



Abstract

Internet technology facilitates connectedness but often fails to foster collaboration. Advanced modeling techniques can provide insight for development discussions, but in many cases, these tools infrequently result in integrated knowledge for real time decision making. Cognitive engineering (CE) fuses human expertise and creativity with technology and provides the strategy for maximizing human, company and product potential. CE is based on a classic model of strategic decision-making – the OODA loop (observe, orient, decide, act). The power of the OODA loop exists in its conversion of information to knowledge, and the communication of that knowledge, in real time, to a global team at key milestones when flexibility still exists to rationally adjust or change course. The successful implementation of CE has three critical components: aggressive data management and assembly processes; innovative data analysis, modeling and simulation strategies; and capability to engage globally dispersed teams in the use of knowledge. CE requires individuals to function at a demanding and creative level. However, the use of generated knowledge often challenges pre-conceived notions of the desirable dosing and development strategy and the collective bias that may exist as to whether a target product profile is being met. Failure to generate, critically evaluate, and utilize knowledge at critical milestones can result in lost opportunities.

Introduction

In an attempt to address the various challenges of modern drug development, pharmaceutical and biotechnology companies have embraced new technologies and methodologies. But while Internet technology facilitates connectedness it often fails to foster collaboration. And while advanced modeling techniques can provide insight for development discussions, too often, these techniques fail to generate the knowledge required for real time decision-making.

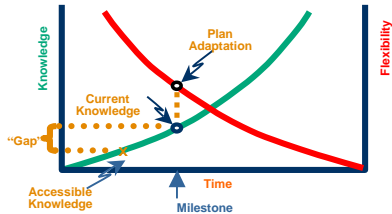
Section 115(a) of FDAMA allows the Agency to consider “data from one adequate and well-controlled investigation and confirmatory evidence” to constitute substantial evidence. This provision opens the door to use PK/PD analyses to play a crucial role in streamlining development strategies and subsequent regulatory decision-making. The design of these studies, the generation of knowledge in a timely fashion, and the incorporation of this knowledge into real time decision-making are emerging as critical issues.

Objectives

- Describe the barriers to implementation and acceptance of integrated development.
- Describe a strategy for ensuring the availability of knowledge when it is needed at key development and regulatory decision-making milestones.
- Describe the key components of this strategy, including,
 - Aggressive data management and assembly processes,
 - Data analysis, modeling, and simulations, and
 - Internet-based collaboration strategy for globally dispersed teams.

Human Resource and Process Barriers

The “Gap” Between Current and Accessible Knowledge That Reduces the Ability to Adapt Clinical Development Plans at Critical Milestones



- Current Internet technology and electronic communications systems facilitate contact among dispersed people, but they often fail to foster collaboration and infrequently result in integrated knowledge for real time decision-making.
- Data has come to be viewed as a commodity, processed through a system, and converted into a technical report. This approach has led to a silo mentality in which data management, data analysis, and report preparation are viewed as discrete activities, resulting in few opportunities for collaboration, creative thinking and synthesis of knowledge. Collaboration is often overlooked in the urgent effort to complete projects on time.
- Getting teams to consider the knowledge being generated can be difficult. There can be a tendency to overlook outliers, the act of questioning challenges pre-conceived notions of the desirable dosing and development strategy, and a collective bias may exist as to whether a target product profile is being met.

- Teams must function at a demanding and creative level in order to realize the return on investment for the clinical development process. The aggressive timelines of development present challenges and stresses. This creates an important problem because the sophistication to perform analysis and modeling activities and the understanding of the strategic value of the results and their implications for decision-making must be deliberately cultivated in the workforce.

Cognitive Engineering

Cognitive engineering provides the unifying precepts that stress the need for, and application of, human experience and creativity; guides the design of technology solutions to support collaboration and automation; and emphasizes the interactions at the human and technology interface. This union of humanity and technology is critical to meeting the aggressive schedules for time-sensitive data assembly, analysis, and collaboration demanded in modern drug development.

Cognitive engineering is the coupling of technology and human intelligence.¹

- Technology enables efficiency and allows continuous collaboration between parties.
- People utilize their intelligence and creativity to make knowledge-based decisions.
- The goal is to generate and use knowledge in real time.

The application of cognitive engineering in drug development can be seen from two different vantage points – process and strategy.

- Process – cognitive engineering enables the rapid completion of time consuming and frustrating activities and ensures that regulatory and clinical milestones can be met.
- Strategic – cognitive engineering fosters a shift in thinking that takes complete advantage of all available knowledge, combined with innovative thinking about marketplace needs, to achieve commercial success.

