A New Paradigm in Pediatric Drug Development: The Application of Cognitive Engineering

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ABSTRACT

Objectives: Design of clinical trials in pediatrics is complicated by sensitive ethical considerations, a small pool of appropriate study subjects, and difficulty in determining drug dosing regimens. Cognitive engineering is the coupling of technology and human intelligence to generate and use knowledge in real time. Using real-time data assembly (RTDA), population pharmacokinetic/ pharmacodynamic (PK/PD) data analysis and Internet communication technology, cognitive engineering can be applied to pediatric drug development in order to address the above issues.

Methods: RTDA is an automated quality assurance program designed to monitor drug dosing and concentration-time data acquired during clinical trials. This process has been further extended by linking dosing and concentration data with safety data, allowing for preparation of timely, blinded interim reports which enhance drug safety monitoring. Critical to this process is the use of electronic communication to facilitate data management and knowledge dissemination. Private, secure Internet web sites are used to communicate data management and analysis activities to the sponsor. In addition, these web sites are used to communicate interim reports (blinded or unblinded) to independent data safety monitoring boards.

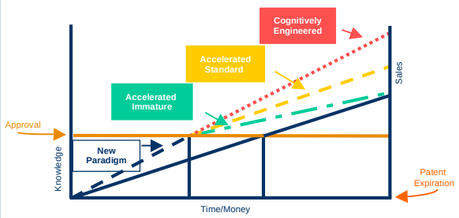
Results: Population PK/PD analysis of data from pediatric studies of an investigational drug suggested that dosage adjustment was necessary for children below a certain age. A multicenter, Phase III trial will evaluate this dosage adjustment in children. Using RTDA and an Internet-based communication strategy, an interim analysis dataset will be constructed, allowing estimation of drug exposure using a minimum of PK samples. This interim analysis will be used as evidence supporting the chosen dosing regimen (i.e., higher daily doses in young children).

Conclusion: Cognitive engineering, as implemented using RTDA, population PK/PD data analysis and Internet communication technology, can improve the process of pediatric drug development. In this example, this model allows for the conduct of a robust interim analysis to support the selected dosing regimen.

INTRODUCTION

- The goal of pediatric drug development is to obtain regulatory approval while assuring appropriate use of the compound in pediatric patients
- Developing medicines for children raises important issues and challenges in pharmaceutical development. Sensitive ethical considerations, considerable intersubject variability, a small pool of appropriate study subjects, and difficulty in determining drug dose regimens are all hurdles faced by scientists when formulating medicines for children
- These hurdles make it critical that knowledge gained while studies are ongoing is readily available to make strategic adjustments and to maximize product potential

Figure 1. Cognitive Engineering Maximizes Product Potential



Cognitive Engineering

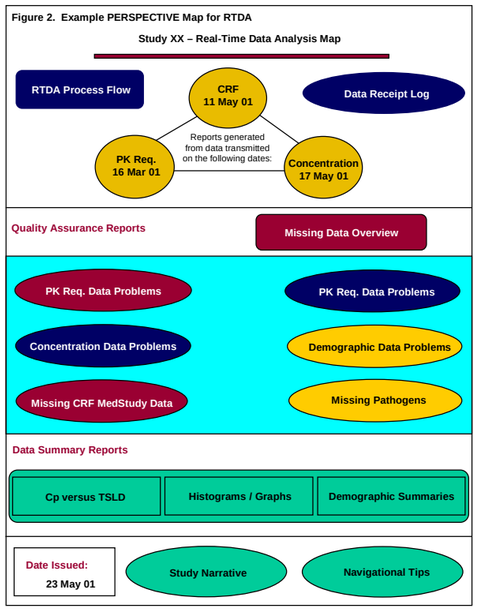
- The coupling of technology and human intelligence to generate and use knowledge in real time
  - People provide strategic, knowledge-based recommendations throughout clinical development
  - Technology allows continuous communication and collaboration between parties
- Optimizes product approvability and marketability
- Components of a pediatric cognitive engineering strategy
  - Consulting
  - RTDA
  - Population PK/PD Analysis
  - Communication

METHODS

Real Time Data Assembly Overview

- Is a structured process for the rapid retrieval, assembly and analysis of data during clinical trials
- When coupled with the use of the Knowledge Portal and PERSPECTIVE there is the capability to provide rapid feedback of analysis
- Helps assure quality of data as well as continuous monitoring of safety from a PK/PD perspective

Figure 2. Example PERSPECTIVE Map for RTDA



Common Data Errors:

- Sample collection dates and times cannot be merged with drug concentration results
  - Unique identifier (barcode, sample code) not utilized, requiring less precise composite primary key to be used for merge
  - Clinical study site uses duplicate sample identifier inappropriately
  - Lab scans incorrect barcode
- CRF does not collect critical data or field label is incorrect resulting in incorrect data collection
- A requisition form collects data that is recorded elsewhere in the CRF. Often, there is a discrepancy between the two that needs to be queried and subsequently resolved.

