover both plots and tables.
- ✓ Vendors have produced a suite of S-PLUS functions for importing and manipulating NONMEM table, model and output files.
- ✓ No additional software overhead. Could be more exportable to third parties (CRO etc.)
- ✓ Vendor already provides training in software across Pfizer
- ✓ Lower cost.

DEVELOPMENT PROCESS

Following the initial meeting, a detailed technical specification was produced, reviewed and agreed. From this, the software was developed and beta tested. Further version controlled releases were received and underwent User Acceptance Testing (UAT).

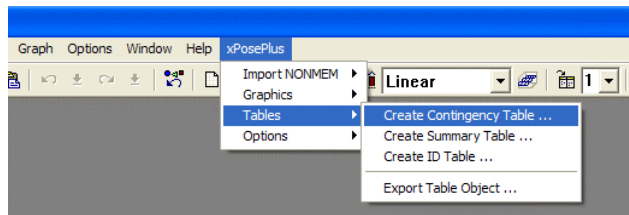
Throughout the development process, Pfizer collaborated closely with Mango Solutions. In the course of testing, discussion and input from both parties, the specification was further refined, and enhancements to the initial functionality were added. The process of development required open discussion with both parties able to raise issues and resolve them as a team.

XPOSEPLUS: WHAT IS IT AND WHAT DOES IT OFFER?

XPosePlus is a sophisticated S-Plus module that provides both a GUI and scripting environment for the creation of Tables and Figures to be used within PK/PD Modelling and Simulation.

Key components of the module include:

- the xPose Library;
- the xPoseTables Functionality;
- NONMEM interface;
- XML reporting library.



Once loaded, xPosePlus can be accessed either through the command line window or through drop down menus from the S-Plus menu bar.

Figure 2: Accessing xPosePlus functionality

COMPONENT RELATIONSHIP

The relationship of the key components of the system can be understood using the following the diagram:

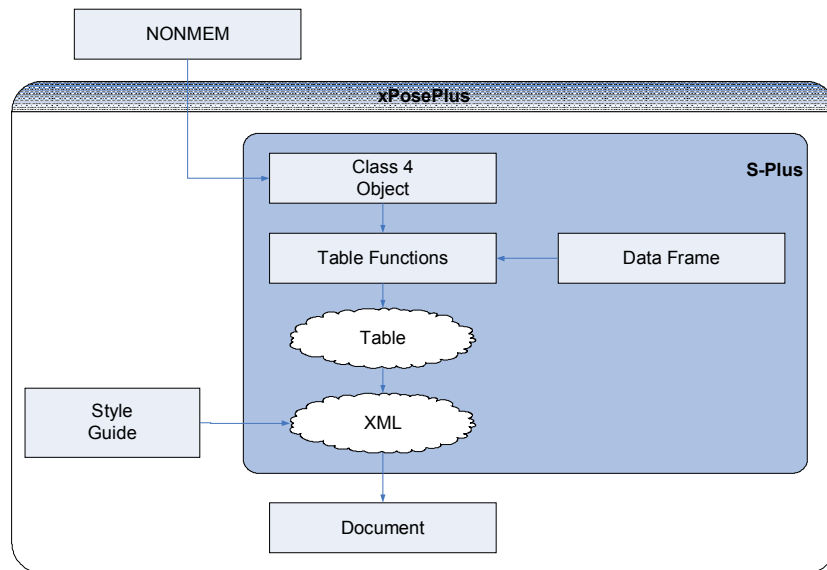


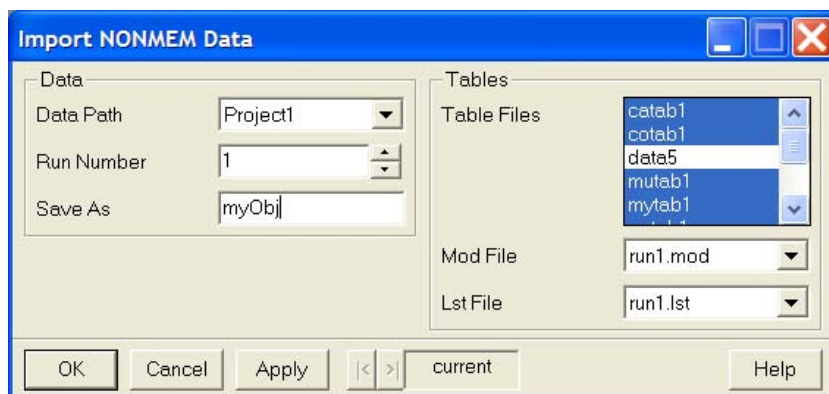
Figure 3: Component Relationship

THE XPOSE LIBRARY

The xPose library, written by Niclas Jonsson and Mats Karlsson, is an S-PLUS library for importing and analyzing NONMEM data. Mango Solutions consultants have worked with Niclas Jonsson to develop a version of xPose 4.0 which will work under S-PLUS or R.