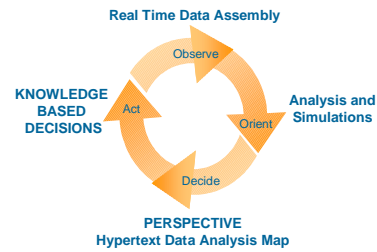
As the guiding strategic discipline, cognitive engineering taps into the full potential of development teams, enables the performance of cutting-edge analyses and simulations, and provides generated knowledge in real time. Cognitive engineering serves to harness the creative and intellectual energy of development teams so they can work more efficiently and maximize human, product, and company potential.

The OODA Loop

The application of cognitive engineering to drug development is based on a classic model of strategic decision-making – the OODA loop (observe, orient, decide, act). Originally developed by Col. John Boyd, USAF (dec.), a military strategist, the OODA loop model has broad practical applications and is used globally by a wide range of businesses and theorists.² The power of the OODA loop rests on its conversion of information to knowledge, and the communication of that knowledge, in real time, to a global team at key milestones – such as the end of phase II – when flexibility still exists to rationally adjust or change course.

The successful implementation of cognitive engineering has three critical components: aggressive data management and assembly processes; innovative data analysis, modeling, and simulation strategies; and capability to engage globally dispersed teams in the use of knowledge.

The OODA Loop As A Paradigm For Drug Development



- Observe:** Compile and organize observations; in clinical development, these are the data points.
- Orient:** Analyze data with respect to previous experience, new environments, and socio/cultural/genetic economic factors.
- Decide:** Collectively apply the knowledge gained to make a decision or propose a hypothesis.
- Act:** Transform the decision into action. The action leads to new observations, thus completing the loop and starting the OODA process again.

The Process to Support the Science

RTDA — Real Time Data Assembly

The implementation of RTDA, with an emphasis on drug dosing and concentration-time data required for analysis and modeling, ensures the quality of data collected during a clinical trial, provides an opportunity to address deficiencies, and expedites data cleanup so that analysis results are available for crucial decisions 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 on Population Pharmacokinetics.^{3,4}

“Real time data assembly prevents the problems that generally arise when population PK data are stored until the end of a clinical trial. Real time data assembly permits an ongoing evaluation of site compliance with the study protocol and creates the opportunity to correct violations of study procedures and policy. Evaluation of pharmacokinetic data can provide the safety data monitoring board with insight into drug exposure safety evaluations and drug-drug interactions. Real time data assembly creates the opportunity for editing the concentration-time data, drug dosing history, and covariates data in a timely manner to meet the pharmacokinetic objectives of a clinical trial and to facilitate the model building process. It also allows practical analysis and development of software protocols for the final analysis, thereby saving much time in data analysis. If real time data analysis will be implemented for an add-on population PK study, adequate policies and procedures should be in place for study blind maintenance.”

Variable Intensity of Real Time Data Assembly

| 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 dev. plan | | X | X |
| Continuous safety monitoring | | | X |
| On-study individualized dose adjustments | | | X |
| Ethical and safety protocol enhancements | | | X |

Rapid Data Flow ≠ Real Time Data Assembly

Data Analysis, Modeling, and Simulations

The last decade has seen the growing use of powerful and flexible statistical techniques that enable the pooled analysis of phase I and II data. Population analyses and simulations are optimally performed using pooled datasets from clinical trials that represent the accumulated knowledge base of the drug and offer the maximum understanding of safety and efficacy determinants.

The role of population-based PK/PD analyses, modeling, and simulation must be taken into account early in the development process. The team of data managers, programmers, analysts, scientists, and product development personnel must understand the implication of this strategy in all aspects of clinical drug development – from protocol design to CRF design, from data management and analysis plans to clinical trial simulations, and from knowledge generation to the development of marketing and pricing strategies.

- Model building and analysis must be initiated early in development and continued through clinical testing and post-launch period. This allows the knowledge base to be continually updated and enhance ongoing product lifecycle management.

Hypertext Data Analysis Mapping

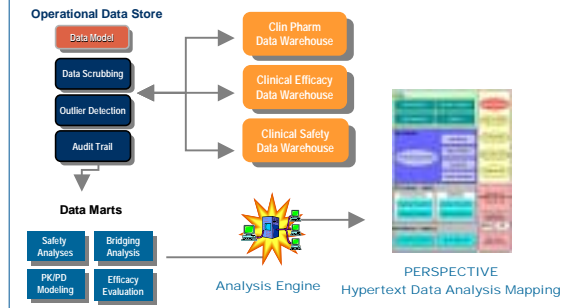
Knowledge management has rightly become an important priority for the pharmaceutical industry. Enormous amounts of information must be catalogued and organized during drug development. The technology engendered under knowledge management, from document management to automated databases of expertise within an organization, is becoming increasingly prevalent.

