Forensic Pharmacometrics: Part 2 - Deliverables for Regulatory Submission

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ABSTRACT

Introduction. As modeling and simulation results become increasingly integral to critical development-related decision-making and program outcomes, the consequences of poor documentation of pharmacometric analyses can jeopardize the role of pharmacometrics in contributing to the transition to model-based drug development. While the EMEA and FDA Population PK Guidance documents recommend pharmacometric report content, forensic assessment of analysis inputs and outputs may enable the development of standards to define measures of acceptability and support the continued evolution of these methods.

Objective.

- Define and apply a process for the prospective forensic assessment of regulatory deliverables to gain understanding of common problems

Methods. A review of recent externally generated pharmacometric analysis inputs (analysis-ready datasets, analysis plans) and outputs (models, final technical reports), intended for submission to regulatory authorities, was performed using a systematic process for forensic assessment. For each deliverable, descriptive statistics summarizing categories of common problems were generated.

Results. The process included the following steps: (1) initial review and identification of issues for further investigation, (2) request for additional supporting information, (3) verification of consistency of supporting information, and (4) suggested strategy for correction. For analysis-ready datasets, the supporting information may include source data collection methods, additional exploratory graphical displays, or a flowchart of the programming logic applied in the data manipulation process. For analysis plans, a series of questions addressing how likely scenarios would be handled might be generated. For models described in technical reports, consistency between output tables of results, NM-TRAN code, NONMEM® report files, and text describing results can easily be confirmed. Based on this process, the following types of common issues were identified: systematic errors in the creation of dosing histories, incomplete strategies for assumption violations, and numerous inconsistencies in the reporting of modeling results.

Conclusions. The process developed for this assessment can be used as a basis for independent validation of pharmacometric deliverables intended for regulatory submission, as well as in the development of standards for quality assurance activities for pharmacometric analyses.

INTRODUCTION

- The 2006 Critical Path Initiative advocated model-based drug development programs to reduce uncertainty about dose selection, product design, and other safety and efficacy issues through better use of data to improve knowledge of key aspects of product development such as exposure-response relationships, and by supporting innovative trial designs.[1]
- Given this directive, the quality and accuracy of analysis datasets and the appropriate presentation of pharmacometric analysis results is essential to ensure the appropriateness of model-based recommendations and provide a level of detail that will enable a secondary evaluation (that is, assessment by regulatory authorities of the conducted analysis and conclusions drawn) as suggested by the EMEA guidance on reporting of population pharmacokinetic analyses.[2]
- Based on relevant regulatory guidances and current practice standards, a retrospective review of random samples of Pharma-generated pharmacometric analysis inputs (analysis-ready datasets, analysis plans) and outputs (final technical reports describing model development and evaluation) was performed to better understand compliance with and appropriateness of judgment-making within the context of these guidances and standards.[2-13]

METHODS

A review of recent Pharma-generated analysis-ready datasets, analysis plans, and final technical reports describing model development and evaluation, intended for submission to regulatory authorities, was performed using a systematic process for forensic assessment as described below. For each deliverable, descriptive statistics summarizing categories of common problems were generated.

Analysis-Ready Datasets

A sample of analysis-ready datasets received by Cognigen for use in contract consulting projects was reviewed based on the rules and structure governed by the software to be used for analysis, coupled with an understanding of the data collected and the study design(s).

Data Analysis Plans

Relevant regulatory guidance documents, published literature, and other available sources regarding pharmacometric data analysis plan content were reviewed.[2-13] Commonly cited suggested content was assembled into an outline of data analysis plan sections. For each section, specific questions were developed as a basis for evaluation and assessment as shown in **Table 1**. A sample of externally generated data analysis plans received by Cognigen for use in contract consulting projects were reviewed against the outline of data analysis plan sections and questions for assessment.

