Integrating Real-Time Data Assembly (RTDA) and Population Pharmacokinetics as Tactical Components of Cognitive Engineering

Mary Eileen McPhee, RN, MS, Jill Fiedler-Kelly, MS, Elizabeth A. Ludwig, PharmD, Kathleen Reitz, BS, Thaddeus H. Grasela, PharmD, PhD.
Cognigen Corporation, Buffalo, NY

www.cognigencorp.com

ABSTRACT

Objectives: The goal of drug development is to produce a safe and efficacious drug that will thrive in a competitive marketplace. Cognitive engineering couples technology and human intelligence to generate and use knowledge to optimize drug approvability and marketability. Data management and analyses in drug development are often delayed with insufficient time to apply the knowledge generated for crucial program decisions. Real-time data assembly (RTDA) and population pharmacokinetics (POP PK) can facilitate this process so the relationships between dose selection, patient characteristics, and drug disposition are defined earlier.

Methods: RTDA is a structured quality assurance program for rapid retrieval, assembly, and analysis of data while a clinical trial is ongoing. Data transfers can be scheduled periodically (middle and end of study), monthly, or even daily to allow for continuous safety monitoring. RTDA can provide prompt feedback of drug exposure estimates for dose adjustments during the trial, as well as allow for early initiation of data scrubbing and site compliance monitoring.

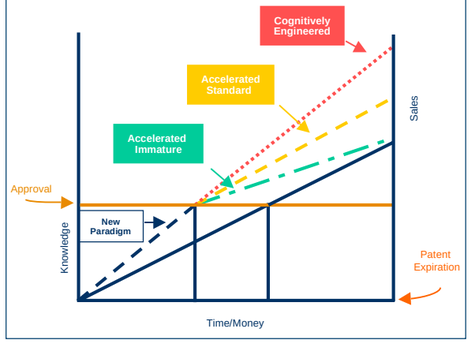
Results: RTDA results in a comprehensive database for analysis of drug-drug interactions, lab data, and adverse events. Utilizing RTDA, additional time for analysis is generated and regulatory submission of integral POP PK results is expedited. Careful integration of RTDA and prospectively planning POP PK analyses into the drug development program can potentially influence decision-making, facilitate FDA review, and streamline development. Data must be available for decision-making to realize these benefits.

Conclusions: RTDA was advocated in the 1999 FDA Guidance on Population Pharmacokinetics and offers a strategy for data scrubbing and analysis before the end of the trial. When coupled with timely POP PK results it allows for cognitive engineering in drug development programs. Efficient data management and integration of results into a flexible, yet comprehensive program will expedite drug approval and ensure successful commercialization.

INTRODUCTION

- The goal of drug development is to obtain regulatory approval to market a safe and effective medication, with optimal competitive advantage and commercial potential.
- Regulatory approval should be secured with the most efficient and productive expenditure of resources and in the shortest timeframe possible.
- Knowledge accumulated during drug development needs to be readily available for global development teams to make strategic program adjustments and take advantage of the knowledge gained while studies are ongoing.
- A systems approach must be used to accelerate the availability of knowledge and development programs must be flexible to implement necessary changes.

Cognitive Engineering Maximizes Product Potential



Cognitive Engineering

- Cognitive engineering is the coupling of technology and human intelligence to generate and use knowledge in real time.
  - People provide strategic, knowledge-based recommendations throughout clinical trial
  - Technology allows continuous communication and collaboration between parties
- During the drug development process, Cognitive engineering optimizes product approvability and marketability.

Cognitive Engineering (The End Result)

Efficient data management and integration of results into a flexible, yet comprehensive program will expedite drug approval and ensure successful commercialization, producing a product that is cognitively engineered to thrive in today's competitive marketplace.

