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Technical note

PKC, a new pharmacokinetic software using SAS®

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1. Introduction

The creation of a new pharmacokinetic tool, called PKC, to replace a set of kinetic programs developed in 1978 on a Wang MVP system which has become obsolete in many aspects (e.g. hardware maintenance problems, quality of printouts, portability,...) was decided in 1993.

As for all software development, the design of the new system was based on the users' requirements, on the problems observed with the previous software version and on the business orientations. Some of the constraints of the new system were: to recover all data from existing studies (around 500) stored through the old system; to be portable on various platforms; to use a technology which is adaptable so as not to preclude further development; to communicate with various other systems and software (RDBMS, corporate data bases, etc.); and to use a standard scientific software, so that the basic algorithms need not to be revalidated.

This paper describes the technical approach and the major functionalities of PKC.

2. Technical approach

For the development of PKC, the data structure was chosen as craft-oriented with a set of reusable macros designed to perform calculations and to provide standard tables and graphics.

Based on the principle of independence between data and functions, PKC system has been developed with a modular design. This would allow non regressive evolutions such as the progressive enhancement of the system concerning data (data handling from toxicokinetic studies) or functions (specific calculations, automation of data input, etc...).

Simple screens have been developed using SAS/FSP®. More complex screens use SAS/AF® ('PROGRAM' type). All the data entry operations are made using menus developed with SAS/AF®. In order to make them more user friendly and to concentrate operations, the FRAME technology was used in some screens.

The calculation algorithms 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).

2.1. The data model

A precise analysis of the data to be handled led to a three-level design of the data model, which helped to further implement the basic functions of the system (Fig. 1). As presented in Fig. 1, the complexity of the information is increasing from the left to right and from top to bottom.

In the first level, or protocol level, the information relative to the study, the treatments and the subjects is entered. A minimum set of mandatory pieces of information must be entered at each level to allow the continuation of the entry process on the next level.

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In the second level called clinical level, the data relative to the randomisation of the subjects in the study, the individual dosing within a treatment, the evolution of the subject characteristic over the study period and the identification of individual scheduled samples (fluid, times and volumes if needed) are entered.

The third level is the analytical level where the couples of analyzed compounds/fluids are first defined with some features of the analytical method and then measured concentrations associated with the exact actual sampling times are entered.

A fourth level, named work data in Fig. 1, has been added and is composed of a synthetic set of the basic data at the lowest level (i.e. sampling time), mainly used for data output and particular functions, and for the basic PK parameters available for each set of subject/administered drug/fluid/analysed-compound (called profile in case of five sampling points minimum).

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, mode of administration, etc. These data, managed by an administrator, are a good warrant for data integrity and data consistency, and are helpful in manual data entry. The link between the various reference tables is such that some final choices can only be made according to previous definitions.

The technical design of the data base uses relational data modelling, which allows an optimum positioning of data and avoids data redundancy.

2.2. Functions

2.2.1. Entry of raw data and import tools

The data are currently entered either electronically or manually. The manual entries follow the information hierarchy (Fig. 1) and can be performed on multiple occasions, at any time during the analysis of the samples.

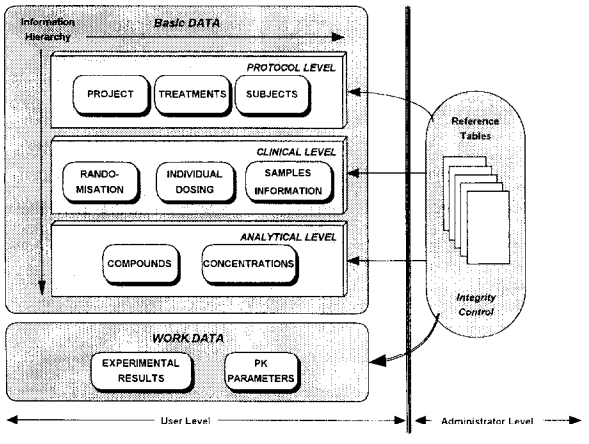

Fig. 1. Data model.

The electronic data entry partly takes the place of the current functions, using customised interfaces with specialised softwares such as Excel®, SAS®, Paradox®, or Millennium® (chromatographic software) or using an import facility of PKC with ASCII files. The basic data of the study (definition of all the information which are not directly related to the concentration) must be completed before any import from Excel®, Paradox® or Millennium®. Only the ASCII import, using a structured format of the files, allows full and direct electronic import in our system.

