A way to handle Pharmacokinetic studies with SAS®

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Abstract

In order to meet the need for the re-deployment of an application allowing the study of pharmacokinetic data, CIBA-GEIGY has chosen SAS because of its functional resources and the scope of its potential. The main constraints to this operation were to take back the existing data (hundreds of studies) and to set up a data model allowing to work on either a single study or on several studies at the same time.

Originally based on a relational craft-oriented data model, as well as on a set of reusable macros, the technical approach has been supplemented by a secured data input process and a relevant packaging. The whole led to an application allowing the storage of the data of a study, the calculation of the model-independent pharmacokinetic parameters, diverse simulations, reports (tables and graphics) that can be exported into office automation softwares.

Besides, specific meta analyses that concern a set of studies are available.

The modules used are: SAS/BASE®, SAS/AF®, SAS/FSP®, SAS/GRAPH® and SAS/STAT®.

1. Introduction

This paper describes the design of a pharmacokinetic software using SAS®. Pharmacokinetics evaluates the variation with time of the fate of a drug in the animal or human body after its administration. In pharmacokinetic studies, fluid samples (blood, urine, ...) are collected at various times after the drug intake (profile) and in each sample the amount of drug is quantified. With the data, some mathematical parameters are calculated. The data can also be used to simulate multiple administrations.

The storage of data from pharmacokinetic studies and their evaluation are often problems in the pharmaceutical industry. Numerous softwares exist which allow a complete mathematical evaluation of the data but most of them do not store in a secure and standardised way the data since they are designed to handle the data from a single study only. In contrary, relationnal data base management systems (RDBMS) allow a consistent and secure storage of the pharmacokinetic data but they are not designed to perform a complete mathematical evaluation.

In the Bioanalysis and Pharmacokinetics center of Ciba in Rueil, a complete set of pharmacokinetic programs was created in 1978. They offered the ability to store the data in a secure and standardised way and to perform a complete mathematical evaluation. This program was written in Wang Basic language on a Wang MVP system. Data from more than 500 animal and human studies have been stored in this bank. About five years ago, this system appeared to be not adapted any longer to the new computer technology: obsolescence of the hardware and basic language, communication problems with other systems, poor quality of the printouts, ... For these reasons it was decided, in 1993, to create a new pharmacokinetic tool (PKC) to replace the old one.
2. **Constraints of the new system**

As for all software development, the design of a new system is based on the users requirements, on the problems observed with the preceding version and on the business orientation. The new system must:

- Recover all the existing studies
- Be portable on various platforms, and have an evolution in its basic technology
- Communicate with various other systems and softwares (RDBMS, corporate data bases, etc.)
- Use a standard scientific software, so that the basic algorithms need not be revalidated
- Handle the data relative either to animal or to human studies in a consistent, secured and structured frame
- Calculate the basic pharmacokinetic parameters automatically or manually
- Simulate various types of administrations
- Be user friendly
- Allow a modular development of new functionalities
- Allow meta and cross analysis.
- Have connection with the standard office tools

Based on this brief description of the needs, various softwares were investigated. SAS® was found to be the best solution as it is running on various hardwares under diverse operating systems, it can communicate easily with various other softwares, it is a standard of the scientific community and it allows a tailor made development.

3. **Technical approach**

3.1. **Design guidelines**

PKC system core is based on:

- a set of craft-oriented data structures,
- a set of reusable macros designed to perform the calculations of the basic PK parameters (AUC, Cmax, Tmax, terminal half-life, AUCinf, Cl, Vd, UE, MRT, etc.).

Besides this core, the currently available functions are:

- manual entry of the basic data for a study,
- output of those basic data as well as calculated parameters, formatted as tables or graphs,
- specific calculations, such as manual determination of the terminal half-life, repeated dosing simulation, statistics...
• data export towards office tools.

Based on the principle of independence between data and functions, PKC system has been developed with a modular design, which allows non regressive evolutions such as:

• progressive enhancement of the system concerning data (implementation of tox studies) or functions (study pooling, meta-analysis, specific calculations, etc.),

• existing functions enhancement (progressive automatisation of data input, enlargement of output, greater variability of calculation rules, ...).

3.2. The Data Model

A precise analysis of the data gave a clear sight on the craft, led to a three-level design of the data model, and has been helpful to further design the basic functions of the system (Figure 1).

Figure 1 : Data model

The three levels of this model are:

• protocol level (definition of the study, treatments and subjects),

• clinical level (randomization of the subjects in the study, compound administration for each subject, individual samples),

• analytical level (couples of analyzed fluids/compounds, measured concentrations).
A fourth level has been added, composed of:

- a synthetic set of the basic data, at the lowest level (sampling time), mainly used for data output and particular functions,
- basic PK parameters, available for each (profile).

Besides the data specific to each study, a set of reference tables have been implemented. They contain high-level stability data, such as: compound definition, ways of administration, fluid types, study types, etc.. Those data are managed by an administrator. They are a good warrant for data integrity and data consistency, and are helpful in manual data entry (choice lists).

The technical design of the data base uses relational data modelling, which allows an optimum positioning of data, avoids data redundancy. Its implementation with SAS® software makes the system homogeneous and takes advantage of SQL language (mainly through the use of logical views).

3.3 Functions

3.3.1 Entry of raw data

Data entry is currently made in a manual way. Its basic guidelines are:

- operations follow the information hierarchy (e.g. the project must be defined before one can enter data to define treatments or subjects),
- maximum use of choice-lists to warrant information integrity and make operations easier,
- possibility to enter raw data at different times, according to information availability.