NONMEM INTERFACE

In addition to the xPose functionality described above, Mango Solutions developers have also produced a suite of S-PLUS functions for importing and manipulating NONMEM table, model and output files. Mango developers used their experience in delivering user-focused application to ensure this procedure is as user-friendly and efficient as possible. As such all functionality, including the generation of graphics and tables can be called from a menu system.



Using the GUI, The user can quickly and easily select the Table, Model and LST files from a specified directory.

The inherent logging capabilities of the software allow for template scripts to be developed that can then be executed as required.

```
# Step 1 - Create the import list
> impList <- getNmFiles(Run=1, "Project1")

# Step 2 - Import based on import list
> myObj <- importNm(impList)

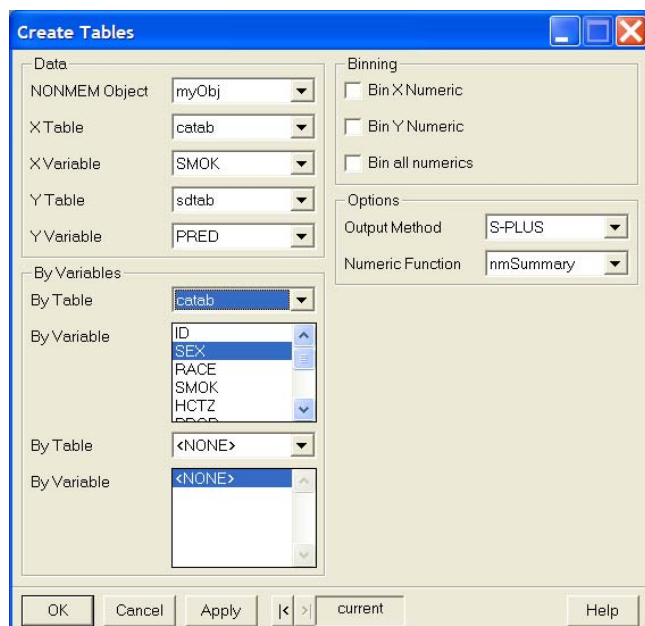
# Step 3 - Print object (demonstrating print methods)
> myObj@Lst
:
:
```

Alternatively, through the command line the user can specify the import details and link together functions to import, process and print NONMEM files.

Figure 4: NONMEM data file import using GUI and S Interface

THE XPOSETABLES FUNCTIONALITY

In parallel with the development of the core functionality of xPose 4.0, Mango Solutions worked with Pfizer's Modelling & Simulation team to design and implement some additional functions to create and export production-quality tables. This functionality was added to the xPosePlus module for Pfizer's use, including methods for the new SV4 "NONMEM" class of xPosePlus.



As not all users are proficient in command line scripting, a GUI was developed to allow the easy selection of variables for table production.

The inherent logging capabilities of the software allow for template scripts to be developed that can then be executed as required.

Figure5: Table creation using GUI and S interface

TABLE INTELLIGENCE

The tables generated are intelligent and can recognize column types and create corresponding output. Within their existing functionality, Mango Solutions developed an extensible rule-based system for creating a table of columns X versus Y.

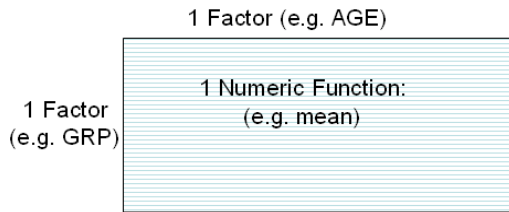


Figure 6: Contingency Table

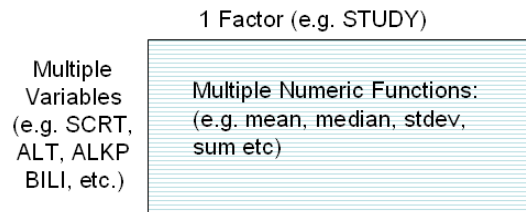
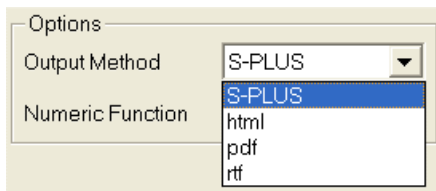


