Forensic Pharmacometrics: Part 1 - Data Assembly

T. Grasela, J. Fiedler-Kelly, D. Hitchcock, E. Ludwig, J. Passarell

Cognigen Corporation, Buffalo, NY
cognigencorp.com

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ABSTRACT

Introduction. Pharmacometric modeling and simulation (M&S) is moving from merely describing pharmacokinetic (PK) and pharmacodynamic (PD) phenomena to informing critical drug development and regulatory decision-making milestones. As M&S results become integral to a program's outcome, the consequences of lapses in data assembly and analytic result quality can jeopardize the role of pharmacometrics in contributing to the transition to model-based drug development. There are few standards available to define measures of acceptability and suggest strategies for assessing the "fit for purpose" of analysis datasets or model building efforts. While there is often attention paid to documenting the amount of data deleted from the analysis datasets and the reasons for such deletion, less attention has been paid to embedding proactive quality assurance activities into the data assembly process. These quality assurance activities might include, for example, a review of programming logic and coding as well as the assumptions used to re-create dosing histories.

Objectives.

- Describe a case study of a forensic assessment of analysis-ready datasets performed as part of a due diligence effort in preparing for re-purposing data to support future development program efforts and regulatory filings
- Describe methods used in the forensic assessment that identified problems and errors in the previously constructed datasets and propose proactive quality assurance activities

Methods. The due diligence effort incorporated a systematic review of the various data elements to identify and focus efforts only on those data warranting correction and rebuild. A series of quality assurance checks comparing the analysis-ready datasets to the source data files were developed by both data programmers and scientists addressing their individual areas of expertise regarding quality assurance. Three teams, operating in parallel and consisting of a scientist and a data programmer, were constituted to focus on different aspects of the PK and PK/PD datasets and modeling. A senior scientist, supported by a medical writing team, served as the overall integrator of efforts and point of contact for various groups within the Sponsor organization. A review of the previously prepared technical reports was used to identify the assumptions and strategies that went into the original data assembly and model-building efforts.

Results. The forensic analysis of the analysis-ready datasets revealed a mismatch in demographic data with corresponding dosing and PK data in a large percentage of patients and systematic errors in the creation of dosing histories, including improper use of NONMEM®-derived data items (ADDL) and incorrect dose amounts in subsets of patients across studies. The descriptions of patient disposition and data deletions in the technical reports were insufficient in supplying reasons or rationale for the programming logic errors discovered.

A summary of the forensic assessment findings was presented to the Sponsor. Given the extent of the issues with the data and the likelihood of significant impact on the modeling results, senior management charged the data assessment teams with re-creating the analysis-ready datasets, re-running the models, and re-writing the technical reports within 4 weeks. Subsequently, the data assessment teams were also charged with a strategic review and update of derivative documents including the proposed product label, the Clinical Pharmacology Summary, and the data definition documentation.

Conclusions. This forensic assessment of a completed analysis demonstrates a gap that currently exists in defining the criteria for judging the quality of data assembly efforts along with the comprehensiveness of data programming, technical report, and other supportive work product documentation. Strategies for this assessment can be used as a basis for independent validation of pharmacometric work products prior to use in critical decision-making activities, as well as in the development of standards for quality assurance activities during the execution of a pharmacometric analysis.

METHODS

Forensic assessment of the provided analysis-ready data (dataset) was used to ensure the dataset had been built correctly (meaning that valid and appropriate assumptions were applied and no critical errors were made in the processing and pooling of study data). Furthermore, the forensic assessment results were used to determine the adequacy of the data for the planned analyses. Examples of data quality checks that were performed on single data elements and relational data elements are categorized below.

Data Summaries and Listings

- Frequency distributions for categorical variables were generated and examined for unexpected values. For continuous variables, summary statistics were generated to detect potential outliers.
- Counts of the numbers of patients, observations, dosing records, and observations per patient were checked against expectations.
- Listings of derived variables and recalculated values were generated to confirm accuracy.

Exploratory Data Analysis

- Graphical displays were employed, as part of an exploratory data analysis (EDA) step, to understand the informational content of the datasets and to assist in determining if any errors were made in the manipulation of the data, including:
  - individual concentration time profiles,
  - frequency distributions of time since last dose, and
  - scatter plot matrices of covariates.

Comparison to NONMEM® Standards

- Verification routines ensured the datasets conformed to NONMEM requirements, such as:
  - the sorting of individual patient records in the correct time order,
  - covariates were varying/non-varying as intended across records, and
  - all NONMEM-derived variables were set correctly.

