A New Paradigm of Real-Time Data Assembly to Support Knowledge-Based Decision Making: A Case Study

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ABSTRACT

Objectives. Real-time data assembly (RTDA) to support knowledge-based decision making was implemented for the development of a compound during Phase II. Program goals were to develop a data warehouse to expedite pharmacokinetic/pharmacodynamic (PK/PD) analyses and perform assessments of factors influencing PK and safety outcomes while maintaining study blinding.

Methods. RTDA, a structured quality assurance program for rapid retrieval, assembly and analysis of data while a clinical trial is ongoing, was implemented. Regular data transfers allowed for construction of a comprehensive database for NONMEM® analysis, drug-drug interaction evaluation, and possible associations of PK with adverse events. Data displays were created in accordance with strict specifications to maintain study blinding.

Results. RTDA efforts expedited data assembly and PK/PD model development with early initiation of data query resolution. After RTDA implementation, the frequency of data queries was reduced by approximately 50% for a subsequent Phase II study.

Early identification of a dosing discrepancy error in the study drug packaging allowed for institution of on-study verification before data analysis and critical decisions were made in error.

Unblinded data discussions with selected project management coupled with program flexibility allowed for resource re-allocation and initiation of analyses while the study was ongoing. Within a week of database lock, population PK/PD modeling and simulation results were presented to senior management. Easy accessibility and collaboration, enabling of PERSPECTIVE Hypertext Data Analysis Mapping, an internet-based hypertext data analysis mapping software, allowed rapid feedback and decision-making and was key to this success.

Conclusions. Data management and analyses in drug development are often delayed with insufficient time to apply the knowledge generated for crucial program decisions. RTDA facilitates data cleaning and allows for safety monitoring. Prospective planning and integration of RTDA into a flexible, comprehensive drug development program is vital to knowledge-based decision making and streamlining the development process.

OBJECTIVE

- Describe the implementation and benefits of RTDA during a Phase II PK/PD analysis.

BACKGROUND

- Real-time data assembly (RTDA) is an automated quality assurance program designed to monitor drug dosing and concentration-time data 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.
- Implementation of RTDA ensures the quality of data collected during a clinical trial, provides an opportunity to address deficiencies, and expedites data clean-up so that analysis results are available for crucial decision-making in drug development.
- The prototype program was implemented during the delavirdine mesylate clinical trials program and was subsequently adopted by the FDA in its *1999 Guidance for Industry Population Pharmacokinetics.*[1, 2]
- There are multiple RTDA intensity levels available [Table 1].
- This case study describes an intermediate intensity level RTDA program implemented to facilitate a population PK/PD analysis during a Phase II program.

Table 1: Real-Time Data Assembly – Benefit Stratification

	Low Intensity Level	Intermediate Intensity Level	High Intensity Level
Frequency of Data Transfers	Periodic (i.e., middle and end of the trial)	Regular (i.e., monthly)	Up to daily
Study Implementation Options			
Data warehouse, relational evaluation	X	X	X
Early data scrubbing and analysis	X	X	X
Head start in model development	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
Enable an adaptive study design		X	X
Continuous safety monitoring			X
On-study individualized dose adjustments			X
Ethical and safety protocol enhancements			X

METHODS

Data Collection

- Sparse sampling for PK/PD analyses was obtained from a Phase II, double-blind, randomized, placebo-controlled, dose ranging study.
- Data required for PK/PD modeling included [Figure1 - data flow process]:
  - Demographics, laboratory data, concomitant medications
  - Dosing and sampling history
    - Measured drug concentrations
  - Safety endpoints

Communications Plan

- An intermediate intensity RTDA level was selected from different levels available for this program.
- Internet-based, electronic communication with a virtual private network and use of PERSPECTIVE Hypertext Data Analysis Mapping, a JAVA-based software program, was utilized [Figure 2].
- Blinded and unblinded reports were regularly published and included the following displays:
  - Concentration versus time
  - Concentration versus concomitant medications
  - Concentration versus vital signs
- Blinded displays containing concentration relationships were appropriately restricted and underwent internal quality control review prior to viewing by the Sponsor project team members.

Population PK/PD

- Standard PK/PD data checks completed during the study included:
  - Missing or invalid critical information
  - Sample date times in conflict with dose date times
  - Sample or dose times not in military time
  - Concentration results in conflict with treatment assigned
  - Concentration results in conflict with dose or sample time

Figure 1: Flow of Study Data and Analysis

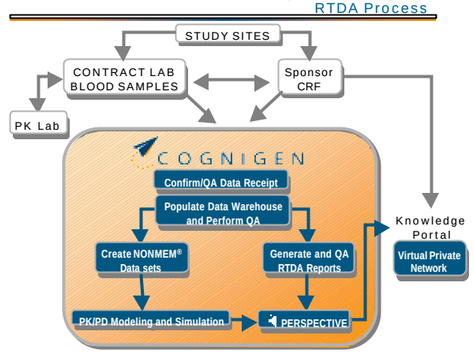


Figure 2: PERSPECTIVE Hypertext Data Analysis Mapping

RESULTS

Population PK/PD

- Data were available as shown in Figure 3.
- PK model development was initiated prior to database lock.
- No clinically significant drug interaction or safety issues were identified.

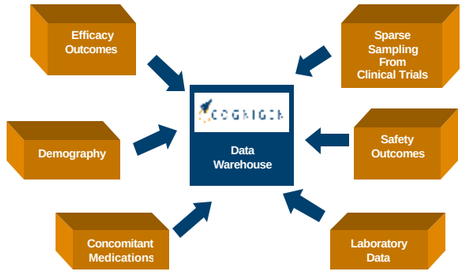
Error Detection and Correction

- A study medication packaging error was identified from examination of drug concentrations and allowed for prompt corrective action prior to data analysis.
- RTDA resulted in approximately a 50% reduction in data queries during this study compared to a prior Phase II study completed without RTDA.

Knowledge Dissemination

- Within a week of database lock, preliminary population PK/PD modeling and simulation results were available to senior management.
- Knowledge-based program strategies were developed for subsequent study designs and included:
  - Identification and collection of additional covariate information
  - Modification of patient selection criteria

Figure 3: Components of the Data Warehouse



CRITICAL SUCCESS FACTORS

- Easy accessibility to Sponsor personnel who provided rapid input, feedback, and decision-making
- Timely receipt of data while study was on going
- Assignment of an unblinded sponsor PK scientist, not directly involved with the project
- A state-of-the-art analysis and communications environment
- Innovative strategies and analyses
- Program flexibility

CONCLUSIONS

- These results demonstrate that implementation of an intermediate level RTDA expedited data assembly and analysis and facilitated population PK/PD model building.
- Early insight was gained regarding drug exposure safety relationships and the lack of drug interactions.
- Implementation of RTDA allowed for rapid availability of knowledge that contributed to crucial decision-making and more informative study design in future drug development.

REFERENCES

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2. Guidance for Industry Population Pharmacokinetics. (1999, February 10). Retrieved August 13, 2001, from US Department of Health and Human Services: Food and Drug Administration Web site: http://www.fda.gov/cder/guidance/1852fnl.pdf