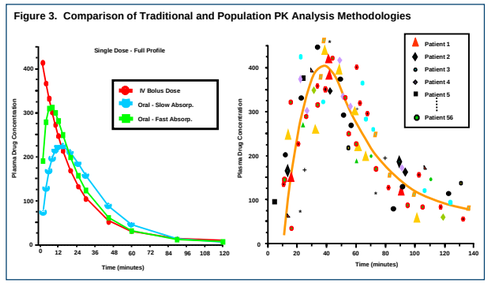
Standard data checks

- Critical information is missing or invalid
- Sample date times are in conflict with dose date times
- Sample or dose times are not in military time
- Concentration results are in conflict with treatment assigned
- Concentration results are in conflict with dose or sample date times

Utility of Population PK/PD Analysis in Pediatric Drug Development

- Minimizes blood sampling requirements
- Allows for definition of sources of variability (e.g., age, body size, etc.)
- Provides description of pharmacokinetics in target population (i.e., children with disease)
- Pharmacodynamic analyses can provide additional marketing ammunition

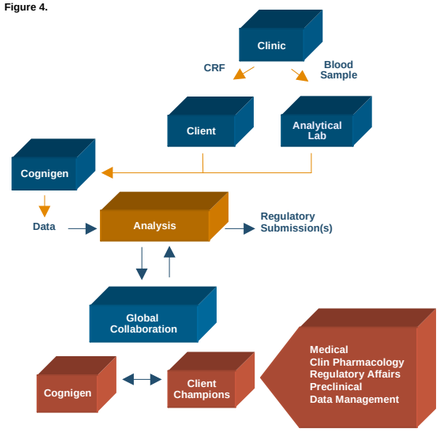
Figure 3. Comparison of Traditional and Population PK Analysis Methodologies



Knowledge Generation and Communication Strategy

- A rapid, secure and efficient means of transmitting data is critical to the success of this strategy and allows scientists at the sponsor and Cognigen to collaborate most effectively

Figure 4.



RESULTS

Overview of Pediatric Development Program

- Cognigen had been involved in the adult development of this compound
- First phase of the program involved determining the pharmacokinetics of the compound in children and performing simulations to optimize pediatric dose.
- Knowledge gained in the first phase was then used to design the pivotal pediatric trial which is now ongoing

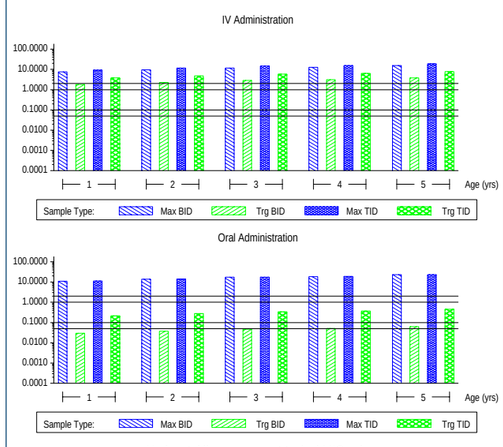
Table 1. Pediatric Studies Pooled to Perform Population PK/PD Analysis for First Phase of the Pediatric Program

Study	Phase	n	Age Range	Dosage Regimen	Dosage Form	Sampling Scheme
A	I	54	0.25 – 17 yrs	Single dose – low vs. high	IV	Full profile
B	I	6	1 – 18 yrs	Single and multiple – high BID	IV	Full profile
C	II/III	72	0.25 – 13 yrs	High dose BID	IV	Sparse
D	II/III	63	1 – 8 yrs	High Dose BID	IV/Oral	Sparse

PK/PD Analysis Methods

- Data management and exploratory analysis using SAS v6
- Population PK Analysis using NONMEM V
  - Structural model development
  - Covariate Analysis
- PD Analysis
  - Predicted PK/Trough concentrations
  - Graphical Presentations

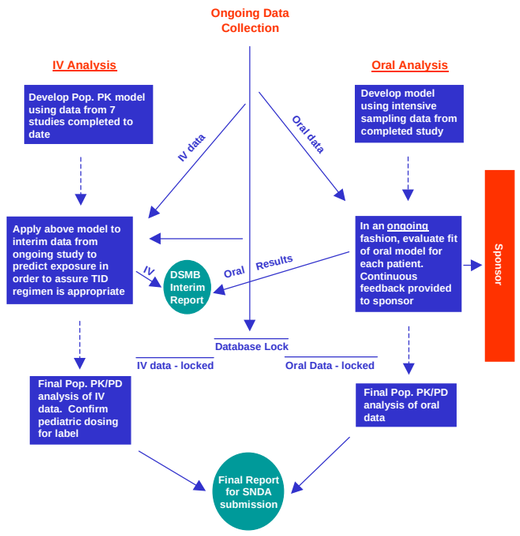
Figure 5. Simulated Peak and Trough Concentrations after hypothetical administration of doses – BID vs TID



Details of the Pivotal Pediatric Trial

- Randomized, open-label, Phase II/III safety/efficacy trial
- Study n: ~300 patients
- Study duration = 1-4 weeks
- IV to Oral switch (at investigators discretion)
- Broad age range – birth to 13 years
- Population pharmacokinetic ('sparse') sampling
- Higher dose (TID) than all previous studies
- New, pediatric-specific oral formualtion

Figure 6. Schematic of Analysis Strategy for the Pivotal Pediatric Trial



Clinical Implications for this Compound

- RTDA and pop. PK/PD analysis will allow rapid confirmation of the exposure secondary to the new dosage regimen
- Confirmation of the performance of the new oral formulation will be provided on a case-by-case basis
- Sponsor will have early indication of the amount of oral use in the study

CONCLUSION

- Cognigen's cognitive engineering process has great value in developing new medicines for children around the world. It provides many important advantages:
  - Allows for the generation of pharmacokinetic and pharmacodynamic knowledge during the care of children with the disease of interest
  - Increases the efficiency and specificity of pediatric drug development by suggesting more informative study designs and analyses
  - Provides sufficient data to make better dosing and design decisions, reduce the study burden, and improve the overall cost-effectiveness of drug development