

Clinetics Data Merge - A Platform for Exchange of Pharmacokinetic Data

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ABSTRACT

Within Bayer Schering Pharma (BSP), a data transfer system was developed, which enables a controlled and standardized exchange of pharmacokinetic (PK) concentrations, calculated PK parameters and related clinical data (CRF/eCRF) between Bioanalytical Laboratories, Clinical Pharmacology and Data Management.

A protected directory tree on the Unix Host serves as a central exchange area for transfer of data. Transfer from this area is started automatically upon presence of delivered data. Tools for data handling and checking are initiated from Unix system and are implemented as SAS macros. A globally harmonized format for the data exchange is specified in the Data Description Document and is implemented in translation tables. All departments can develop their own tools independent of each other, they only have to make sure to deliver the transfer data in the agreed exchange format.

Keywords: Pharmacokinetics, Bioanalytics, Data Description Document

INTRODUCTION

Pharmacokinetics includes the study of the mechanisms of absorption and distribution of an administered drug, the chemical changes of the substance in the body (e.g. by enzymes) and the effects and routes of excretion of the metabolites of the drug.

Many clinical trials, particularly Phase I and cancer studies, make use of the evaluation of pharmacokinetic concentrations and parameters. According to ICH and regulatory guidelines, it is necessary for companies to investigate the extent and rate of absorption, distribution, metabolism and excretion of drugs under development. Demographic and dosing related data from the clinical database, PK concentrations and calculated PK parameters are collected and maintained at different sites. All this information needs finally to be assembled in the clinical database.

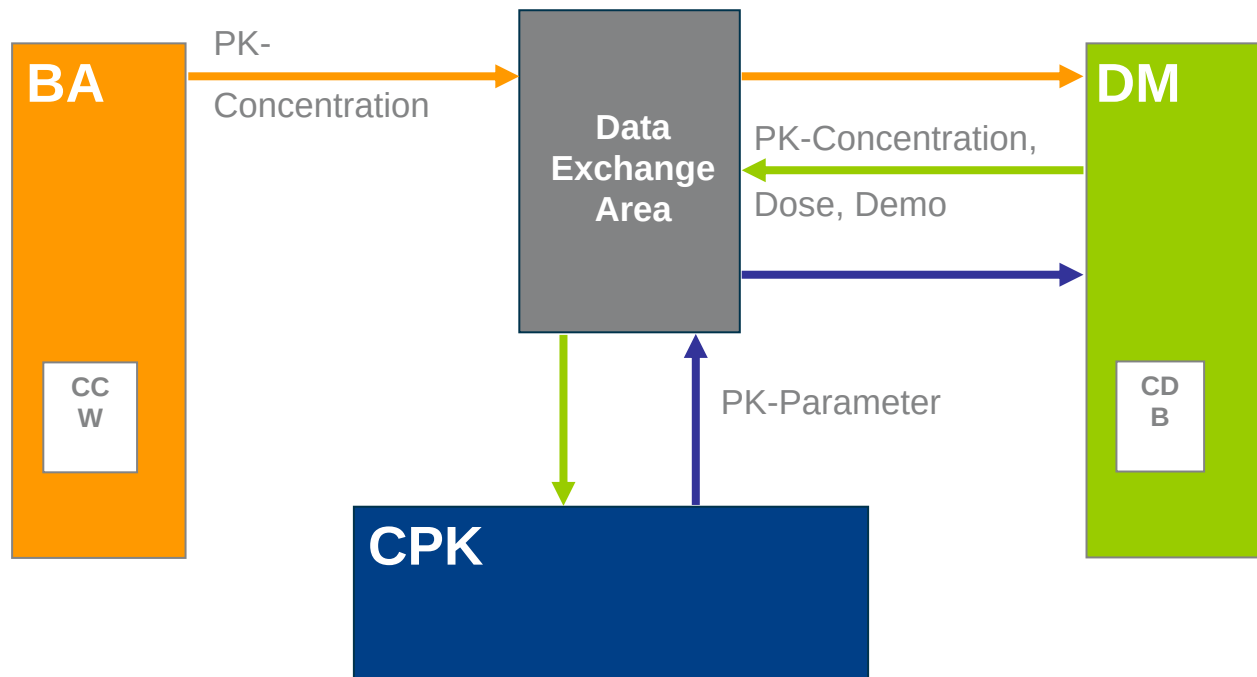
The exchange and transfer of data among the sites needs to be harmonized and organized to ensure that demographic and dosing data is correctly related to associate PK data. Moreover, the evaluation of concentration data which is commonly derived from metabolites of substances administered with study drug jeopardizes the blinding during the conduct of a study. So it is important to ensure that the access to these data is restricted until unblinding of a study. This has to be realized without disturbing the whole data flow.

Within BSP, three departments are involved in exchange and maintenance of PK related data: Bioanalytical Laboratory (BA), Clinical Pharmacology (CPK) and Data Management (DM). These sites agreed to establish a data flow process which is based on a central exchange platform. The complete system is called Clinetics Data Merge. The goal was to harmonize procedures, exchanged files, variable names, related formats and contents in order to fulfill the needs of all departments and to take the company internal Global Medical Standard (GMS) into account. In this paper we describe the principle of data flow among sites, the exchange platform and the structure of data transfer files.