An important gap exists when dealing with the results of complex modeling efforts and statistical analyses performed on pooled datasets amassed over the course of a development program. The thought processes of the scientist, along with interim datasets and results are critical to proper documentation and explanation of conclusions.

PERSPECTIVE Hypertext Data Analysis Mapping Software is used to facilitate the organization and presentation of complex statistical analyses. This software allows a scientist to graphically organize analysis results, including graphs, datasets, and programs, and publish them to a secure website for real time collaborative access and review by globally dispersed teams.

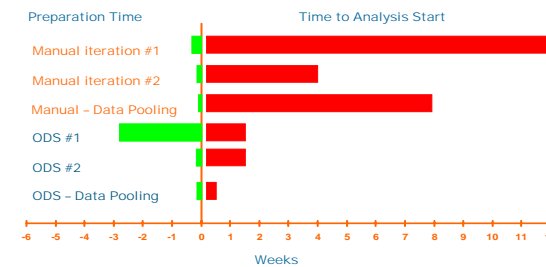
Information Architecture

An Architecture to Support Real Time Assembly, Analysis, and Dissemination of Knowledge



- A PK/PD evaluable patient requires accurate and complete data on:
 - Demographics, lab data, concomitant meds
 - Dosing and sampling history
 - Measured drug concentrations
 - Efficacy and safety endpoints
- These data are used to create a time-ordered sequence of relevant events for each patient from time of first dose until time of last sample.
- This assembly process is time consuming and requires considerable care and planning.
- A critical component of the cognitive engineering strategy involves taking large and complex datasets gathered from diverse sources and transforming these into an “analysis-ready state.” These functions are managed via an Operational Data Store (ODS).
- The ODS provides an integrated solution for acquiring, managing, and communicating data and reports.
- The development of the ODS requires the ongoing identification of process points where automation can be successfully applied.
- It is an efficient, scalable Oracle® database and graphical user interface (GUI) to streamline the clinical data management work processes resulting in decreased processing time from data receipt to analysis initiation.
- The analysis engine includes grid engine technology utilizing clustered compute engines from Sun Microsystems® providing increased systems availability and dramatically reduced run times for compute-intensive applications such as NONMEM®.
- The value of the ODS in streamlining data assembly is dependent upon the extent of advanced planning and communication among stakeholders.

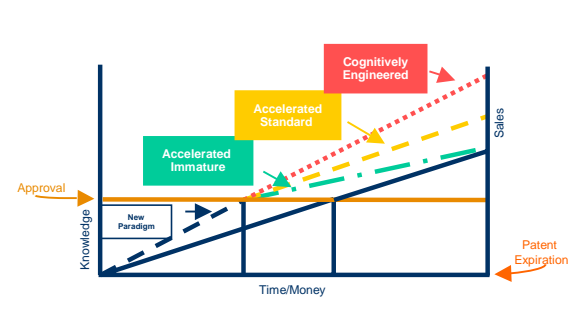
Efficiencies of Time and Effort Realized by the Operational Data Store and Attendant Standard Operating Procedures



Approvability vs. Marketability

Clinical development must look at a drug’s entire lifecycle, from discovery, through early and full development, all the way through patent expiration, lifecycle extensions, or an OTC switch in order to realize the full value of cognitive engineering. Even if development and marketing teams follow ideal target goals and accelerate a product to market, it may still fall short of its ultimate potential.⁵ Cognitively engineered drugs are better equipped to survive and thrive in a competitive marketplace because they are developed in an environment that gives development and marketing teams the opportunity to function collaboratively. Drugs that are accelerated into the marketplace without this type of collective foresight may experience commercial success, but often fail to reach their full value (we have termed this accelerated immaturity).

Maximizing Product Potential Requires Science, Process, Technology, and Vision



Summary

- The current development system has undergone many improvements in recent years; however, there is now a need for a more progressive refined approach – one that is not only fast, but also cohesive.
- The collaborative nature of cognitive engineering gives development teams the knowledge, unity, and agility they need to create products that achieve their maximum potential.
- Cognitive engineering is a living system that continually generates and applies knowledge through the creativity and expertise of all those involved in drug development.
- Technology has taken us a long way, but creative collaboration between departments and people must be developed, challenged, and supported to achieve a new standard in clinical development.
- The ability for development teams to collectively interpret their current state of affairs and make immediate adjustments, as is done with cognitive engineering, is necessary for success. This flexibility and cohesion is how the entire drug development process can continue to evolve.
- The collaborative nature of cognitive engineering facilitates the transition from R&D to regulatory approval to patient care and results in an accelerated – cognitively engineered – product.

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