



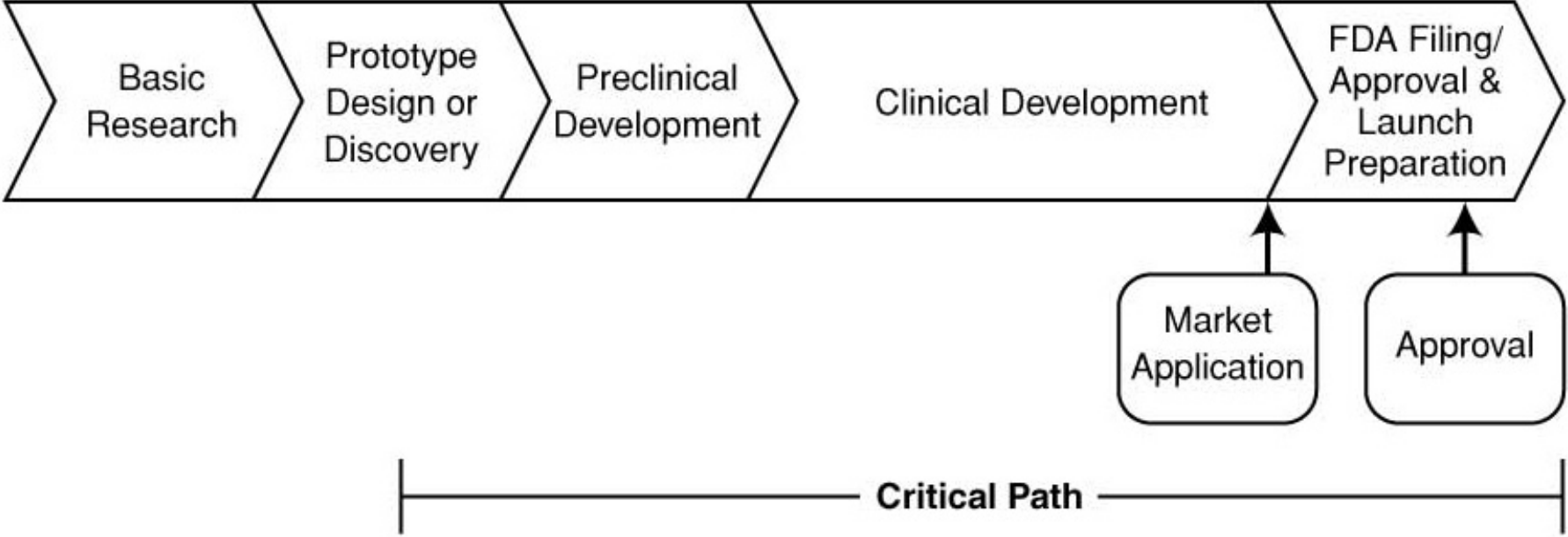
# The FDA Critical Path Initiative— Opportunities and Challenges

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Acting Deputy Director, CDER  
Food and Drug Administration  
September 23, 2005**

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- “Challenges and Opportunity on the Critical Path to New Medical Products”
    - FDA March, 2004

# The Critical Path for Medical Product Development





# FDA's Critical Path Initiative

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A serious attempt to bring attention and focus to the need for targeted scientific efforts to modernize the techniques and methods used to evaluate the safety, efficacy and quality of medical products as they move from initial characterization and product selection approval and marketing



# Biomarkers and The Critical Path Initiative

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- Biomarkers are a key technology for assessing, accelerating development and guiding use of new therapeutic options
- Development of new biomarkers is a central focus of critical path efforts by the FDA



# Outline

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- Uses of biomarkers on the Critical Path
- FDA role in biomarker development
  - Mechanisms for interaction with the FDA in the development of biomarkers
  - Examples of ongoing activities
- Next Steps



# I. Use of Biomarkers in Early Drug Development and Decision Making

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- Evaluate activity in animal models
- Bridge animal and human pharmacology via proof-of-mechanism or other observations
  - Establish pharmacologically active dose in humans
- Evaluate safety in animal models and in early clinical development



## II. Use of Biomarkers in Later Drug Development and Decision Making

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- Evaluate dose-response and optimal regimen for desired pharmacologic effect
- Use safety markers to determine dose-response for toxicity
- Determine impact of differences in drug metabolism on dose and toxicity



### III. Use of Surrogate Endpoints in Later Drug Development

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- Efficacy: Use to assess whether drug has clinical efficacy
- Safety: Use to predict the safety profile when used in the “real world”



## IV. Limitations of Current Biomarker Development

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- No single group (e.g., FDA, academia) 'owns' the development of new biomarkers/surrogates
  - Exploration of new markers is generally ad hoc and inefficient
- Consequence: no rigorous/ organized pursuit of needed data to assess adequacy of new biomarker(s) for regulatory use



# IV. Limitations of Current Biomarker Development

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- Biomarkers ideally bridge between:
  - Mechanism-based preclinical development and early pharmacologic clinical evaluation
  - Early mechanistic clinical evaluation and later clinical trials measuring clinical efficacy
- Regulatory assessment focused on empirical testing:
  - Sponsors use of biomarkers often not discussed with FDA
  - These links not made clearly, with resultant loss of information and clarity