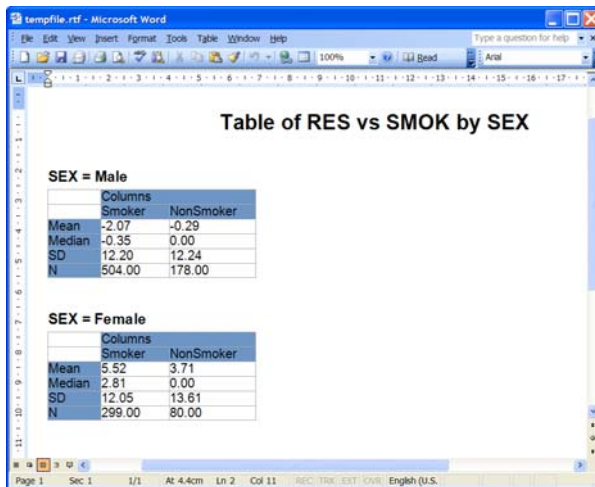
Figure 7: Summary Table

REPORT GENERATION

The table functionality described above produces a text-based table output in the S-PLUS environment (e.g. in a report window). This output can be saved to an external file for use in reports. To maximise flexibility, several report destinations were developed.



An additional argument was added to the existing table generation functionality. This argument controls the output format of the table. The options for this argument can be accessed using the “Output Method” field of the dialogue box (pictured here).



The default value (“S-PLUS”) produces a table in the S-PLUS environment.

However, alternative selections include *html*, *pdf* or *rtf* to produce and open external files.

Figure 8: Report destination selection

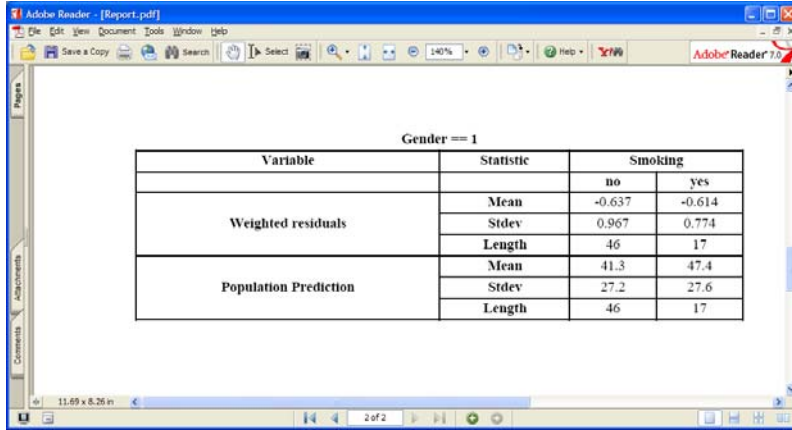
THE XML LIBRARY

An S-PLUS library called XML is distributed with S-PLUS version 6.2 and above. This library enables users to create XML documents based on custom schemas. Reports such as the one shown above can then be created using XML and XSLT technologies. Using this library permits the development of specific XML schemas, e.g. PfizerReport, which would capture information on the table output contents, together with information that can be used for auditing purposes (such as the actual S function call for reproduction of output at any time).

Once a “PfizerReport” XML document was created, a master XSL-FO style sheet could be used to translate the XML information into either RTF or PDF documents. The XSL-FO style sheet is able to import styles information in order to produce format-specific reports.

```
> createXMLFile(demog.frame[1:5, ], "tempfile.xml")
> xml2rtf("tempfile.xml", "tempfile.rtf")
```

To demonstrate this process, this example exports a sample dataset to XML then transforms it to PDF using the default S-PLUS style sheet.



The default style sheet outputs an object class, together with object dimensions, then outputs the data using standard columns.

Through the development of different style sheets, open control over various aspects of the report layout, including margin size, page orientation, fonts, titles and footers is provided.

In addition, the style sheets control the layout of tables to ensure page breaks are not placed within a table.

Figure 9: Generation of an XML output file

CONCLUSION

By properly evaluating customer requirements, skill set and knowledge base the business was able to select the appropriate technology to meet its needs. Through close collaboration, Pfizer and Mango Solutions were able to realise the requirements of the business and deliver a high quality tool that will add real benefits to Pfizer's drug development process.

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