MODEL-BASED DRUG DEVELOPMENT: A FDA CRITICAL PATH OPPORTUNITY

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The Pharmaceutical Pipeline: A Critical Contributing Factor

- Progress in basic biomedical science has surpassed investment and progress in the medical product development process
- We are using the evaluation and development tools of the last century to develop this century's basic science advances
- The medical product development process – the "critical path" is becoming a serious bottleneck to delivery of new therapies

Challenge and Opportunity on the Critical Path to New Medical Products

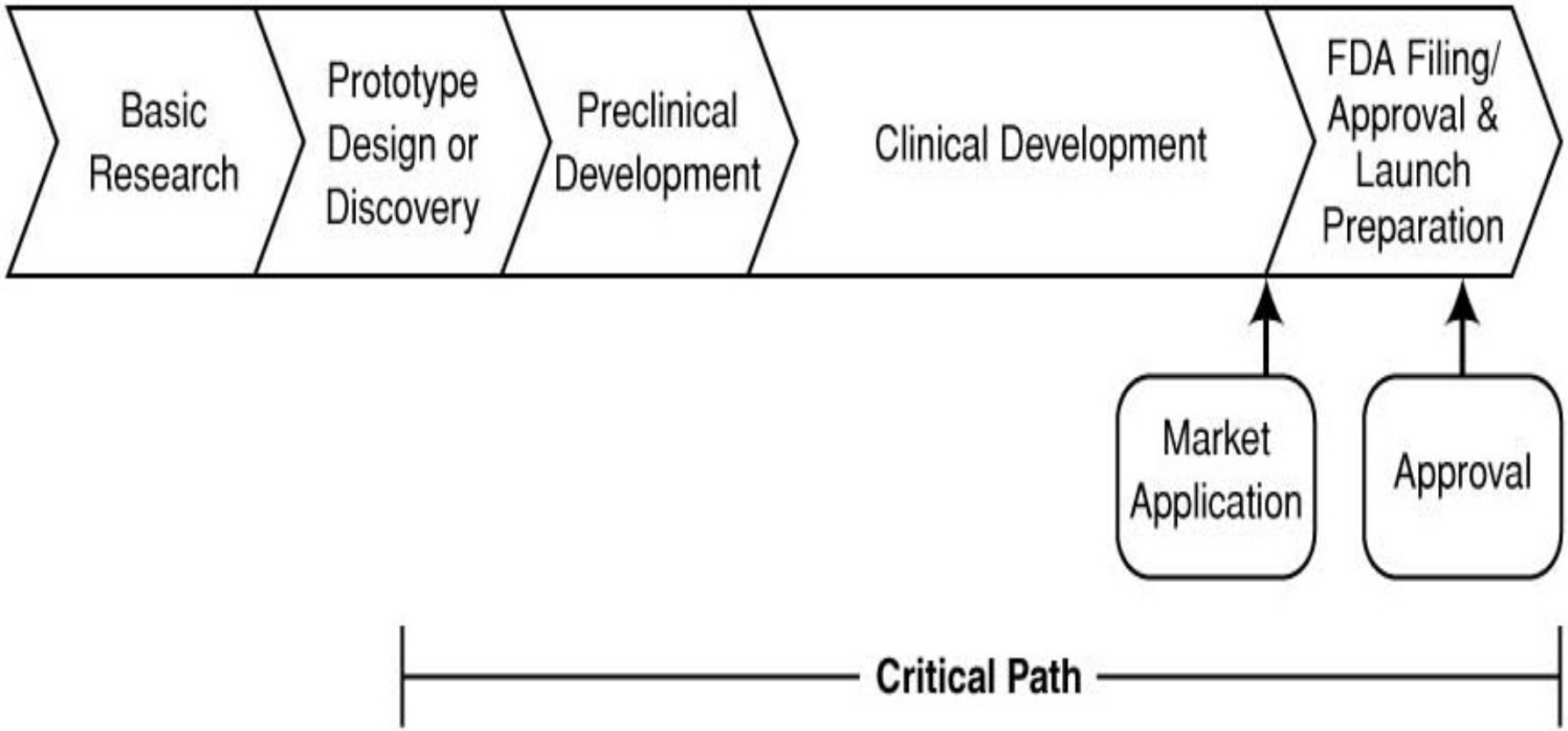
View from The U.S. Food and Drug Administration

FDA

FDA's Critical Path Initiative

A serious attempt to focus attention on modernizing the evaluation of safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture

The Critical Path for Medical Product Development



Why Has This Happened?