METHODS

Real-Time Data Assembly

- Real-time data assembly (RTDA) is a structured quality assurance program for the rapid retrieval, assembly, and analysis of data while a clinical trial is ongoing.
- Data transfers can be scheduled periodically (middle and end of study), monthly, or even daily when continuously monitoring for safety.
- RTDA yields a comprehensive database for analysis of drug-drug interactions, lab data, adverse events and can provide prompt feedback of drug exposure estimates for dose adjustments during the trial.
- RTDA offers a strategy for data scrubbing and analysis before the end of a trial. Results are available for crucial program decisions, facilitating the review process and allotting additional time to prepare a fully integrated regulatory submission.

RTDA – Process Options

Indication for use:	Low Level	Intermediate Level	High Level
Small Phase 1 Study	X		
Short-term study or short treatment duration	X		
Interim analysis or FDA presentation	X		
When robust analyses are needed ▪ Investigating additional doses, routes or regimens ▪ When covariates are unknown		X	
When compliance is an issue (i.e.: pediatric trials)		X	
Safety concerns ▪ Continuous safety monitoring ▪ On-study individualized dose adjustments			X
TDM in long-term trials			X

RTDA – Benefits

Benefit	Low Level	Intermediate Level	High Level
Data warehouse, relational evaluation	X	X	X
Early data scrubbing and analysis	X	X	X
QA and safety monitoring		X	X
Improved overall site compliance		X	X
Sample tracking		X	X
Reduced data discard rates		X	X
Rapid PK/PD analysis with timely feedback		X	X
PK results integrated into development plan		X	X
Continuous safety monitoring			X
On-study individualized dose adjustments			X
Ethical and safety protocol enhancements			X

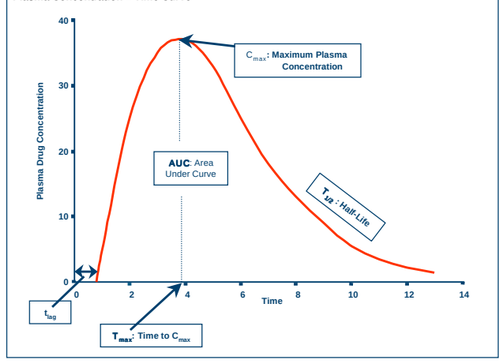
Population Pharmacokinetics

- POP PK is the study of inter-individual variability in plasma drug concentrations after standard dosage administration.
- POP PK allows for:
  - the integrated analysis of data from a variety of different studies which may be observational (unbalanced and fragmentary)
  - having sparse or dense sampling
  - studies that do not lend themselves to traditional PK methods (e.g., seriously ill, elderly, or pediatric populations)
- The ability to integrate these data increases the understanding of a drug by identifying factors that may affect the pharmacokinetics (PK) of the drug (i.e.: sex, race, age, weight, disease, medication, etc.).

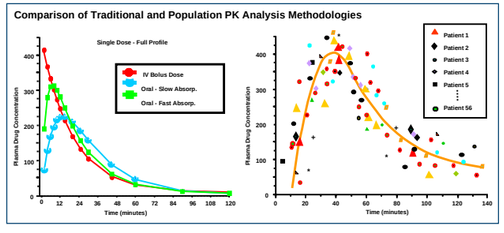
The goal of POP PK analysis in drug development:

- Estimate PK parameters and variability
- Determine the influence of patient covariates
- Determine the influence of concomitant medications
- Address FDA concerns for special populations and product labeling

Plasma Concentration – Time Curve



Comparison of Traditional and Population PK Analysis Methodologies

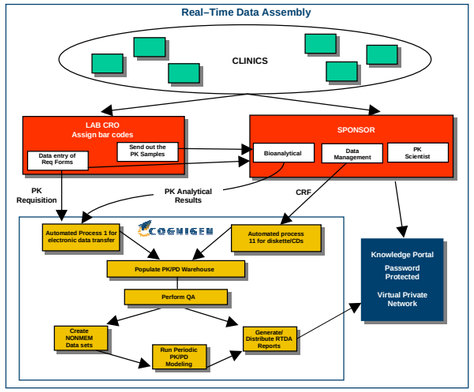


RESULTS

Real-Time Data Assembly - Advantages

- Real-Time Data Assembly facilitates the conversion of information to knowledge and communication of that knowledge in real time to a global team.
- RTDA expedites an informed decision-making process with a focus on key milestones to adjust or change program course.
- Real-time monitoring has financial and quality benefits:
  - Saves time (money) in completion of study and delivery of reports
  - Minimizes waste resulting from protocol non-compliance and non-informative data