## IV. Limitations of Current Biomarker Development

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- Pathway to regulatory acceptance of biomarkers and surrogates not clear
  - FDA/NIH Consensus Conference: Clin Pharm Thera 69:89, 2001
  - 'Prentice Criteria': Stat in Med 8: 431, 1989
  - Temple. "A Regulatory Authority's Opinion about Surrogate Endpoints". Clinical Measurement in Drug Evaluation. Wiley and Sons. 1995
  - FDA Pharmacogenomics Guidance



## V. Limitations of Current Surrogate Development

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- Historically, successful surrogates have linked effects on markers (e.g., BP, HIV mRNA) to single effects in large populations
  - At odds with current goals for individualized therapies
  - Does not recognize multidimensional quality of clinical response
  - Does not include possibility of multiple biomarkers providing useful information in aggregate (e.g., 'biomarker basket')



# VI. Challenges to New Biomarker and Surrogate Development

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- Biomarkers must be USED to be accepted
- Add-on costs in clinical trials have been a significant barrier
  - Analyses of biomarker data collected often ad hoc
- Requires government-academic-industry collaboration and focus



# More at Stake than Efficient Drug Development

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- Biomarkers are the foundation of advances in targeted therapies:
  - who should be treated, with what dose and with what drug
- Absent new markers, advances in more targeted therapy will be limited and treatment will remain largely empirical/population-based
- It is imperative that biomarker development be accelerated along with therapeutics



# FDA Response

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- FDA considers biomarker and surrogate development a critical part of its “Critical Path” Initiative
- FDA is working on a process for refining the framework for biomarker development as well as individual projects on biomarker and surrogate endpoint development



# FDA Activities in Biomarker and Surrogate Development

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- Agency-level WG
  - Coordinate activities
  - Expertise in 'mechanics' of FDA partnership
    - CRADAs, MOUs, Contracts (small)
  - Partnership for large, cross-Agency issues
- Center-Specific activities
- Potential Types of Interactions:
  - FDA and Academic Partnerships
  - FDA and Private/Industry Partnerships
  - FDA and NIH Partnerships
  - FDA and other entities (other government, non-profit etc.)



# FDA and Private/Industry Partnerships (Examples)

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- Sponsor: Renal Safety Biomarker development
  - Issue: animals models poorly predictive of clinical toxicity, no good biomarkers for clinical toxicity
  - Sponsor database of 5 clinical nephrotoxicants
  - Progress:
    - Target biomarkers identified
    - Animal model selected to try to link to clinical outcomes



# FDA and Private/Industry Partnerships: PhRMA

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- Development of Biomarkers
  - Issue: Development of needed regulations to support initiatives, need for large databases to facilitate biomarker/surrogate development
  - Safety as pre-competitive



# FDA and Private/Industry Partnerships: ECG Warehouse

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- Issue:
  - Current non-clinical models inadequate to predict clinically relevant effects
  - QT interval prolongation imperfect surrogate for arrhythmic risk
  - T-wave morphology changes poorly understood
- Mortara electronic ECG waveform warehouse
  - CRADA
  - Format for electronic ECG submissions agreed to (HL-7)
  - 10,000's of ECGs anonymized, submitted
  - Analysis tool developed



# FDA and NIH Partnerships

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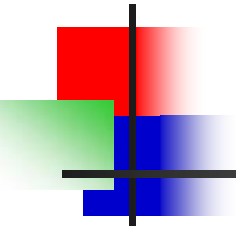
- Issue:
  - Need for new measure of progression (like tumor shrinkage)
  - Assess not just anatomy (RECIST) but tumor function
- FDA-NCI IOTF
  - Evaluation of use of FDG-PET in therapeutic cancer trials with NCI
    - Ongoing gap analysis: Current data from particular tumors: validation and (perhaps) use as general response measure in trials



# FDA and other entities: Universities

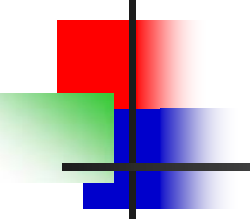
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- Multiple issues identified of interest (including biomarkers):
  - Fostering career development in clinical trial planning/analysis
  - Legal issues
  - CV biomarkers (e.g., volumetric/radiographic or soluble markers to assess atherosclerosis)



# Next Steps

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# Next Steps: How to Get Needed Work Accomplished

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- FDA activities (discussed above)
- New opportunities for FDA collaboration (discussed above)
- Many stakeholders will have to chance participate: FDA, NCI, drug, device and biologic developers, ?payers
- Use of ongoing trials and available data
- Need to respect Intellectual Property issues



# Next Steps Specifically for Biomarkers and Surrogates

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- “Gap analysis”: Current data on biomarker (good and bad) and identification of missing pieces
- “Trial analysis”: What trials, using what active agents, would be needed to fill in these gaps?
- Identify mechanisms to conduct such studies



# Summary

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- Accomplishing this will require extensive collaboration across many stakeholders
  - No one entity has all the needed resources
- Strong need to invigorate biomarker and surrogate characterization to maximize:
  - The efficiency of medical product development
  - The best uses of new medical products

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