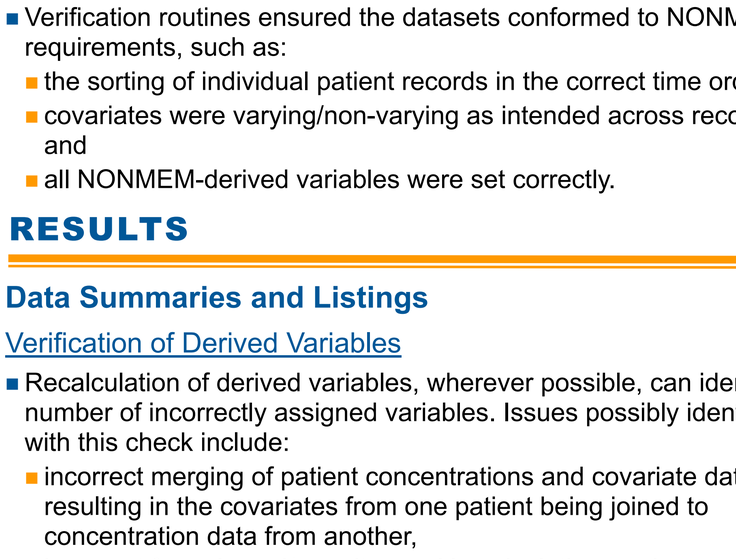
RESULTS

Data Summaries and Listings

Verification of Derived Variables

- Recalculation of derived variables, wherever possible, can identify a number of incorrectly assigned variables. Issues possibly identified with this check include:
  - incorrect merging of patient concentrations and covariate data resulting in the covariates from one patient being joined to concentration data from another,
  - incorrect formula and/or units used in calculation, and
  - special population flags (for example, renal impairment) set incorrectly.
- In this case, differences in the recalculated values for CrCL and BMI were identified. Further investigation revealed that the demographic file was not correctly merged to the patient concentration file resulting in a mismatch of demographic data with drug dosing and sampling data.
- In **Figure 1** below, the result of a misalignment of demographic data results in the lack of detection of a true relationship.

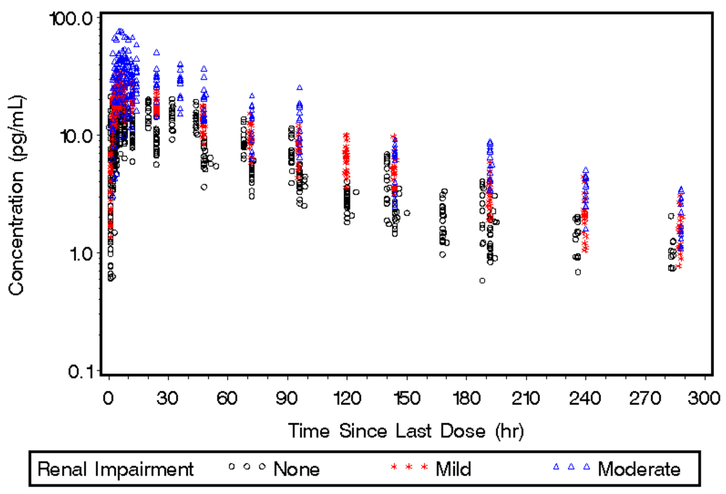
Figure 1. Concentration Versus Time Categorized by Renal Impairment Prior to Data Correction – No Apparent Relationship



Encore:
Previously presented at American Conference on Pharmacometrics (ACoP)
Mashantucket, CT; October 4-7, 2009

- **Figure 2** below shows the corrected demographic data and reveals the drug has a relationship with renal impairment. Furthermore, the calculation of other patient factors, dependent on the mismatched demographic factors (for example, BMI and CrCL) would similarly be incorrect.

Figure 2. Concentration Versus Time Categorized by Renal Impairment After Data Correction – True Underlying Relationship Revealed



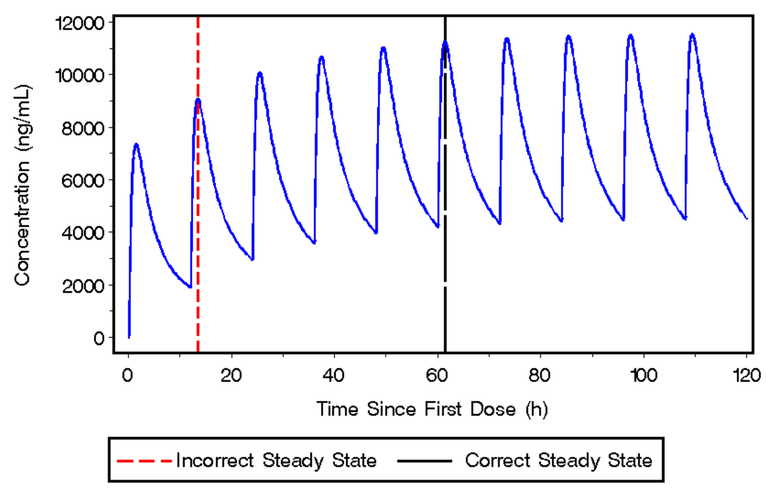
Verification of NONMEM Variables: AMT and ADDL