Simple screens have been developed using SAS/FSP®. More complex screens use SAS/AF® ("PROGRAM" type). All the data entry operations are directed using menus developed with SAS/AF®. Furtherly, FRAME technology will be used to design the screens in order to make them more user-friendly and to concentrate operations.

As soon as it will be possible, electronic data entry will partly take the place of the current functions, using customised interfaces with specialised softwares.

3.3.2 Calculation

The automatic calculations are performed on the complete set of available profiles. As a basic rule, the data are read once whatever the number of profiles to be processed. In contrary some manual calculations are available to explore and finalize the data evaluation (manual determination of terminal half-life, simulation of repeated dosing). The calculation algorithms are defined as a set of reusable macros which mainly use SAS/Base® and SAS/Stat® modules.

SQL was widely used in the data handling: inner and outer join of tables (simpler and safer than in a data step), complex logical views, shortening of the code (a SQL view can replace a large code portion).

3.3.3 Outputs

The creation of the outputs and files uses extensively PROC TABULATE, DATA STEPS, and PROC GPLOT. Two sets of outputs are created: one for direct printing and the other for the inclusion into Word® or other office tools.
3.3.4. Utilities

The customisation of graphics is performed within the PKC application using the GEDIT facilities (SAS/Graph®) through a set of screens which guide the user. The modified graphics can either be stored, printed or exported into Word® or other office tools. In the same way, a special tool was created to build Excel® spreadsheet directly from PKC after the selection of the relevant data (rows and columns, raw data and parameters to be included, internal or external grouping).

3.4 Technical informations

The minimum configuration to have an acceptable response time with the current SAS® 6.08 version is: PC 486 DX2 50, 16 Mb memory, Hard disk minimum 250 Mb, Postscript printer.


4. Description of the application

4.1. Study level

This application was designed to be userfriendly and self explanatory. In our center the technicians who perform the drug quantification, enter the results in the system and afterwards calculate the basic pharmacokinetic parameters. As a mean, they enter the data relative to studies twice a year, so the entry was specifically designed to be as simple as possible and reproduce the basic common workflow of a standard study. If the analytical instrument is connected with a software called Millennium® which performs integration and calculation of concentration, the concentration data can be captured directly into our application. In this last case, only the general information must be manually entered.

This application allows to :

• Manually enter the data related to a study (Figure 2):
  • Data relative to the protocol : general information (study description, ...), treatment definition (including administered compound), subject number....
  • Data relative to the clinical part : randomisation list, definition of the individual dosing by treatment/subject, definition of the fluid and analysed compound , individual samples (sampling times, ...).
  • Data relative to the analytical part : list of all the couples fluid/compounds analysed and the concentrations

The data input can be performed on multiple occasions, at any time during the analysis of the samples. The files can be easily updated. As an example, new subjects can be added during the input of data and the subject characteristics can only be entered at the end of the study. A lot of reference tables exist (i.e. administered, measured compound, fluids, type of studies, units, ...) and are an help to have standardised codification of the studies in the data entry base.
• Perform non compartmental analysis of concentration-time data either in an automatic or in a manual mode: AUCt, Cmax, Tmax, T1/2, AUCinf, MRT, VRT, CI, VB, UE (quantities or percent), .... The units of the parameters are automatically created from the time, dose, volumes and concentrations units entered (Figure 3)

Figure 3: The results of the manual calculation of terminal half life is presented on a graphic format, both manual and automatic results are presented, the results (graphic and parameters are also presented on the screen)
• Import data from ASCII, SAS®, Excel® files, Paradox® or Millennium®.

• Export data on ASCII, SAS®, or Excel® format.

• Create the run table for chromatography software Millennium®.

• Send the data to a corporate data base.

• The system manage conversion between molar and mass units.

4.2. Application management

The management of the application: updating of reference tables, management of the access rights, etc. is a separate module. All those management tools are only available for the system manager.

4.3. Further developments planned

New pharmacokinetic modules are planned to be added before the end of 1996: peeling, nonlin, modelling, absorption (Wagner-Nelson, Loo-Riegelmann, deconvolution), Pharmacokinetic / pharmacodynamic relationship, etc.

4.4 Integration of PKC (Figure 8)

Figure 8: Integration of the application
4.4.1 Functional integration

Based on the consistent data structure and standardized codes fields across all the studies, the pooling of studies is simple. This allows to select and perform meta or cross analysis of studies for a specific drug.

4.4.2 Technical integration

The data step allows to import and export data from or to various systems and softwares (informs and formats, DDE). The direct link with analytical instruments, planning tools and external data bases is possible due to the above mentioned features of SAS®.

4.5. Validation

The application was validated using data sets (plasma and urine) extracted from pharmacokinetic literature. Commercial pharmacokinetic softwares as well as Excel® spreadsheet were also used. For all the literature datasets evaluated, the results from PKC showed good agreement with those quoted in the literature or obtained with commercial packages.

5. Conclusion

SAS® was the best tool to develop this application in that:

- The migration from Basic was easy and rapid (one year)
- The existing data were recovered (500 studies)
- The migration across various platforms was optimum, the application has been in use first on a DEC VAX and now on a PC.
- The functionalities of SAS® allow to create a userfriendly and modular software, the users are globally satisfied with data entry, calculations, edition of tables and graphics but the links with the office tools (such as Word, Excel) has to be enhanced.
- The evolution is assured (portability, constant comptability between SAS® versions over 20 years, modular developement of the application)
- Presence of numerous links with other softwares and hardwares

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