Table 1. Data Analysis Plan Quality Questionnaire

Data Analysis Plan Content Category	Questions for Consideration
Introduction	Does the background information include a clear statement of the purpose for the analysis, the intended use of the model, and the context for the effort in the development program? Does the introductory material include a statement of the objectives of the analysis?
Data	Is the study design of the relevant study/studies described? - Dosing - Pharmacokinetic sampling, biomarker sampling, pharmacodynamic endpoint definition and sampling - Collection of relevant demographics, laboratory values, clinical chemistries, concomitant medications, other covariates, etc. - Bioanalytical methods
Analysis dataset creation	Is the data to be included specified? Is the population to be analyzed defined? Are the covariates to be evaluated cited, along with the parameters upon which they are to be evaluated? Is the handling of missing data described? Are any other relevant data editing rules cited?
Pharmacokinetic and pharmacokinetic/ pharmacodynamic analysis methodology	Is an overview of the modeling methodology provided? Is the software and/or hardware to be utilized cited? Are the planned exploratory (graphical or other) data analyses described? Is the identification and treatment of outliers described? Is the base structural model development described, along with the modeling assumptions, fixed and random effect models, and a description of the process to be followed if the assumptions are not met or the intended model is found inappropriate? Are the methods for covariate evaluation, including the relevant α-value for decision-making, clearly specified? Are the methods for model evaluation (validation) described? Are the methods for the generation of individual exposure measures described? Has an assessment of the clinical significance of covariate effects been considered and described?

Final Technical Reports

Content acceptability criteria for review of technical reports describing pharmacometric analyses were developed (as shown in **Table 2**) using the FDA and EMEA guidances on population pharmacokinetics and exposure-response, and the Cognigen canonical technical report documentation for pharmacometric report preparation.[2,3,4,12,13] A random sample of final technical reports prepared by Pharma companies external to Cognigen was reviewed based on these criteria.

Table 2. Criteria For Report Content Acceptability Review

Report Section	Content Acceptability Criteria
Introduction/ objectives	• Drug pharmacology and relevant prior knowledge of pharmacokinetics and/or pharmacokinetics/pharmacodynamics adequately described • Intent of the analysis and the developed model(s) stated within the context of the clinical development program • Special features of the analysis stated • Analysis objective(s) clearly defined
Data	• Study design of the relevant studies (for example, treatments and duration, baseline run-in or treatment titration periods, cross-over, drop out plan) described • Sampling schemes defined: pharmacokinetic, biomarker, pharmacodynamic endpoint (efficacy/safety) • Collection of relevant demographics, clinical laboratory tests, concomitant medications, other covariates, etc. is described • Bioanalytical methods are stated, including limit of quantitation
Analysis dataset creation	• Data for inclusion is specified • Analysis population defined • Procedures for handling missing data described • Relevant data editing rules cited • Calculation methods for derived variables provided • Transformation of data described and justified
Analysis methodology	• Overview of modeling steps included • Hardware and software, including version to be used is cited • Plan for exploratory data analysis is included • Plan for identification and treatment of outliers is described • Information regarding potential structural models and modeling assumptions is provided and a plan to be followed if the intended model or assumptions are found inappropriate is described • Variability models are described (interindividual variability, residual variability, interoccasion variability as needed) • Covariates to be tested for model inclusion and rationale is stated • Plan for parameterization of covariate model is specified • Covariate building and selection methods (statistical significance and clinical relevance) are described • Model evaluation (validation) plan is provided • Methods for the generation of individual exposure measures are described, if needed

Table 2. Criteria For Report Content Acceptability Review (cont'd.)

Report Section	Content Acceptability Criteria
Analysis results	• Data are adequately described using summary statistics tables and graphics, with consideration of missing data, outliers, and patient deletions • Base model development steps and major decisions are described • All fixed and random effect parameters (with SE or CI) are presented in tabular form, with supportive goodness-of-fit plots and interpretation • If appropriate, plots used to screen for potential covariate relationships are provided • Details of covariate model building and criteria for decision-making about model inclusion or deletion are outlined • The final covariate model results are presented in terms of parameter estimates and graphical displays, with a statement of parameter values at the extremes (5th and 95th percentiles) • Model refinement steps are appropriately described and justified • The final model with parameter estimates (SEs), statement of extent that interindividual variability is reduced by covariate inclusion, key goodness-of-fit plots for population and relevant sub-populations are presented • If the final model includes multiple covariates, simulations were performed to assess various combinations of covariate effects in a typical subject on a parameter of interest (for example, AUC) • Outcome of model evaluation (validation) is presented
Discussion	• Discussion of how well model describes the data included • Agreement with previous pharmacokinetic results is considered, if available • Clinical relevance of covariates discussed • Discussion of how analysis results will be used is included • Influence of study drop out is considered as appropriate

RESULTS

Analysis-Ready Datasets

Figure 1 shows the issues detected with the analysis-ready datasets (n = 15) requiring correction and **Figure 2** further details the origins of the most common issues.