- A cross-tabulation of the number of additional doses and the dose amount revealed unexpected combinations of values that differed from the protocol-defined treatment groups.
- Further investigation of the raw data confirmed that the additional dose flag (ADDL) was incorrectly set, resulting in NONMEM interpreting that the dose was doubled on some occasions immediately before samples were collected. The dose amount was also assigned incorrectly to the amount of the next dose to be taken rather than the previously taken dose.

Verification of NONMEM Variables: SS

- A cross-tabulation of visit, day since first dose, and NONMEM steady-state flag (SS) showed that patients were set to steady-state conditions based on a visit label, but the actual number of days since first dose revealed that insufficient time had elapsed since the start of dosing to assume that steady state would have been reached in some patients.
- **Figure 3** illustrates the difference between the time at which steady state was incorrectly assumed given the coding error and time at which it would appropriately have been assumed.

Figure 3. Concentration Versus Time

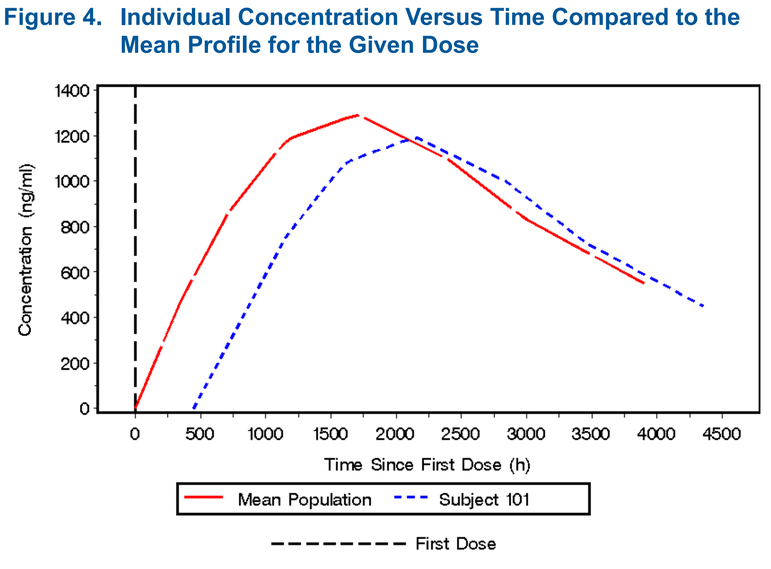


Exploratory Data Analysis

Dosing History Problems

- Examination of individual patient profiles can highlight obvious data errors when compared to others with similar dosing regimens and/or sampling strategies or to the population.
- In **Figure 4**, errors in dosing history are evident as obvious gaps between dose and sample times. In this case, the sample collection date was incorrectly entered as Day 20 instead of Day 1 following a single dose on Day 1.

Figure 4. Individual Concentration Versus Time Compared to the Mean Profile for the Given Dose



Comparison to NONMEM Standards

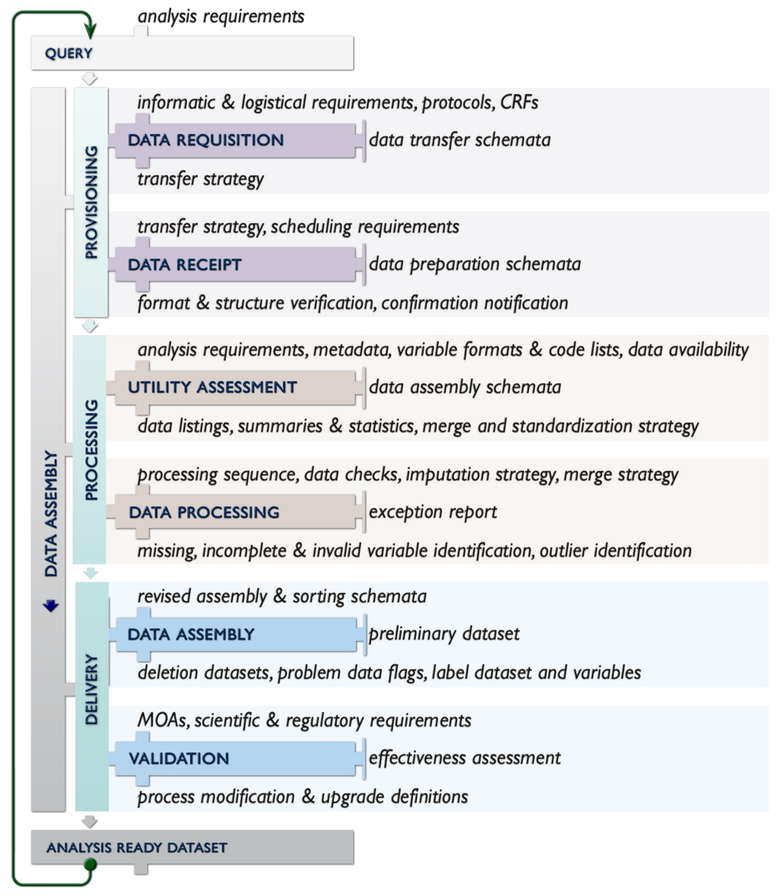
Identification of Duplicate Sample Records