CLINETICS DATA MERGE

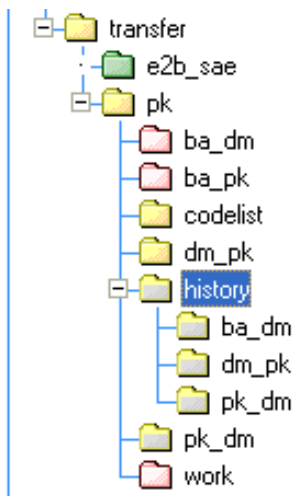
The Bioanalytical Laboratory measures the concentration of metabolites from samples delivered by the clinical sites. Samples are mostly taken at different time points before and after drug administration. All data related to sampling as well as to drug administration are entered into the clinical database via electronic data capture (EDC). The results of measurements provided by BA need to be unequivocally related to sampling and demographic data. This has to be done by Data Management using SAS macros. The combined data are then delivered to Clinical Pharmacology which calculates pharmacokinetic parameters based on PK concentration, drug related information and demographic data. The three sites, Bioanalytical Laboratory, Clinical Pharmacology and Data Management are working with different platforms for data processing but have to establish a data flow among them:

- Bioanalytics (**BA**) delivers concentration data to Data Management (**DM**) upon availability of results
- Concentration data files are transferred to a locked directory in the study repository on the UNIX server
- Data are integrated into the Clinical Database by **DM**
- The transfer file to Clinical Pharmacokinetics (**CPK**) is created by **DM** to initiate the pharmacokinetic evaluation
- **CPK** performs the PK evaluation and transfers the results back to **DM**
- **DM** integrates the PK parameters into the final Clinical Database



Exchange area:

The exchange area is a static directory tree on a UNIX server with subdirectories for transfer files and archiving, named according to the direction of data transfer, e.g. BA_DM for transfer from Bioanalytics to Data Management. All data for one transfer are compressed in a ZIP archive. The access to server and directories is realized via a network drive which is implemented via Server Message Block protocol of the Samba Software. As a result, the Unix drives are mapped within the environment of other operating system, e.g. Windows. In this way, all parties can read and write data in the exchange area regardless the operating system and software they are working with.



Concentration data in some of the subdirectories could lead to premature unblinding of treatment assignment. Unix based ACLs (Access Control Lists) are used to deny read or write access for departments or persons which should not have access to this information. The transfer from the departments to the exchange area depends on the operating system and software they use. The transfer from the area to the departments is performed automatically by a cronjob, which is set up within the Unix environment. This cronjob checks in predefined time intervals (e.g. every 30 minutes) the subdirectories for new data. In case of any findings a transfer will be initiated with the following basic steps:

- Check ZIP file name to obtain Project and Study number
- Check and extract data files from the ZIP archive
- Check filenames to obtain further information about contents
- Call of a number of cascaded SAS macros which checks the contents of the files
- Send the data files to the destination of the respective sites
- Send an Email to the associated departments and persons notifying them about the transfer in case of successful transfer as well as in case of any error

Upon completion, all data in the directories are erased and a copy of the ZIP files is stored in the respective subdirectory of the 'History' folder. Access to contents is still limited to the associated departments. In case of transfer

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of files to Data Management the read and write access to the destination directory is restricted until the study is unblinded.

Transfer Data File Structure

All data files exchanged among parties are compressed into a ZIP archive. The integrity of data during transfer between different platforms of departments is provided by cyclic redundancy check of the ZIP software. The naming convention is the same for ZIP file names and for files in its archive:

<project>_<study>_<matrix>_<analyte>_final.

The files containing the data are ASCII based CSV (Comma Separated Values) files. All files contain a general data section at the beginning of the file (Worksheet section). In addition, specialized data sections enclosed by keywords can follow. Variable names are declared in the first line of the worksheet and each specialized section. Each name defines a column. Values listed in the following lines with columns related variables are separated by a semicolon, each line represents a record. The set of column names and their order is specific for requirements of the departments involved in the transfer process.

The specification of variables to be exchanged during parts of the data flow among departments is itemized in a document called Data Description Document. For each transfer part the mandatory and optional variables and the associated numeric and character formats are determined. These specifications are implemented in more detail within Unix environment as a set of translation tables stored as SAS datasets. The tables contain the column names of transfer files, the corresponding SAS variable names, their type, and associated formats and codelists. In addition a flag whether a variable is mandatory or optional, and a description is provided. Codelists used in the transfer are only standardized codelists from GMS which are updated continuously.

During each transfer between any sites a cascade of SAS macros is called by the Unix cronjob in order to check whether the contents of transfer files adhere to the specifics of the translation tables. In case of any deviation the transfer is aborted and the associated departments and responsible persons are notified by Email. The Email contains reports generated by the SAS macros containing the type of deviation and the source of error.

In case of transfer to Data Management, the ASCII files are imported into SAS data sets by SAS macros. The SAS variable names in the translation tables are then used to assign the columns of the transfer file to the corresponding SAS variables.

In case of any changes in Global Medical Standards, e.g. change of mandatory variables or change of codelists, it is sufficient to make changes in the translation tables rather than rewriting the SAS macros.

CONCLUSION

The Clinetics Data Merge is a data exchange system allowing all departments to exchange PK – related data independent from their preferred environment. The consistency of data exchanged among departments is checked by SAS macros invoked during each transfer. Read and write access is controlled, Email notification automatically carried out. The use of translation tables allows further adjustments to future changes of standards and codelists. Hence, the Clinetics Data Merge system provides a considerable amount of flexibility in conjunction with a secured environment.

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