

Tools to Reduce Phase III Trial Failures

Session VII: Innovation or Stagnation:
The Critical Path Initiative
AGAH Annual Meeting 2006
February 21, 2006
Dusseldorf, Germany

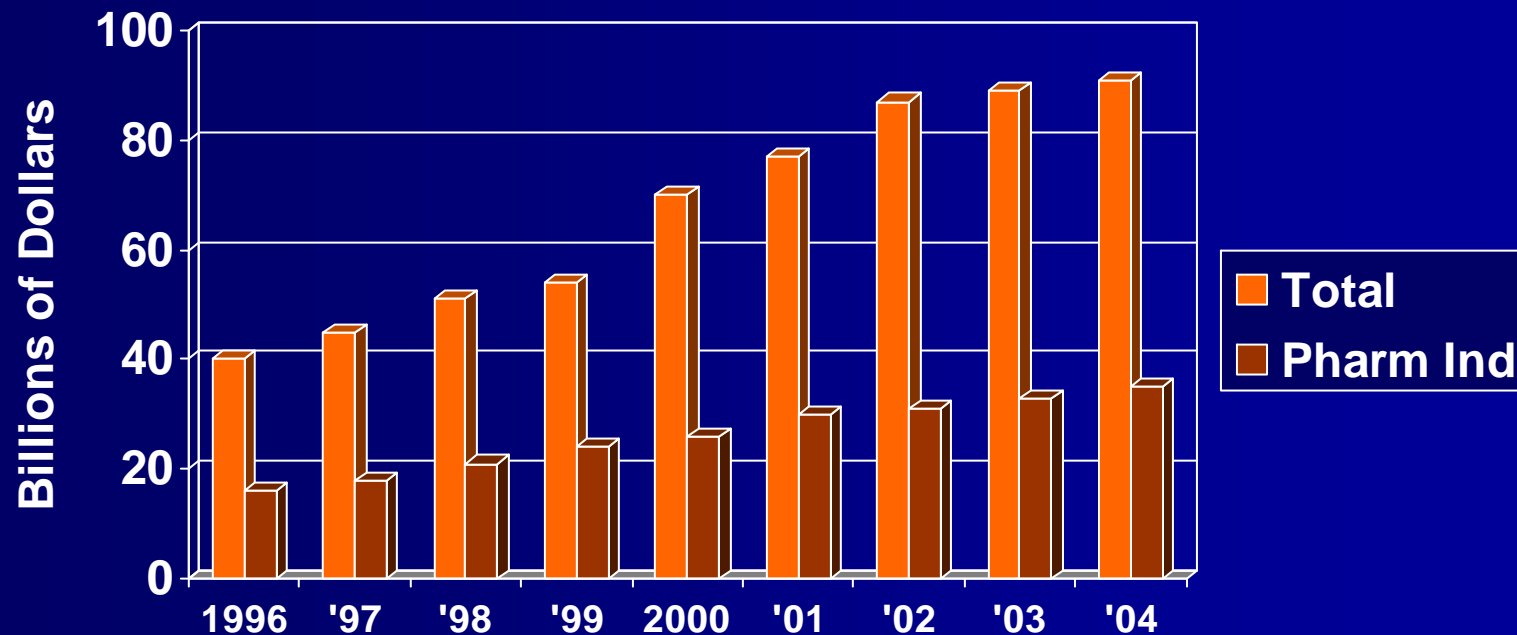
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Overview

- The productivity problem to be solved by critical path initiative
- Critical path opportunities that can influence early drug development and regulatory decisions

