Pharmacokinetics standardization: patients’ healthcare is becoming central

Ingrid Burton, ClinBAY, Genappe, Belgium
Sascha Ahrweiler, UCB Bioscience, Monheim, Germany
Vincent Buchheit, Roche, Basel, Switzerland
François Vandenhende, ClinBAY, Genappe, Belgium

ABSTRACT
Drugs must be therapeutically effective with limited adverse side effects. Understanding of pharmacokinetic (PK) compound properties is crucial to identify the best dose for patients. Therefore, PK analyses are necessary for all new therapeutics. The development and adoption of data standards over the last decade has shown significant promise in improving efficiencies in the product submission and review process. To emphasize this effort of standardization of clinical trials, the FDA/PhUSE Computational Sciences Symposium (CSS) Working Group 5, project 8 (http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08) deals with the creation of white papers providing recommended displays and analyses including Table, Listing and Figure shells. As part of this project, our aim is to define PK guidelines and recommendations in order to perform high quality PK analysis. In this poster, we present a first draft for the main rules and some standardized tools in order to quickly and automatically create outputs based on validated SAS macro. Improving PK analysis tools is a major step to make patients’ healthcare becoming central.

INTRODUCTION
Pharmacokinetics (PK) is the study of the time course of a drug concentration within the body. Knowledge of drug disposition, together with drug response and therapeutic effect becomes increasingly important in the design and development of new drugs and also in a better comprehension of existing drugs.

The objective of this working group is to define PK standards, recommendations, imputations rules, analysis flows, standardized tables, figures and outputs shells through discussion within FDA/PhUSE CSS wiki WG5 project 8 (which will get together PK and programmers experts).

PK REPORTING WORKFLOW
While performing PK analyzes, one of the most important point is to clearly define a standard workflow and rules that need to be applied at each step of the process. In this poster we will focus on non compartmental analysis (NCA). Modeling activities have some more particularities that we won’t discussed here. The diagram below illustrates various steps that could be considered in the reporting of PK results. A set of rules needs to be defined for each step. Each rule has a list of possible options. Their choice is often company- and compound-specific. It depends on historical practices, procedures and requirements. We won’t discuss the preference for any particular option here. Rather, our goal will be to emphasize the fact that a framework of standard rules can be built to cover the entire spectrum of PK analysis and reporting activities.
DATASETS STANDARTIZATION

Industry has now largely accepted CDISC standards for clinical trial data. In this sense, PK data should also follow this standardization, e.g. PK concentration stored in the PC domain and PK parameters in the PP domain. Coming to an agreement about a CDISC compliant workflow is one of the goals of the working group (e.g. SDTM.PC only contains sample results as collected; PK parameters are derived by PK experts and will be available to statistical programmers in SDTM.PP; all other derivations are done in the analysis ADaM datasets).

TABLES, FIGURES AND LISTINGS STANDARTIZATION

Another objective of the working group is to propose a library of recommended outputs shells for PK results. As PK analyses is widely depending on different factors like study design, this template library will include recommendations and standards for the most common types of PK trials. It will contain standardized templates for both PK concentrations and parameters (listings, summary tables, individuals and mean plots, specific analysis tables and plots). An example of concentration summary report is presented below.
VALIDATED REPORTING PROGRAMS

Standardization of programming activities and creation of automated validated tools is an important step to ensure uniformity and guarantee quality of produced outputs.

A set of macros (e.g., SAS® or R) will be developed within the FDA/PhUSE CSS WG5 based on recommendations and shells defined in the project 8 white paper.

CONCLUSION

FDA/PhUSE CSS WG5 project 8 will be an important contribution to the standardization of analysis reports. The planned white paper will focus on PK. It will involve subject matter experts from various pharmaceutical companies, contract research organizations, and regulatory agencies. During the next months, the discussion group will strive to propose recommendations for the reporting of PK analyses. Standards will be proposed for the reporting flow, the datasets, and the output shells. The white paper will then be the basis for the creation of automated, and validated reporting programs for PK analyses. These programs will be published on the PhUSE Standards Script repository.

If you want to participate in the creation of this white paper please contact one of the paper authors.

REFERENCES

CDISC Submission Data Standards Team. Study Data Tabulation Model Implementation Guide: Human Clinical Trials v 3.1.3., 2012-07-16.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at: Ingrid Burton
PhUSE 2013

ClinBAY
30 rue Bon Air
1470 Genappe
Belgium
Email: ingrid@clinbay.com
Web: http://www.clinbay.com

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