Figure 1. Most Common Analysis-Ready Dataset Errors

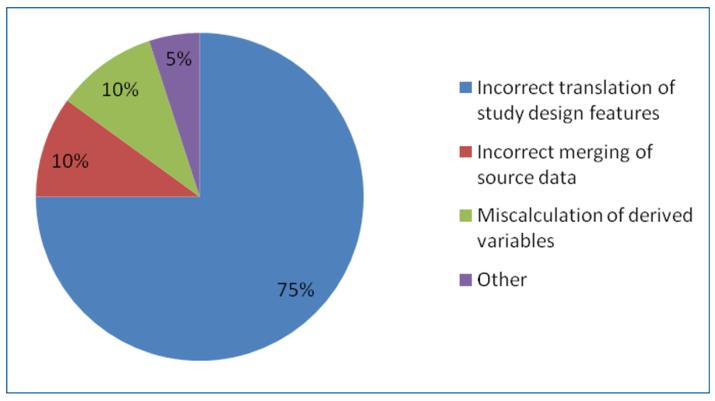
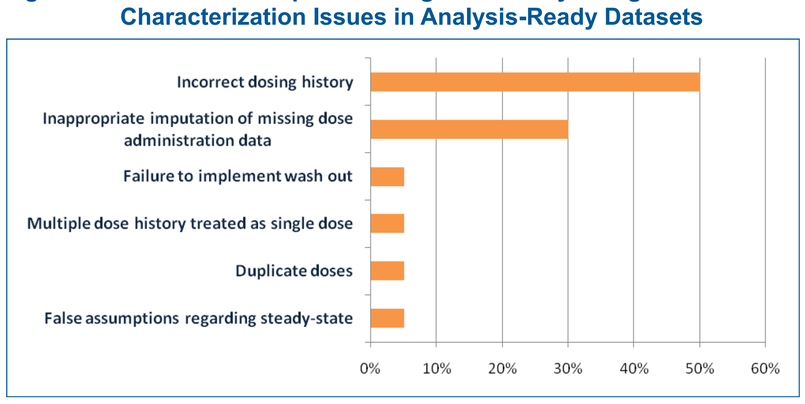


Figure 2. Detailed Description of Origins of Study Design Characterization Issues in Analysis-Ready Datasets



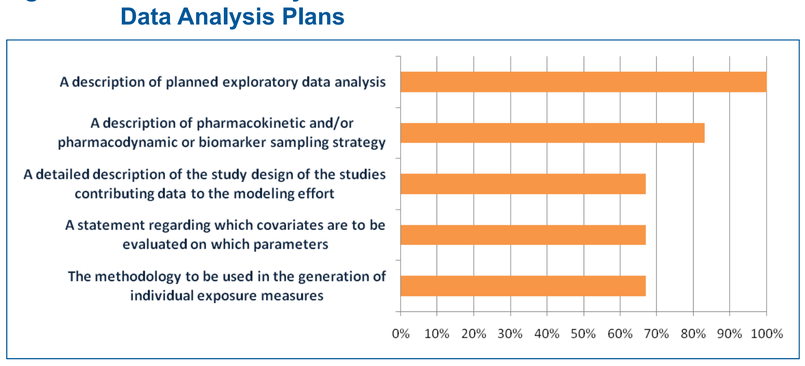
All datasets reviewed required revisions or corrections prior to their subsequent use in further analyses.

- By far, the most prevalent issue detected with analysis-ready datasets had to do with an incorrect translation of study design details, especially dosing history characterization, into dataset content, as required by the software.

Data Analysis Plans

While much of the suggested content was included in the data analysis plans reviewed (n = 6), the specific content most often not included in pharmacometric data analysis plans is detailed in **Figure 3**.

Figure 3. Most Commonly Identified Omissions From Pharmacometric Data Analysis Plans