General Agreement on the Problem to Fix: Rising Costs

US Funding for Medical Research



Data from JAMA, Sept 21, 2005; NIH, and PhRMA Annual Surveys

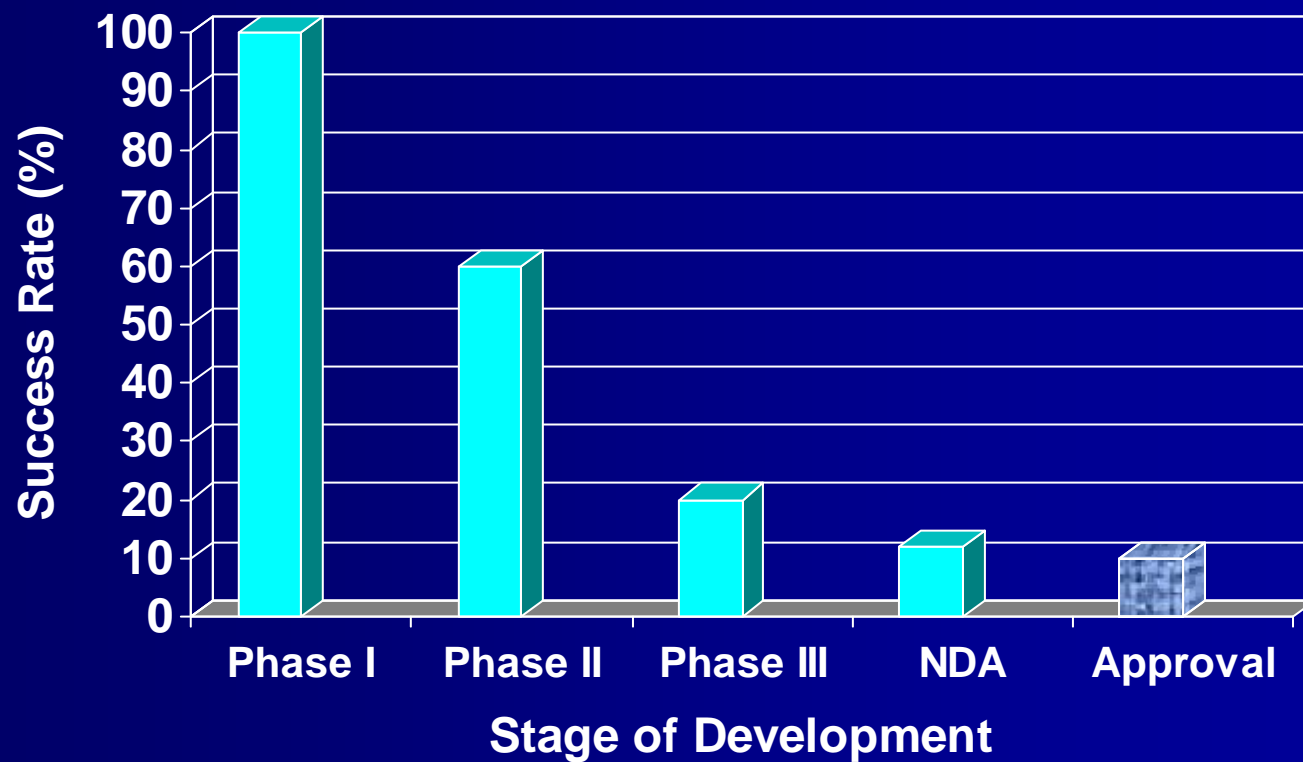
But New Drug Applications Are Not Rising at the Same Rate

Total Number of NDAs Filed with CDER



Data from FDA; beginning in 2004, numbers include BLAs transferred from CBER to CDER