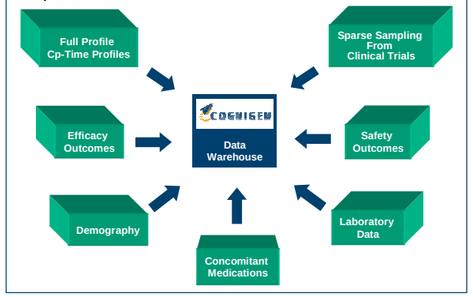
Real–Time Data Assembly



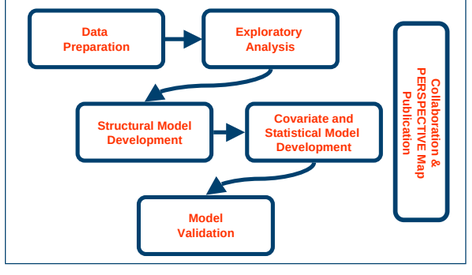
Real-Time Data Assembly – Clinical Application

- Data are received from the Sponsor on a regular or pre-determined basis.
- QA procedures are initiated and timely feedback is provided.
- Data is entered into a Data Warehouse.
- Analysis is performed and reports are generated as appropriate.

Components of Data Warehouse



Population Analysis Phases



Real-Time Data Assembly: ***Case Study***

A Strategy for Monitoring Delavirdine PK During the Phase III Clinical Development Program

Program Results:

- April 9, 1994 to September 30, 1996
- 1,544 patients receiving DLV
- 10,233 DLV concentrations
- On average, 80 samples per week
- Average time to generate drug concentration was 7 days
- Average turnaround time from receipt of data to transmission of recommendation was 2 hours
- RTDA was advocated in the 1999 FDA Guidance on Population Pharmacokinetics

DIA Journal vol 33, pp. 273-279, 1999

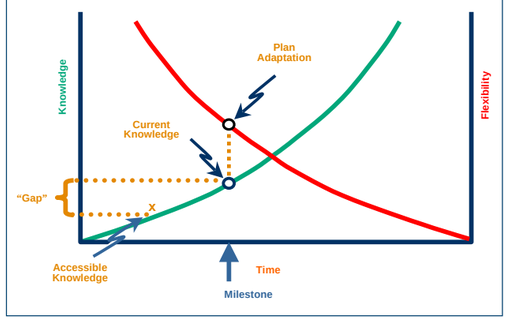
RTDA and POP PK – Results from Actual Studies

- An age/gender study was waived
- The scope of a renal impairment study was reduced
- RTDA and POP PK modeling allowed timely and meaningful conclusions to be drawn using only one PK sample from each patient.
  - This sparse sampling strategy met program objectives
  - Enhanced enrollment

Knowledge and Flexibility

- The accumulation of knowledge during development must be leveraged to adjust development strategy and create competitive advantage.
- Time frames are extraordinarily aggressive.
- A systems approach must be used to accelerate the availability of knowledge.

Knowledge and Flexibility During Drug Development



CONCLUSIONS

- RTDA was advocated in the 1999 FDA Guidance on Population Pharmacokinetics and offers a strategy for data scrubbing and analysis before the end of the trial.
- POP PK can increase the efficiency and specificity of drug development by suggesting more informative study designs and analyses, and can provide sufficient data to make better dosing and design decisions, reduce the study burden, and improve the overall cost-effectiveness of drug development.
- RTDA when coupled with timely POP PK results allows for Cognitive Engineering in drug development programs and commercialization.