- Huge private & public basic research & specific product development investment, but…
- Societal investment in R&D to improve the drug development process missing
- Minor investment in development tools & public standards
  - Academia not funded
  - Not previously understood as FDA's role
  - Efforts in private sector not generalizable or are proprietary

FDA Critical Path Goals

- Get more innovative products to patients through development pathways that are efficient and predictable
- Develop new toolkits that bring scientific advances into the product development process
- Perform research on tools that remove specific identified obstacles in product development

What Critical Path Is Not

- NOT about the discovery process
  - Not our area of expertise
  - NIH getting more involved via "roadmap" initiative
- NOT a short-term effort that will go away in six months or so
- NOT an effort to either:
  - Benefit industry
  - Get more money from industry

Why FDA? Unique Role in the Critical Path of Product Development

- FDA scientists are involved in review during product development--they see the successes, failures, and missed opportunities
- FDA guidance documents are known to foster innovation and improve chances of success
- FDA has convening and coordinating role

Guiding Principles of FDA Initiative

- Collaborative efforts among government, academia, industry and patient groups
- Infrastructure and "toolkit" development, not product development
- Build support for academic science bases in relevant disciplines
- Build opportunities to share existing knowledge & database
- Develop enabling standards

Critical Path:
One Year Later

What We Have Learned?

- General agreement about problem, but widespread recognition of barriers
  - No research funding source
  - Concerns about I.P.
  - Lack of business model
  - Concerns about antitrust
  - No academic rewards (tenure)
  - Lack of trained interdisciplinary personnel

Broad Project Categories

- Biomarker Development
  - General conceptual framework
  - Specific biomarker qualification
- Clinical Development
  - Early clinical work
  - Model-based development
  - "Clinical Trials Modernization"
- Disease or Population – Specific Projects

Regulatory Strategies: Early Clinical Trials

- Exploratory IND draft guidance
- Laboratory production of clinical supplies
- End of Phase 2A meetings
- Modeling and simulation of clinical development plans

Late Clinical Trials: Design & Analysis

- Analytical issues
  - Multiple end points
  - Non-inferiority
  - Imputation of missing data
- Design:
  - Bayesian design
  - randomized withdrawal
  - enrichment designs
- Specific design projects – including modeling and simulation

Remaining Barriers

- FDA does not have funding for critical path/lack staffing
  Industry/academic/FDA/NIH working out arrangements for research consortia
- Multiple uncoordinated efforts in/by various sectors
- Need better incentives for diagnostics

Remaining Barriers: Current FDA Thinking

- Multiple consortium arrangements probably needed
  - Freestanding/academic e.g. Ray Woosley's C-Path Institute
  - Academic/industry: ie UCSF
  - NIH where institutes are engaged
  - FDA-partner CRADAs
  - Other

FDA Next Steps

- Publish "Critical Path Opportunities" List
- Publish description of FDA projects
- Further develop consortia
  - Some as umbrella organization
  - Others around specific projects
- Continue with workplan – try to gather a resources to accomplish work

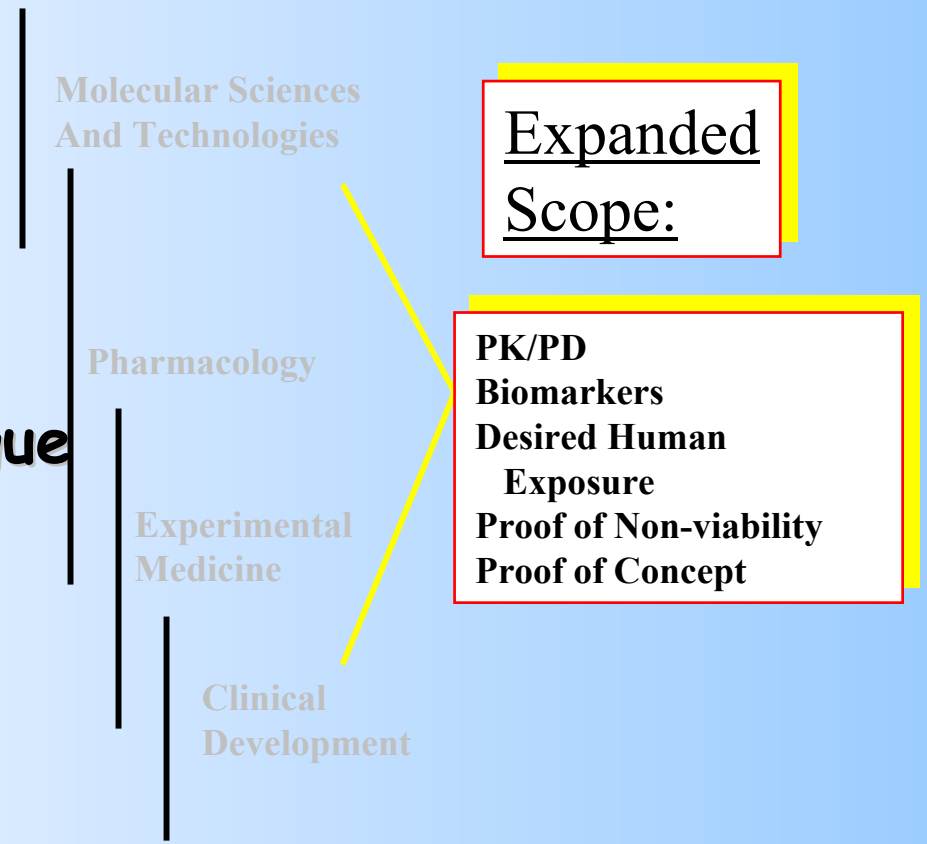
MODEL-BASED DRUG DEVELOPMENT:

UNIFYING THE DOSE-RESPONSE MODEL
(INFORMATION-TIME)
FROM DISCOVERY TO POST-MARKET DEVELOPMENT

(WHAT THIS MEETING IS ALL ABOUT!!)