Barrier to Improving Productivity is the High Attrition Rate



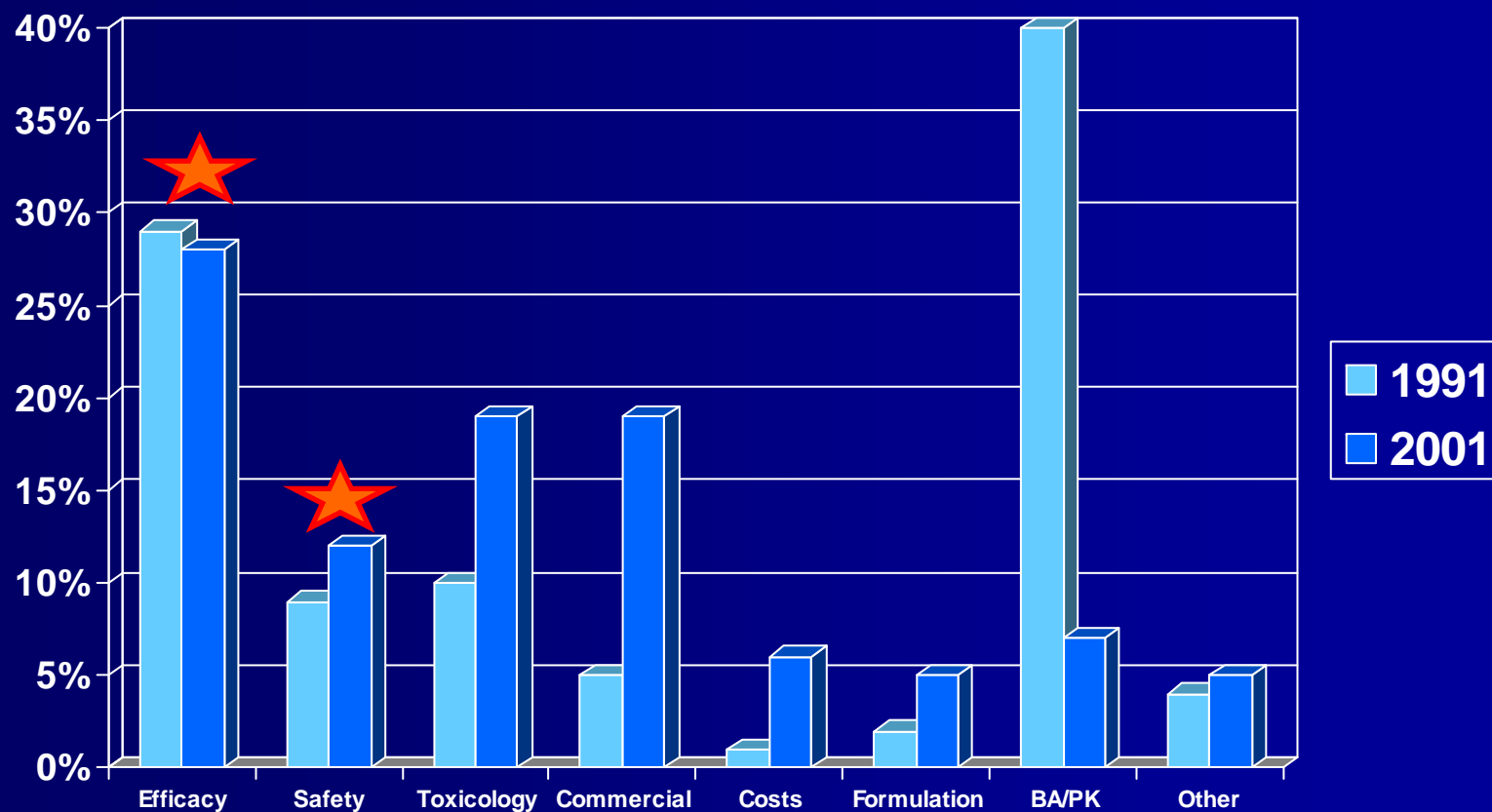
Kola and Landis, Nature Review Drug Discovery, 2004 (3):711-715

Driver for Industry to Seriously Commit to Critical Path Concepts

“We are an industry with a 98% failure rate.....The only thing we have to do to double our success rate is to drop our failure rate by 2%”