2.2.2. Calculation

The standard calculations were based on non compartmental analysis of profiles: AUCt, Cmax, Tmax, T1/2, AUCinf, MRT, VRT, Cl, V, UE(quantities or percent),.... The units of the parameters are automatically created from the time, dose, volumes and concentrations units entered. The basic descriptive statistics (mean, S.D., median, percentile) are calculated either for the raw data (concentrations) or on the derived data (pharmacokinetic parameters). Those calculations can be performed either automatically on the complete set of available profiles (as a basic rule, the data are read once whatever the number of profiles to be processed) or manually, profile by profile, to explore and finalise the data evaluation. The program allows to perform simulation of repeated administrations based on the superposition rule and adds, if needed, the observed concentrations on the final graph. Some more sophisticated calculation are possible: peeling and non linear parameters estimations based on one to three compartment models after intravenous bolus, infusion or extravascular administration. Four different algorithms are available for the non linear estimation: Gauss-Newton, Marquardt, steepest descent (gradient) or secant method (DUD); deconvolution [1] to determine either the entry kinetic from an e.v. profile (having the i.v. bolus as reference profile) or the i.v. bolus curve from an infusion profile (knowing the infusion characteristics); convolution to reconstruct from the i.v. and any entry kinetic the resulting profile; the determination of all the model micro-constants from curve equations and vice-versa; and the determination of absorption and elimination kinetics based on the Wagneer-Nelson or Loo-Riegelman equations [2,3]. Some simple statistical tests are available to the users such as ANOVA, t-test, regression, bioequivalence analysis (Proc GLM followed by the calculation of 90% CI, power, two-one-sided-t-tests and bayesian approaches).

The system integrates some automatic functionalities as for example the automatic conversion between the molar and mass units. If the dose is expressed in mass unit and the concentration in molar units, the conversion of the dose is performed automatically (using the reference table containing the administered drug and

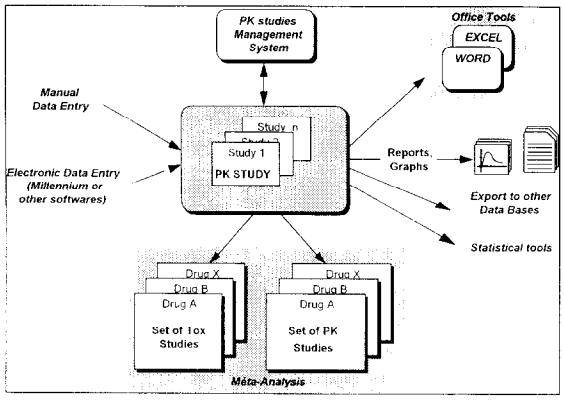

Fig. 2. Integration of the application.

the molecular weight) in order to obtain the pharmacokinetic parameter combining the two sets of information (i.e. clearance,...).

2.2.3. Outputs, customisation and export tools

The creation of the outputs and files uses extensively the SAS data steps and the two SAS procedures: PROC TABULATE and PROC GPLOT. Two sets of outputs are created (Fig. 2): one for direct printing and the other for the inclusion into office tools (Word®, etc.). 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 office tools. In the same way, a special tool was created to build Excel® spreadsheet tables directly from PKC (using DDE links) after the selection of the relevant data (rows and columns, raw data and/or parameters to be included, internal or external grouping). Other export tools exist to create either ASCII or SAS files. Special modules were devoted to the creation of the run table for Millennium®, to retrieve the final concentrations from Millennium® and another one to send the data directly to corporate data bases (Fig. 2).

2.3. Integration of PKC and pooling of data

Based on the consistent data structure and standardised code 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 (Fig. 2).

2.4. 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.

3. Validation

The program development has been documented and a prospective validation scheme has been set up according to the OECD [4] and Ciba internal guidelines. This validation used data sets (plasma and urine) extracted from pharmacokinetic literature [5–8], data from real studies and simulated data sets. All the functionalities and calculations were tested. Commercial pharmacokinetic software as well as Excel® spreadsheet were also used to reproduce all the calculations. For all data sets evaluated, the results from PKC showed good agreement with the expected results.

In addition, an audit tool is provided which records all the modifications occurring in the data base associated with the user name, date, and the previous value of the data.

4. Conclusion

The full migration from Wang MVP Basic was easy and rapid (one man year). All the existing data were recovered and the migration across various platforms (first on a DEC VAX and now on a PC) was found to be feasible. The evolution is assured by the portability, and the constant compatibility between SAS® versions over 20 years associated with the modular development of the application.

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References

[1] D. Vaughan, M. Denis, Mathematical basis of the point area deconvolution method for determining the in vivo input functions, J. Pharm. Sci. 64 (1978) 663–665.
[2] J. Wagner, E. Nelson, Kinetic analysis of blood levels and urinary excretion in the absorption phase after singler dose of drug, J. Pharm. Sci. 53 (1964) 1392–1403.
[3] J.C. Loo, S. Riegelman, New method for calculating the intrasec absorption rate of drug, J. Pharm. Sci. 57 (1968) 918–928.
[4] OECD, The application of the principles of GLP to computerised systems. ENV/EPOC(95) 18 (1995) 5–8 December.
[5] M. Gibaldi, L. Prescott, Handbook of Clinical Pharmacokinetics, ADIS press, New York, 1983.
[6] B. Clark, D.A. Smith, An Introduction of Pharmacokinetics, second ed., Blackwell, Oxford, 1986.
[7] J. Wagner, Pharmacokinetics for the Pharmaceutical Scientist, Lancaster, Basel, 1994.
[8] J. Wagner, Fundamental of Clinical Pharmacokinetics, Drug Intelligence Publication, Hamilton, 1971.