FDA's Critical Path Initiative — Progress to Date and Direction

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Agenda

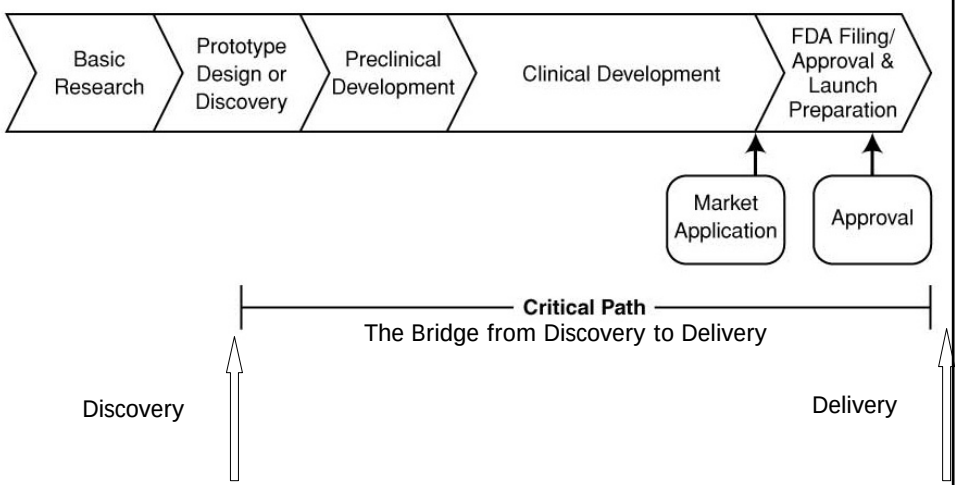
- Conceptual framework for Critical Path
- Specific Areas of accomplishment
- Assessment
- What's next?
  - Areas of focus for 2008
  - Longer term future

Conceptual Framework

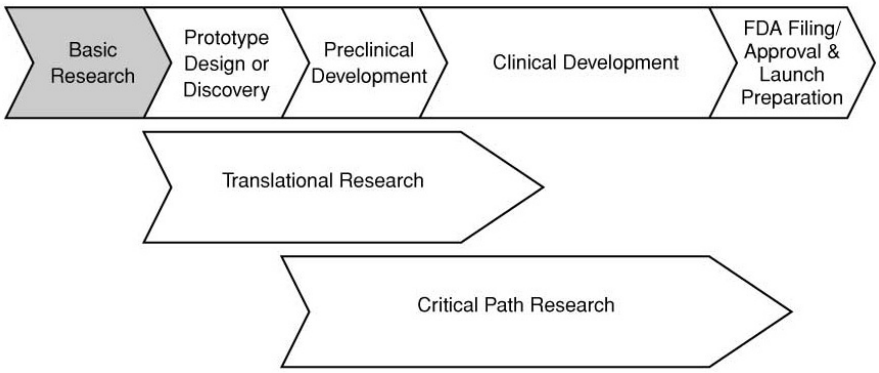
- Drug and medical device discovery and development in the 2000s did not appear to be producing at the expected level both in terms of quantity and quality (amount of information produced)
- Multiple explanations had been offered by various experts
- *Critical Path* offered a new explanation:

lack of investment in development sciences

The Critical Path for Medical Product Development



Science Underlying The Critical Path of Medical Product Development



Science to evaluate safety & efficacy of new products, and enable manufacture, is <u>different</u> from basic discovery science

First Achievement — Defining the Problem

- Most nontechnical stakeholders (Congress, medical community, etc) did not (and many still do not) grasp this issue
- No one entity "owns" the problem, although FDA is uniquely placed to understand it
  - FDA often blamed for development problems—undiscovered safety issues as well as slowdowns in approval of important drugs and devices
  - Agency generally not resourced to support applied science necessary to modernize development
    - Biologics and device programs have (very modest) research funds
    - Drugs program does not have any significant funding

Reaching Agreement on Addressing the Problem

- Stakeholders (e.g., patient advocacy groups, medical professional societies, some academics) rapidly on board
- Industrial representatives agreed with problem definition, but not sure of its relative importance or the potential return on investment
- Slow buy-in by FDA staff (generally group-by-group as projects in their regulatory areas are addressed)
- Clear that we are in this for the long term

Approach to Date

- Critical Path emphasizes collaborative ways of accomplishing objectives
- Funds are scarce, so pool resources, especially those that have been underutilized (i.e., data from development programs)
- Use industry data generated during compound development in a collaborative and pro-competitive manner
- Use NIH-funded trials and research to help qualify promising biomarkers

Specific Areas of Progress

- Biomarker Development
- Clinical Trial Modernization
- Bioinformatics
- Manufacturing

Biomarker Development

- Framework for adoption and regulatory use
- International progress
- Pharmacogenomics
- Safety biomarkers
- Cancer
- Targeted therapy
- Imaging

Biomarker Qualification

- Broad acceptance of notion of *qualification* or *fitness for use*
- FDA concept paper on topic under development – will clarify terminology
  - CDER review divisions surveyed on their use of and terminology for biomarkers (highly variable)
  - Regular meetings between CDRH and CDER on use of diagnostics with drugs
- Formal biomarker qualification process set up at CDER
- Agency-wide biomarker qualification process being developed