Hank McKinnell, Pfizer CEO, at <http://www.bio-itworld.com>, 2/14/06

Why Drugs Fail in Development: Root Cause Analysis is Needed



Kola and Landis, Nature Review Drug Discovery, 2004 (3):711-715

Shift Failures Earlier: Quick Win – Quick Kill Paradigm

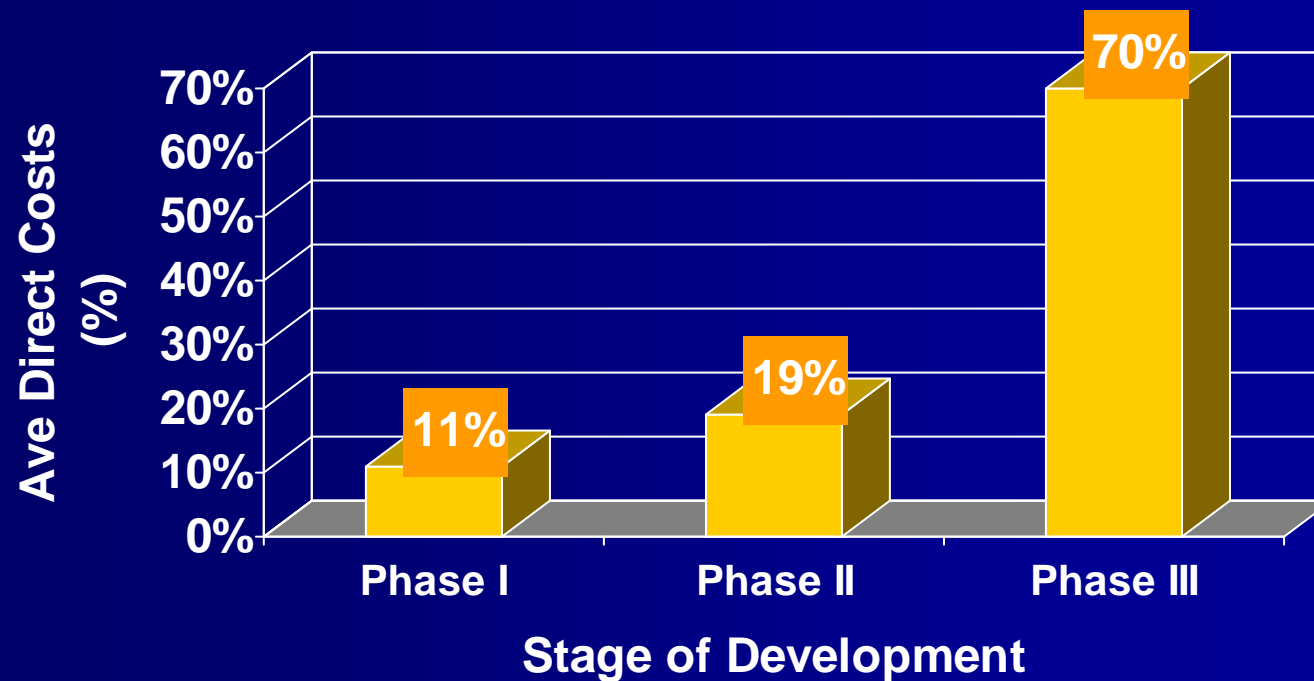
“50% of phase 3 studies fail in 2005 as compared to 35% in 1997”*

Predicting phase 3 clinical outcomes from phase 2 study results is no better than a coin flip

