

“FDA Critical Path: Where Does It Lead?”

Kitasato University/Harvard Conf.

October 24, 2006

Daniel Weiner, PhD



- FDA's Evolving View of Modeling and Simulation
- Need for IT Infrastructure to Support Modeling and Simulation
- Strategies for Increasing Modeling and Simulation Productivity Using Automation of Reporting

Innovation



Stagnation

**Challenge and Opportunity
on the Critical Path
to New Medical
Products**



U.S. Department of Health and Human Services
Food and Drug Administration

- Discusses the fact that beginning in 2000, a slowdown in new drug and biologic submissions to regulatory agencies has occurred worldwide, due in part to soaring costs and complexity of development.
- “The main causes of failure in the clinic include safety problems and lack of effectiveness: inability to predict these failures before human testing or early in clinical trials dramatically escalates costs.”
- The paper proposes utilization of model-based approaches to improve drug development knowledge management and decision making.

<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>

FDA News Digest
March 20, 2006

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-- 'Critical Path' Projects Aim to Advance Product Innovation

'Critical Path' Projects Aim to Advance Product Innovation

As part of its Critical Path initiative, FDA has released a list of 76 high-priority research projects designed to modernize and advance medical product development. The program aims to bring medical innovations to patients faster and at a lower cost. As part of the initiative, FDA and the Critical Path Institute have formed a consortium with five drug companies to share information that will help predict the safety of new treatments before they are tested in humans.

-- Critical Path priority research projects:

<http://www.fda.gov/bbs/topics/news/2006/NEW01336.html>

-- Consortium to predict treatment safety:

<http://www.fda.gov/bbs/topics/news/2006/NEW01337.html>

FDA News

FOR IMMEDIATE RELEASE

P06-40

March 16, 2006

Media Inquiries:

301-827-6242

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888-INFO-FDA

FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to **predict the safety** of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List -- 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

- Inefficient decision-making process (poor knowledge management)
 - Lack of necessary information to make informed decisions (both a technical and a tactical issue)
 - Decisions not based on quantitative inputs
 - Focus on the wrong areas (e.g., speed to market as opposed to understanding the dose response)
 - Loss of knowledge due to changes in staff and assignments
 - Inability to capture information (such as how and why decisions were made, intellectual property, etc.)

What Are Some of the Causes of the Productivity Slowdown, and What Can Be Done About It?

- Lack of (efficient) utilization of technology – need for Model Based Drug Development
 - Computer assisted trial simulation
 - Data repositories
 - Lack of standardization of tools, databases and practices

- End of Phase IIa meeting and use of simulations to evaluate future study designs
- Modeling of disease progression
- Biomarkers

PhRMA-FDA meeting on 'Proof of concept' in November, 2005.

FDA Experience with End of Phase IIa Meetings: An Attempt to Improve Drug Development Decisions

Acknowledge: Larry Lesko, Don Stanski, Joga Gobburu, Peter Lee, Yaning Wang, Jenny Zheng and many others

- Bob Powell, Pharm.D.
- Office of Clinical Pharmacology
- FDA
- powellr@cderr.fda.gov

The above is the reference for slides 9-10. I am grateful to Bob Powell, PharmD, for use of these materials.

Model Based Drug Development: What is it?

- **Objective:** improve decision quality by employing drug-disease models & clinical trial simulation
- **Model:** mathematical explanation of relationships thought to explain outcome over time period of interest
- **Drug-Disease Model** (empiric & mechanistic)
 - *Disease model:* relationship of patient (e.g., gender, age, genotype), biomarker (e.g., biochemical, imaging) relationship to disease morbidity and mortality
 - *Drug-Disease model:* addition of drug (dose, concentration, combination, placebo) and patient (e.g., size, age, adherence, dropout) effects and adverse effects to the disease model
- **Simulation- Target**
 - Clinical trial design- optimal
 - New designs-enrichment, randomized withdraw, adaptive
 - Dosage regimen(s) selection
 - Go/No go- Sponsor &/or FDA
 - Labeling- Sponsor &/or FDA

- Given recent Guidances on Exposure-Response Relationships, Population Modeling and Exploratory IND Studies, along with the new focus on End-of-Phase IIa meetings and the Critical Path White Paper, there is a clear message from FDA regarding their view of the importance of M&S in drug development.
- I believe that FDA OCP also recognizes the role that efficient management and reporting of clinical pharmacology data plays in supporting M&S activities.