COMMUNIATION BETWEEN THE FDA AND INDUSTRY NEEDS TO OCCUR EARLY IN DEVELOPMENT

- Target Validation
- Screening
- Lead Development
- Pre-Lead
- Lead
- First in Human-FDA dialogue
- Proof of Concept-FDA dialogue
- Full Development-FDA dialogue



MODEL-BASED DRUG DEVELOPMENT REQUIRES MULTIPLE LEVELS OF SUPPORT

- Support from upper management
- Strategic thinker serving multiple project teams
  - Identify valuable questions which can be answered using models
  - Timeline
  - Budget
  - Communication
- Evaluation analyst on project team
  - Answer questions
  - Execute within budget according to timeline
  - Communication

INDUSTRY INTERACTIONS WITH THE FDA

- **More complete integration of the available knowledge of a drug candidate early in development using a drug and disease model**
  - Start in the pre-clinical phase
  - FDA feedback at the pre-IND meeting
- **Clinical trial modeling and simulation to evaluate the behavior of proposed clinical trials of a development plan**
  - Model initial trials to the proof of concept phase
  - FDA feedback at the pre-IND meeting
- **Define the uncertainty in efficacy and safety (risk assessment) in the drug and disease model**
  - Define ways to decrease or define this uncertainty
  - FDA feedback at pre-IND and end of Phase 1/2A

INDUSTRY INTERACTIONS WITH THE FDA

- **Uncover and face the implicit assumptions of a drug's risk management profile**
  - Focus on criteria for efficacy and risk (clinical, economic)
  - FDA feedback at end of Phase 1/2A and end of Phase 2B
- **Fail drug candidates early, but with increased confidence in the decision**
  - Define criteria for failure
  - FDA feedback on criteria for risk assessment
- **Update the drug and disease model as new information is generated**
  - Shared with the FDA over time
- **Use the drug and disease model as a knowledge management tool**
  - Label can be written from the drug and disease model

INDUSTRY INTERACTIONS WITH THE FDA

- A new timetable and nature of interactions:
  - **Pre-IND, End-of-Phase 1/2A*,**
  - End-of-Phase 2B, pre-NDA
- Dialogue with the **"drug development team"** vs regulatory affairs
- Increased focus on the early phase of development
- Maximize information sharing using the models as a communication tool

- * a new interaction

FDA RESPONSIBILITY TO THE INDUSTRY

- A integrated team of medical officers, biostatisticians, clinical pharmacologists and pharmacometricians to review and utilize the drug and disease models
- Timely, responsive turn-over of information exchanged
- A new format for FDA/industry meetings (B. O'Neal)
- New guidance for the preparation and updating of drug and disease models
- Metrics of both industry and agency performance relative to value and impact

POTENTIAL FDA IMPACT ON THE INDUSTRY

- Establishing the routine use of drug and disease modeling and advanced pharmacometric concepts early in clinical drug development
- Optimizing clinical drug development focus on establishing exposure-response relationships to allow correct choice of dose(s)
- Promoting the use of innovative clinical designs early in clinical development to establish proof of concept and exposure-response relationships
- Providing the industry direction and guidance early in clinical development when there is opportunity to change direction and plans
- Creating a library of drug and disease models for relevant therapeutic areas to allow this accumulated knowledge to be used to improve clinical drug development

SUGGESTIONS TO IMPLEMENT MODEL-BASED DRUG DEVELOPMENT

- GOOD INTERNAL EXECUTION WITHIN A COMPANY
- START EARLY AT THE FDA, ie pre-IND
- GET PHARMACOMETRICS EXPERTISE TO FDA MEETINGS
- USE END OF PHASE 2A MEETINGS
- MAKE MODELING TRANSPARENT TO THE THREE LEVELS OF FDA REVIEW
  - MEDICAL OFFICER, CLINICAL PHARMACOLOGIST, PHARMACOMETRICS EXPERT

IMPLICATIONS FOR THE PHARMACEUTICAL SCIENCES WORKFORCE

- Who will provide the multi-disciplinary education and training needed to implement model-based drug development?
  - Pharmaceutical sciences
  - Clinical medicine
  - Bioengineering
  - Statistics
  - Epidemiology/outcomes research
- What is the role of the academic community in creating model-based drug development given the limited access to the competitive (patented) knowledge?