* From PhRMA at <http://www.pharma.org>

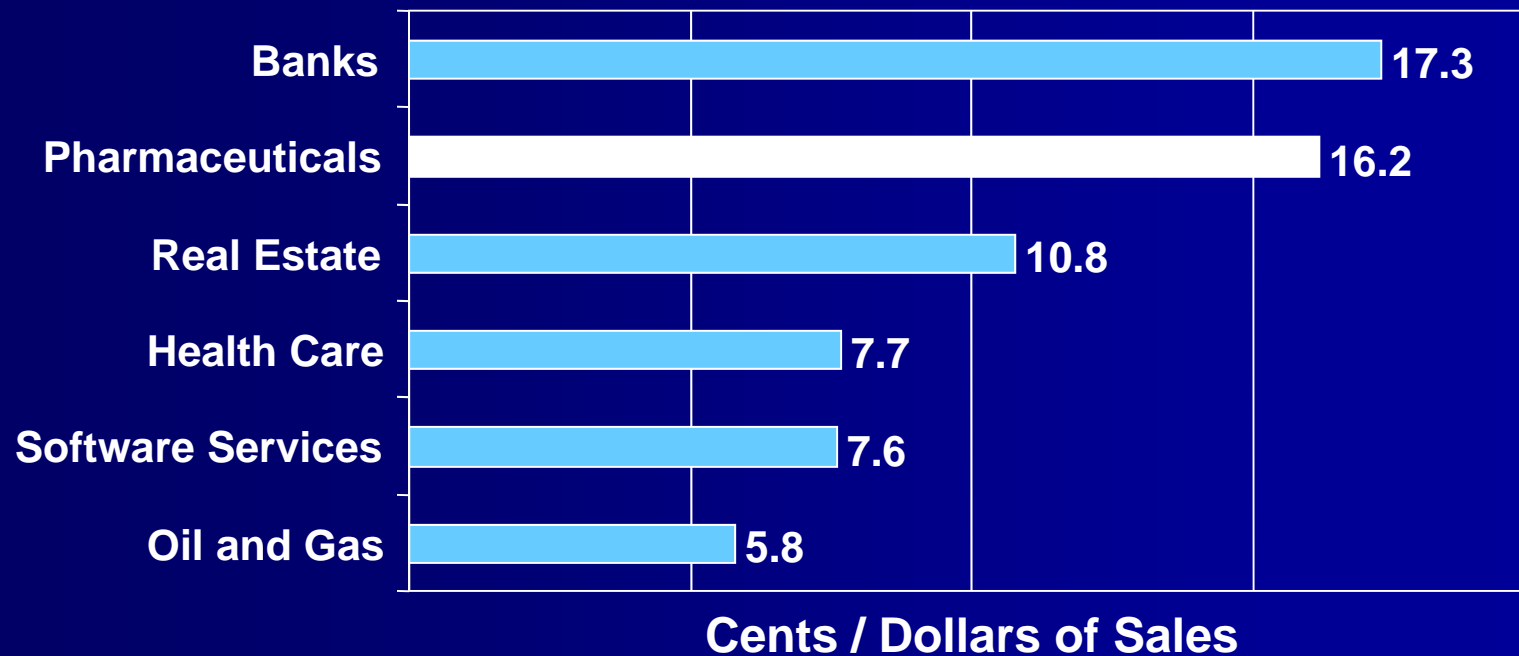
Phase 3 Trials Have Become Larger and More Costly

Distribution of Total Costs of Clinical Trials



Paradox of Decreased Productivity: Sustained Profitability (Inertia to Change)

Earnings of Major Industries For 2000-2005



*From Federal Government API Calculations and Price Waterhouse-Coopers
LLP, Reported February 8, 2006*

Pillars of Industry Profitability: Changing Fundamentals

- | | |
|--|--|
| <input type="checkbox"/> Product Life Cycles | <input checked="" type="checkbox"/> Shrinking |
| <input type="checkbox"/> Flexibility Pricing | <input checked="" type="checkbox"/> Fixed Pricing |
| <input type="checkbox"/> Blockbuster Market | <input checked="" type="checkbox"/> Segmented Market |
| <input type="checkbox"/> Patent Expirations | <input checked="" type="checkbox"/> Increasingly Important |
| <input type="checkbox"/> R&D Productivity | <input checked="" type="checkbox"/> Absolutely Essential |