International Progress on Biomarkers

- Biomarker discovery and development a major theme of EU's "Innovative Medicine Initiative" (IMI) — proposed funding 1B Euros over 2007-13 from EU, with matching contributions from industry
- EMEA and Japanese regulators participating in FDA biomarker qualification process
- Step 2 guidance at ICH on pharmacogenomics terminology (E15)

Pharmacogenomic Biomarkers

- Announced relabeling: 6MP, irinotican, warfarin, codeine…more to come
- Policy arena: ASR guidance, draft IVDMIA guidance causing a great deal of controversy
- *Pharmacogenomic Data Submissions: Companion Guidance* (draft issued 8/07)
- Multiple consortial efforts (to be discussed)

Safety Biomarkers

- Side effects don't happen to everyone: so what causes a specific individual to have one?
- Need to improve drug safety through better *mechanistic* understanding of AEs
- Certain biomarkers may be low hanging fruit in improving drug safety

Safety Biomarkers

- Genomic markers offer new promise for identifying subpopulations at risk e.g.
  - Abacavir and genomic marker for skin reactions
  - HLA markers for carbemazepine skin reactions
  - Genomic markers to identify populations that metabolize warfarin at different rates
  - Genomic markers for ultra-rapid metabolizers of codeine resulting in morphine toxicity
- New (non-genomic) biomarkers for nephrotoxicity are under investigation

Future opportunities

- A framework for assessing the performance of safety biomarkers
- Approaches to enriching study populations for the detection of rare adverse events normally only seen in very large studies
- Opportunities:
  - pharmacogenomics;
  - Micro-arrays to identify genetic differences in drug metabolism
  - genetic basis of AE's
  - cardiac repolarization
  - new empirical safety biomarkers

Safety Biomarkers — What are the Obstacles?

- Another area where "no one has been in charge"
- Much academic research in this area
- Real world always more complex and requires much more study
- Consortia are taking first steps, will need worldwide cooperation to achieve robust clinical qualification
- Need links with informatics-based safety surveillance and datamining

Biomarkers in Cancer

- FDA has robust partnership with NCI (IOTF)
- OBQI= Oncology Biomarker Qualification Initiative: FDA/NCI/CMS
- Cancer steering committee of "The Biomarker Consortium"
- AACR/FDA/NCI project on technical aspects of biomarker development
- ASCO/FDA/NCI project on clinical trials using markers (e.g., adaptive trials)

Imaging Biomarkers

- Great promise — slow progress
- Need to enhance agency review function
- Alzheimer's Neuroimaging Initiative one effort to study natural history along with imaging biomarkers
- Need way to support general human research use of molecular probes
  - Without repeating preclinical workup
  - With due respect to IP

Biomarkers — Overall Issues

- Pharmaceutical industry experiencing financial concerns — some reluctance to embark on collaborative projects
- Other funding sources for biomarker qualification remain tenuous; NIH in general more focused on basic research
- Clinical skepticism remains: in particular, confusion with surrogate endpoint clouds discussion
- Insurers undervalue diagnostics: lack of viable business model for IVDs a problem; payers want outcomes data for new markers

Clinical Trial Modernization

- FDA regulation of trials
- Design and methodology issues
- Modeling and Simulation

FDA Regulation of Trials — Guidance Development

- *Exploratory IND* final guidance 1/06
- *Computerized Systems used in Clinical Trials* final /07
- *Adverse Event Reporting to IRBs* draft 4/07
- *Supervisory Responsibilities of Investigators* draft 5/07
- *Using a Centralized IRB Review Process* final 3/06

FDA Regulation of Trials — Regulation Development

- Part 15 Hearing: Exemption from informed consent requirements for emergency research 10/06
- Part 15 Hearing: Adverse event reporting to IRBs 3/05
- Direct final rule on CGMPs for Phase 1 clinical supplies 1/06 with companion guidance (had adverse comment, so final expected soon)

FDA Regulation of Trials — Modernization

- FDA ***BiMo Initiative*** officially announced (6/06), creation of cross-Agency steering committee 12/06
- DIA/FDA meeting: Defining and Implementing Quality in Clinical Investigations 5/07
- PPP forming, Duke hosting
  - FDA-Duke MOU, announced 11/23
  - FDA cannot bring about change alone: much is in the hands of the development and clinical communities

Design and Methodologic Issues

- PDUFA 4: drugs program will develop various methodologic guidances
- Center for Biomedical Innovation (CBI) at MIT working on adaptive designs
- Hope to see adaptive dose-finding trials become more common

Bioinformatics

- Bioinformatics Board Structure set up at FDA supported by Critical Path Programs staff, Office of the CIO, and Office of Planning
- Goal: Agency-wide systems
- Five Business Review Boards (BRBs) to set business needs for specific cross-agency business processes