IT Infrastructure Is Critical to Success

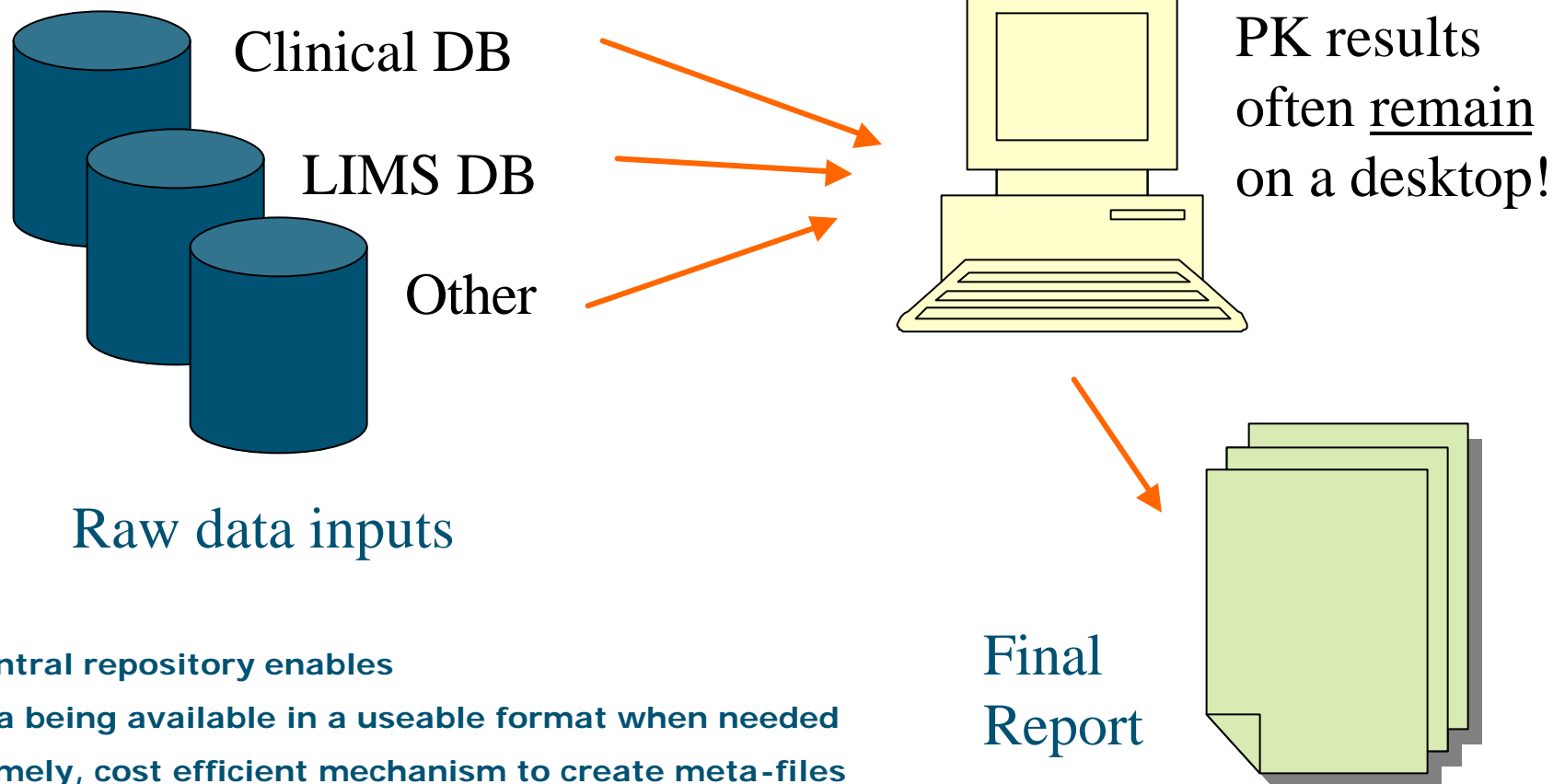
- **Tactical**

- Lack of a central repository for data
- Too many handoffs – poor processes
- Lack of standards/best practices
- Too much manual effort in report production and QA
- Scientists (both statisticians and kineticists) spend too much time on data management, edits, report production (including cutting and pasting figures and tables from Excel™ to Word™, etc.

- **Strategic**

- Need increased focus on tools and methods (such as Computer Assisted Trial Design) to better design trials and assess risk.

Why a Central Repository? Current Scenario



A central repository enables

- Data being available in a useable format when needed
- A timely, cost efficient mechanism to create meta-files
- Necessary information for M&S to be readily available
- Capture of intellectual property

IND/NDA Data Review & Analysis

FDA Clinical Pharmacology Work Plan

Data Visualization &
Data Set Creation
(I-Review)

Data Input

- EDR
- CDISC
- SAS data set (Janus)

Data Warehouse
(PKS)

NDA Quantitative Analysis & CP Review Report (Disease specific)

- Benefit/Risk
- Dose-Response
- Drug Interaction
- Special Populations
- Pharmacogenomic

Data Analysis

- Nonmem
- SAS
- S-Plus

NDA

Disease Modules

Presented by Robert Powell, FDA,
At Pharsight's 2005 PKS UGM

End of Phase 2a
Recommendation
(2b/3 trial design)

Clinical Trial
Simulation
(TS2)

EOP2a

Disease Models

- Until recently, reviews of safety data were carried out by each individual Medical (TA) group
- But in order to improve safety assessments, reviews of QT data are now being consolidated under one safety assessment team, which is part of the Cardio-Renal Division
- Like the Pharmacometrics team in OCP, they are also assessing strategies to efficiently manage and process QT data.

- **21 CFR Part 11 Non-Compliance** with regard to a pharmacokinetic data stored for internal & regulatory review as well as electronic submission. (21 CFR Part 11 - Electronic Records & Signatures)