Adapted in Part From a Presentation by Dr. Eiry W. Roberts, Lilly

The FDA Critical Path Initiative: An Opportunity to Change



Goals

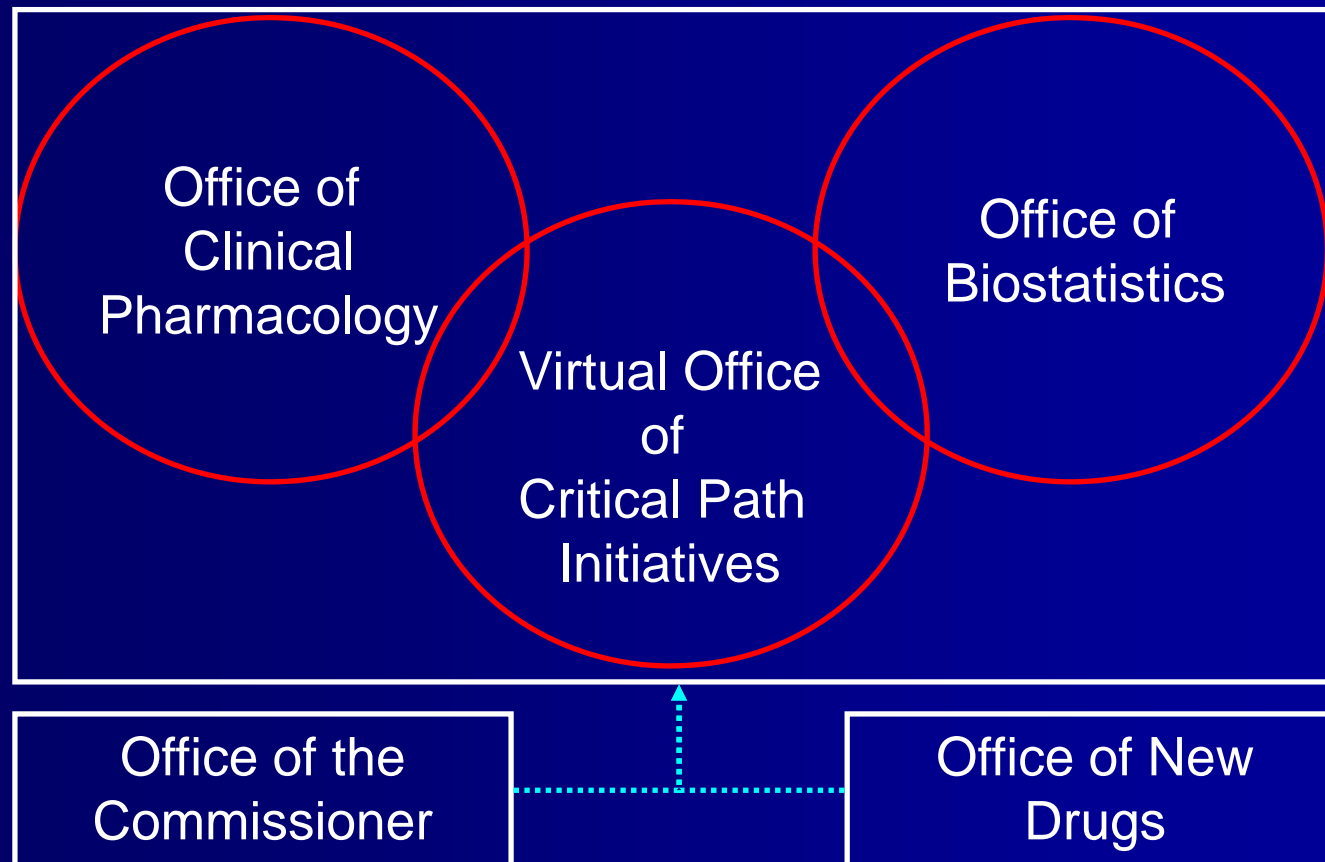
1. To develop new predictive “tools” and bring innovation into the drug development process
2. To improve the productivity and success of drug development
3. To speed approval of innovative products to improve public health

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

Progress Is Steady But Slow: Widespread Recognition of Barriers

- FDA role is largely to act as an enabler, convener or stimulator of critical path
- Agency does not have staff exclusively dedicated to critical path initiatives
- Research must be spearheaded by outside non-profit consortium (few academic rewards)
- 2006 budget is supposed to have \$10 million dollars allotted to critical path
- Drug companies must be persuaded to share their data and pool information (concerns about IP)
- FDA has been distracted with safety issues

Need for New Organizational Paradigms: Formation of New FDA “Super Office”



To be completed by June 2006

Other Changes in FDA Infrastructure to Achieve Critical Path Goals

- CDER-wide centralized consulting groups
 - Pharmacometrics (applying quantitative methods)
 - QT protocols, analysis of thorough QT studies
 - Pharmacogenomics, diagnostics and VGDS
 - Pediatric written requests, data analysis, and exclusivity
- New interface opportunities with industry
 - End-of-phase 2A meetings
- New information management system using CDISC standards and data warehousing
- Fellowship and sabbatical opportunities
- “Soft skill” training in negotiation and communication