Bioinformatics, *cont.*

- Data standards council also supported by CPI
  - Relevant data standards to HL-7
  - Structured Product Labeling standards
- Pertinent BRBs
  - Premarket: electronic submission, tracking, and review processes
  - Postmarket: electronic adverse event reporting and database management
  - Quality: manufacturing regulation and tracking inspections, product movement
  - Scientific computing/computational science: needs of laboratories and quantitative scientists

Bioinformatics — Future

- Why focus on these agency-wide systems? Part of *information supply chain*
- FDA needs a systematic method of knowledge management to regulate efficiently – must receive all information in a computer readable and analyzable form!
- Essential to efficient transfer of regulated product information into and out of FDA and across various sectors
- Opens door for data mining and other techniques
- Ultimately create a structure that can link findings in the healthcare system to what is known scientifically

Drug Manufacturing — Product Quality for the 21st Century

- This initiative begun in 2004 and now part of CPI
- Why is this important? Manufacturing costs approximate R&D investment; lack of flexibility in production limits agility
- In implementation phase:
  - New drugs: pharmaceutical development assessment
  - Generic drugs: Question-based review
- International cooperation: EU and US working together on change control process (EU=*variations*); (*US=manufacturing supplements*)

Drug Manufacturing, *cont.*

- Focus on the science = ***Quality by Design***
- Pharmacology of the drug very important
- Understanding critical process and product parameters can lead to larger *design space* = freedom to operate
- Additional focus on new technologies such as PAT

2007 CP Initiative Expands — All Regulated Products

- Critical Path Initiative for Generic Drugs, report issued 5/07
- Established monthly FDA-wide Critical Path Steering Committee to facilitate program integrations

2007 CP Initiative Expands — New Deliverables Expected

- New rapid tests for biological/chemical contamination of animal-derived foods
- Technologies for detecting and mitigating microbial contamination of food
- Analysis technologies to assess safety and nutritive value of foods/food ingredients
- Need to be able to perform sophisticated cross-disciplinary scientific evaluations; evaluate safety and effectiveness of new technologies aimed at reducing various pathogens

For example, a therapeutic intervention for the reduction of E. coli O157:H7 in cattle immediately prior to slaughter would help reduce the exposure of humans to E. coli O157:H7

Has CP Initiative Changed Drug Development?

Definitely has changed the dialog: agreement on the problem definition

Unprecedented level of new collaborations, often between *unexpected* partners

- Wins: VXDS process a big success; manufacturing changes; consortia are making significant progress
- Buy-in, enthusiasm, and participation widespread at FDA (but by no means is everyone convinced)

What's Next?

- Depends in part on funding
  - FDA Amendments Act signed 9/07 (PDUFA renewal, FDA Foundation, postmarket surveillance, more)
  - Government FY began 10/1; as of December, no $$
- But, external collaborations are robust and will grow
- All centers poised to aggressively take up new projects pending available resources – massive outpouring of ideas and potential projects will dramatically dwarf any and all appropriated funds

Areas of Drug Focus in '08

- Quantitative disease models
- Drug-Diagnostic co-development
- Nanotechnology (affects all regulated products)
- Clinical trial modernization
- Numerous indication-specific projects
  - Pain
  - Cancer
  - Rheumatic diseases

Quantitative Disease Models

- Good early progress at FDA
- In my opinion, this is part of the future of drug development
- Basis for systematizing biomarker information linked to clinical course; simulations of interventions
- Need infusion of resources at FDA

Drug-Diagnostic Co-Development

- Issue guidance: policy and scientific development
- Procedurally, will require close CDER and CDRH collaboration
- Methodologic approaches to development, program will keep advancing
- Hope to see more actual cases!

What is Vision for Future Drug Development?

- Preclinical toxicology and clinical development move from empirical evaluations to quantitative, model-based, learn-confirm cycles
- Links between preclinical and clinical development data
- Necessary degree of confirmation premarket dependent on indication (as is the case currently)
- Predictive capacity of development system greatly enhanced
- Amount of information generated by system greatly increased

Vision for Postmarket Safety Surveillance?

- We (collectively, collaboratively) ***must*** build postmarket evaluation system
- Electronic health records
  - Emerging EHR will provide robust data on real-world outcomes of product use
- Amalgamation of national databases
  - Will need to continue to exploit vast quantities of claims data
  - PPPs are being developed to expedite access to diverse databases containing electronic patient information
  - Methods for adverse event surveillance and signal generation are being explored
- Provisions in section 905 of FDA Amendments Act

Critics

- Initiative not tightly focused; too diffuse
- Lacks few specific, compelling goals
- Not sure all FDA staff on board or that findings can and will penetrate to all levels of FDA
- Few deliverables so far

FDA Response

- Real progress has been made, as detailed in previous slides
- Can do more with more - Critical Path unfunded till late FY 07 (received $5M)
- Agency taking long-term, transformative point of view, rather than few quick wins
  - Current practices have been in effect for 20 years, difficult to change on a dime; need cultural change
  - Broad and long-term vs more narrow focus worthy of debate
  - Needed investments take time because they involve scientific research

FDA Response, *cont.*

- FDA must commit to ensuring an engaged and modern scientific work force
- FDA must articulate transparent and methodologically sound plan for identifying, evaluating, and implementing Agency CP priorities — will do so in 2008

Thank You