- **Lack of Central Management** of the wealth of PK-related knowledge generated in discovery, lead optimization and development, for optimization via modeling and simulation of clinical trial designs and clinical development programs. Leverages all available data.
- **Facilitates Productivity Improvements by Reducing:**
 - **Quality Assurance Overhead** to uncover unavoidable data mismatches caused by manual data transformation steps
 - **Long Data Preparation Cycles** for PK analysis, interpretation and presentation, due to fragmented source data from multiple heterogeneous systems with incompatible formats
 - **Extensive Lead-out Time** due to cumbersome manual data transcription and transfer steps for the preparation of report tables and graphs

So How Do We Move Forward In Implementation of A Repository?

- **Standards, standards, standards** – without standards the value of a central repository is severely limited
- **Use automation wherever possible** – needs management mandate. This frees up QA staff as well as the staff actually doing the work. It also reduces costs and turnaround times. One of our clients estimates they spend an average of 40hrs on QC for each clin-pharm report.
- **The value of automation** was illustrated in the following case study by Pfizer.



REVIEW ARTICLE

Releasing the Human Spirit in Developing Drugs

Increasing Clinical Pharmacokinetics Productivity

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- **2 individuals** conducted all routine analysis previously done by 15 staff
 - Handled **45 new studies** in the first year
 - Report cycle time reduced from 16 to **3 months**
- Other departments were pleased with report timeliness and quality
- Staff that were freed up were trained and deployed to support M&S activities

- FDA plans to use more modeling and simulation
- New IT Infrastructure is needed to support modeling and simulation
- Automation of PK-PD analyses can improve productivity more than 80%
 - 15 people --> 2 people to do same work (87% reduction)