One of the First Products of Critical Path: Exploratory IND Guidance

- Exploratory IND precedes traditional IND to reduce time/resources on molecule unlikely to succeed (“quick kill” concept)
 - Conduct early in phase 1
 - Very limited human exposure (e.g., < 7 days)
 - No therapeutic intent
 - Preclinical toxicology and CMC requirements scaled to type of study (e.g., microdosing)
 - Flexible clinical stop doses

Focus on Clinical Pharmacology Efforts in Critical Path Initiative

- Areas of greatest potential gain
 - Improve predictions of efficacy and safety in early drug development
- Biomarkers ~ better evaluation tools
 - General biomarker qualification, qualifying disease specific biomarkers
- M&S ~ better harnessing of bioinformatics
 - Disease state models, clinical trial simulation
- Clinical trials ~ improving efficiency
 - Enrichment designs, adaptive trial designs

Biomarkers: Classic Thinking Inhibits Their Development

- Overemphasis on surrogate endpoints as an objective confounds biomarker development
 - Uncertainty over what is needed for “validation” and difficulty in getting “validation” data frustrates progress
 - Need to reassess the idea of “validation” perhaps to “qualification”
- Regulatory agencies have focused too much on empirical testing of treatment vs placebo
 - Skewed research away from mechanistic biomarkers that would provide a better understanding of clinical evaluation
 - Provide incentives to use biomarkers throughout preclinical and clinical development

One Incentive: Show How Biomarkers Benefit in Regulatory Decision-Making

October 3, 2005, Volume 67, Number 40, Page 15

“Pharmacometrics Can Guide Future Trials, Minimize Risk -- FDA Analysis”

- 244 ~ number of NDAs surveyed in cardio-renal, oncology and neuropharmacology
- 42 ~ NDAs with pharmacometric (PM) analysis**
- 26 ~ PM pivotal or supportive of NDA approval
- 32 ~ PM provided evidence for label language

**** Number not higher because sponsor application lacked necessary data**

Re-emphasize 5 Fundamental Principles to Greatly Improve Biomarker Predictions

- Develop reliable standards for the technology and analyte being measured
- Clearly state the intended use of the biomarker, i.e., what is the question?
- Define the necessary performance expectations and assumptions to make a binary decision
- Express biomarker predictions in terms of probabilities of seeing clinical outcome of interest, i.e., inform decisions
- Evaluate the cost and benefit of biomarker development vs alternative approaches, i.e., when does it really make a difference

Example: Can EGFR Expression Distinguish Between Aggressive and Non-Aggressive Pancreatic Tumors?

- What is the definition of overexpression and how is this related to the technology platform used (quality)?
- What is the definition of aggressive? Locally advanced or metastatic? Survival of 3 months or 6 months?
- What kind of performance attributes are required? Is a PPV ~ 90% to distinguish between aggressive and non-aggressive acceptable? How about 75%?
- Is it necessary to predict aggressiveness for patients that received combination therapy with gemcitabine or not?
- What endpoint will I use to link clinical outcome to EGFR overexpression? Tumor size? Progression-free survival?

FDA-NCI Collaboration: Develop Such a Grid for Biomarkers Used in Cancer Drug Development

- Defined most important primary and secondary oncology biomarkers and how they are used
- Primary list
 - 4 kinases (VGEF, EGFR, PISK/Akt and Src)
 - 1 cell surface antigen (CD20)
- Secondary list
 - 3 kinases (JaK, ILK, cell cycle checkpoints)
 - 2 cell surface antigens (CD30 and CTLA-4)
- Developing detailed performance specifications and plan conduct “gap” research
 - Couple with complimentary biomarkers, e.g., imaging to improve predictability of outcomes

Define Regulatory Framework for Technical Qualification of Biomarkers as Surrogates

- Develop inventory of biomarkers used as surrogate endpoints for full approval, accelerated approval, supplements and for support of one-clinical-study approvals in each of CDER review divisions