- While logically it is impossible to have 2 different drug concentration measurements at exactly the same time, duplicate concentration records could exist based on assay procedures or a recording error of the date and/or time.
- Although the existence of both records in the analysis dataset will not result in an error from NONMEM, it could inappropriately increase the residual variability estimate, bias the actual exposure estimations, and/or present a problem with matching multiple exposure measurements to a single pharmacodynamic measurement at that same time point.
- To resolve this problem, more information needs to be collected from the lab to discern the reason for such duplicate and disparate results and/or these points may need to be examined in relation to the rest of the information available for this patient in a graphical format of concentration versus time since first dose.

Recommended Proactive Quality Assurance Activities

- Implementation of applicable programmatic data checks on the due diligence datasets, based on Cognigen's systematic approach to creating analysis-ready datasets, revealed important errors not previously detected.
- Typically, this systematic approach is applied during the dataset assembly process, but was utilized in this case for the forensic assessment of the due diligence datasets.
- **Figure 5** depicts the core tasks required to create an analysis-ready dataset. In response to a query for pharmacometric analysis, data are requested and received, reviewed, and converted from raw data to information based on analysis requirements, reassembled, tested for effectiveness, and ultimately delivered for use in the pharmacometric analysis.[1]
- For the forensic assessment of the due diligence datasets described herein, the process started with Validation, and continued with the Data Requisition and subsequent processes when the quality checks revealed problems.

Figure 5. Systematic Approach to Data Assembly



- It is recognized that dataset errors are often subtle and difficult to detect and additional non-programmatic data checks should be employed, such as requirements management,[2] code review, program verification, and comparison to raw data. Additionally, while not required by NONMEM, establishing certain internal standards may contribute to consistency in data structures and eliminate possible errors as data are pooled or repurposed. Examples of internal standards include:
  - establishing a unique identification number for each patient,
  - requiring CMT, EVID, and MDV are present,
  - starting each patient with a dose record (if appropriate), and
  - eliminating dose records following the last sample record in pharmacokinetic datasets.

CONCLUSIONS

- Detection strategies implemented in these forensic assessments were successful in characterizing distinct types of errors in data assembly, and can be further refined to target specific data structures based on study design.
- Prospective quality assurance checks should be employed for independent validation of datasets for pharmacometric analysis prior to critical decision-making activities.
- Applying a systematic approach during the data assembly process (see **Figure 5**) is critical to assuring the accuracy and improving the quality of the analysis-ready dataset.
- Exploratory graphical data analyses of analysis-ready datasets prior to modeling provides yet another mechanism to detect possible data errors.
- The proposed process for forensic assessment of analysis-ready datasets may be applied in due diligence scenarios to ascertain the quality and accuracy of pharmacometric analysis-ready datasets. As pharmacometric modeling and simulation efforts become more integral to critical path decision-making, standards for assessing dataset quality will be a necessity.

REFERENCES

1. Grasela TH, Fiedler-Kelly J, Cirincione BB, et al. Informatics: the fuel for pharmacometric analysis. *AAPS J*. 2007;9:E84-E91.
2. Grasela TH, Fiedler-Kelly J, Hitchcock D. Improving the efficiency and ensuring the quality of data assembly for pharmacometric analysis. Poster presented at the American Conference on Pharmacometrics (ACoP); March 9-12, 2008; Tucson, AZ and at the Population Approach Group in Europe (PAGE); June 23-26, 2009; St. Petersburg, Russia.

Nineteenth Meeting of the Population Approach Group in Europe (PAGE); Berlin, Germany; June 8-11, 2010

For additional information, please contact: Darcy Hitchcock
Cognigen Corporation; 395 South Youngs Road, Buffalo, NY 14221 USA
(716) 633-3463, ext. 222 or Darcy.Hitchcock@cognigencorp.com.