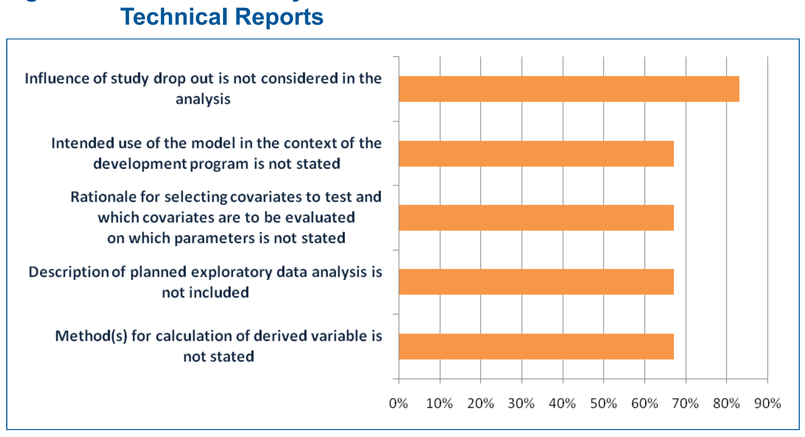
Data analysis plan content omissions occurring less frequently (that is, 50% or less), are listed below:

- The purpose for the model and/or the context into which the modeling effort is placed
- Statement regarding the software and/or hardware to be used for modeling
- Description of the planned handling of missing data and data editing rules
- Description of model assumptions or alternative methods or models to be considered if the anticipated models do not fit
- Consideration of the clinical significance/relevance of covariate effects

Final Technical Reports

In general, the content of these reports (n = 6) was clearly stated and informative. The findings listed below indicate opportunities to increase consistency of report preparation and suggest that broader use of canonical report templates to promote inclusion of content recommended in current regulatory guidances is needed.[13] The most commonly observed report content deficiencies are detailed in **Figure 4**.

Figure 4. Most Commonly Identified Omissions From Pharmacometric Technical Reports



Other issues that were identified less commonly (50% or less) were:

- Methodology to be used in the generation of individual exposure measures was not stated
- Version of the software to be used for the analysis was not stated
- Overall plan for modeling was not stated or changes from planned analysis were not stated in a common section
- Alternative models that were evaluated were not described
- Decisions made during the model building process were not clearly stated
- Clinical significance/relevance of covariate effects was not discussed

In some cases, the organization of the report was such that related information was not considered in the same section, and, therefore, was difficult to assimilate. This issue was particularly troublesome if an overall plan for modeling was not stated.

Statement of methods for calculation of derived variables will become more important as the FDA draft guidance for renal impairment is increasingly used since multiple calculation methods are provided for this common covariate.[14]

Increased placement of supportive material in the study report appendices (data analysis plan, alternative models tested) provides a means of providing additional content detail while maintaining a concise focus in the report body.

CONCLUSIONS

- The findings of this review of analysis inputs and outputs, relative to available standards, highlight a number of areas requiring improved compliance with existing standards.
- Given the importance of dataset accuracy in modeling efforts, a checklist is proposed to ensure that the dataset is structured appropriately to meet the requirements of the analysis software, and that, given this structure, the dataset accurately represents the clinical trial designs.[9]
  - Care should be taken to ensure that the dosing history captured in the dataset for modeling is an accurate representation of the trial design, and the dosing circumstances are based on the available source data.[15]
- Greater emphasis should be placed on the development of specialized training in pharmacometric dataset creation and associated informatic issues.
- To avoid the possible perception that the methods of the modeling effort were adapted to meet the needs and wishes of the pharmacometrician, and to improve the efficiency of modeling and simulation execution, care should be taken to adequately describe the data to be modeled, and to pre-specify the modeling methodology according to the commonly suggested data analysis plan content.
- For pharmacometric data analysis plans and technical reports summarizing pharmacometric analyses, the use of a quality questionnaire or content acceptability criteria (**Table 1** and **Table 2**) or the development of an institution-specific canonical document containing standard document sections and content suggestions may facilitate consistent adherence to suggested content standards.[12,13]
- The process developed for this assessment can be used as a basis for the independent validation of pharmacometric deliverables intended for regulatory submission.
- The tools and criteria proposed herein may provide a basis for the continuing evolution of commonly accepted measures of acceptability for pharmacometric analysis inputs and outputs.

NEXT STEPS

- The development of criteria for review of dataset content acceptability would ensure consistency of dataset quality, thus contributing to the overall value of the pharmacometric analysis.
- Based on the identified deficiencies with the analysis inputs and outputs, more consistent adherence with current standards for data analysis plan and pharmacometric technical report content is warranted.
- Pharmacometric groups should self-audit on a continual basis to track compliance with relevant standards and appropriateness of judgment-making within the context of these standards.
- While this assessment focused on dataset content and pharmacometric analysis documentation, future efforts could more specifically address the development of criteria for the acceptability of pharmacometric models in support of the continuing evolution of model-based drug development.

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