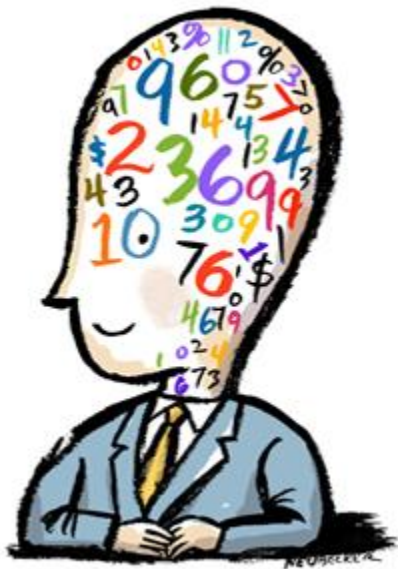




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Harnessing the Power of Data Assembly for Pharmacometric Analysis



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The Challenge

The lead time required for development of population pharmacokinetic (PK) and pharmacodynamic (PD) models places enormous pressure on data programming to expedite the transformation of disparate data into an analysis-ready dataset. Only then can modeling and simulation efforts be initiated as quickly as possible. The creation of the analysis-ready dataset is complicated by the complexity of the modeling to be performed. These datasets typically require pooling disparate data from multiple studies, including PK information, the drug dosing history, patient demography, laboratory data, concomitant medicines, and measures of efficacy and safety to create a time-ordered sequence of relevant events for each patient from the time of enrollment in a trial until its conclusion.

This data must be secured from numerous databases managed by different functional groups, either internal or external to the company, so accessing and pooling the data can be cumbersome and time consuming. Furthermore, it's important the requirements for the analysis serve as the basis for assessing the content and structure of the analysis-ready dataset. This means the data programmers must be skilled in the interpretation of these requirements and translate them into programming specifications that meet the needs of the scientists performing the modeling and simulation activities.

Why Cognigen

Our experience is unique and extensive

Cognigen's data programming staff has extensive experience in dealing with the unique issues involving the merging of databases and relational editing of data for population analysis. We have developed the processes and tools to help foster communications between the scientist and

programmer to minimize miscommunication about analysis requirements and programming specifications.

Each year we provide data assembly and programming services for 20 to 30 different development programs in nearly every therapeutic area. Our experiences have earned Cognigen a tremendous amount of credibility within the pharma and biotech industries, as well as regulatory agencies. We understand the special requirements of submitting datasets to the FDA. In fact, out of the 17 new drug applications submitted to the USFDA in 2007, almost a quarter of them incorporated our work for dose selection and justification.

Our preparations are comprehensive

Before beginning any project, we review the Investigator Brochure and the Final Protocols, including amendments, of all studies that will contribute data to the analysis-ready dataset. We also review the Annotated or Sample CRFs of all studies, and any previously prepared study reports, which would provide assistance in preparing the programming specifications. The data transfer instructions, data requirements, analysis plans, and assumptions are finalized during a kick-off meeting between you and Cognigen. Our goal is to deliver an analysis-ready dataset that allows you to begin your modeling work with a minimum of delay.

Our process is efficient

We create a time-ordered sequence of relevant events for each subject from time of first dose until time of last drug concentration sample. Derived variables are created,

including NONMEM-required terms. Descriptive labels are defined for all created variables for use in graphing and data definition. We take care to retain variable names and labels when sponsor-supplied variables are used “as is” in the analysis dataset. This is an important step to ensure data compatibility with the case report tabulation (CRT) datasets when population datasets are included as part of the submission package.

Once we begin to receive data, we verify the data are complete and perform rigorous validation of individual data entities. We also perform extensive relational edit checks to verify the quality and accuracy of the data.

When tight timelines are an issue, we can implement our real-time data assembly (RTDA) approach that allows us to put programming code in place and to begin to identify critical data quality issues before database lock. This way, adjustments to processes or procedures may be made in real-time in an effort to improve the quality of the data collected and reduce the delay for you to begin the modeling process.

Our communications are secure and to the point

We establish a secure, password-protected web site for each client. Any issues that arise during our work are communicated to you via our innovative communication interface that provides for a secure communication solution and rapid resolution of uncertainties. All discussions, decisions, and implications for data handling and programming are documented. Data corrections, imputations, and exclusions are performed, as prescribed by the programming specifications. Listings of changed values and excluded records are documented in a data disposition table created for each analysis-ready dataset. Security can be implemented to address blinding issues.

Our quality is assured

We place a premium on our quality assurance process. All data manipulations are tracked through the data assembly process. Each program is verified to assure that it conforms to user requirements and provides the expected results. Data deletions will be identified and tracked throughout the programs, and subject and record counts will be maintained. Additionally, several subjects will be selected at random from the final analysis datasets, and a 100% check to the original data will be performed. This selection will be based upon study design or program specification. Documentation of these verification activities will be archived.

Our reputation is hard-earned

In the past three years, Cognigen has undergone thirteen routine client audits, as well as internal quality assurance activities to assure compliance with our policies and procedures. The results of our client audits have all been very positive with only minor observations and no major findings. Cognigen's philosophy is to continuously improve our system and very often we are able to incorporate suggestions made by the audit teams into our processes.

Cognigen's comprehensive Quality Management System has been developed to support our project teams in efficiently utilizing best practices, consistent with the FDA's current regulations and guidance. Our policies and standard operating procedures cover many of the typical activities which arise during data assembly, including establishing and maintaining data management plans, data receipt and verification,

program documentation, data editing, program verification, quality control of deliverables, and employee training.

Our deliverable brings value to your modeling efforts

Typical deliverables from Cognigen's data assembly service include formalized requirements specifications, analysis-ready datasets, programming code, data deletion listings, and complete data definition documentation, including define.pdf files. This define.pdf file will include a table detailing the purpose of each analysis dataset created by Cognigen, with separate links to the respective SAS transport-formatted file and its corresponding variable definition table. Each variable definition table includes variable names, labels, and code list definitions for all variables included in the dataset. Algorithms will also be provided for any Cognigen-created derived variables in a comments column. This file can also be provided in Microsoft® Word format for integration into client-specific data definition files.

ABOUT COGNIGEN

Cognigen is a state-of-the-art scientific, technical, and strategic partner for our clients in the pharmaceutical and biotechnology industry. Our focus is on providing scientific support for dose selection and justification at all drug development and regulatory milestones.

Our vision

To advance the science and engineer the systems for model-based drug development.

Our mission

- To help our clients understand the determinants of safety and efficacy of new medicines in order to:
 - Increase stakeholder confidence at decision-making milestones
 - Improve the chances for success with innovative therapies
 - Enhance the value of new medicines for patients and providers
- To provide a challenging and rewarding work environment for the professional growth and development of our scientists and staff.

We provide pharmacometric services for approximately 20 to 30 drugs per year. In 2007, 4 of the 17 NDAs submitted to the FDA incorporated our work as a basis for dose selection and justification. We have had experience in most therapeutic areas and have worked on projects in all phases of drug development from pre-clinical to clinical development,

from discovery to commercialization and post-marketing surveillance. We have a well-established reputation for the credibility of our work and track record of successfully utilizing pharmacokinetic and pharmacodynamic modeling and simulations to influence regulatory and clinical decision-making.



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