1. *What surrogate endpoint is being used and what is the required effect size, if there is any?*
2. *Which category of approval was it used for?*
3. *When was it first used, what was the exact claim that was granted, and what did the label say?*
4. *What was the evidence basis for reliance on a surrogate?*
5. *What other surrogate endpoints are under consideration?*

Model-Based Drug Development: An Extension of Dose-Response

- A mathematical, model-based approach to integrating information and improving the quality of decision making in drug development
 - Preclinical and clinical biomarkers
 - Dose-response and/or PK-PD relationships
 - Mechanistic or empirical disease models
 - Clinical trial simulations and probabilities of success
 - Baseline-, placebo- and dropout-modified models
- Ten disease models created internally including HIV-AIDS, osteoarthritis, alzheimers, parkinsons and pain
 - Exploring feasibility of creating a public space where models can be shared and grown

Build a Drug Disease Model: Example of HIV/AIDS

Mechanistic Model of
Disease
Ex: HIV/AIDS

Mathematical Model of
Dose – Conc. (PK)
Ex: HIV, viral load vs. time

Biomarkers of Efficacy
Ex: viral RNA over time

Biomarkers of Safety
Ex: GIT events over time

Patient Co-
Variates

D/R and/or PK/PD
Ex: viral RNA and GIT
events as $f(E, t)$

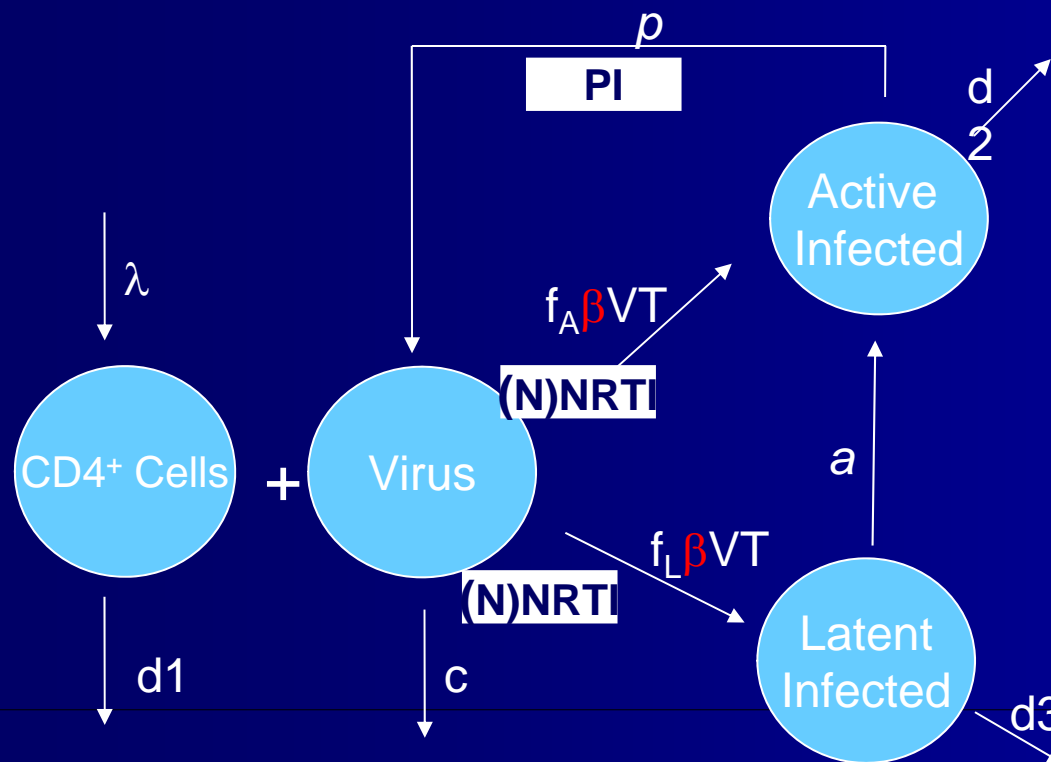
Placebo
Response

Biomarkers (clinical outcome) Over Time

Example: New CCR5 Inhibitor

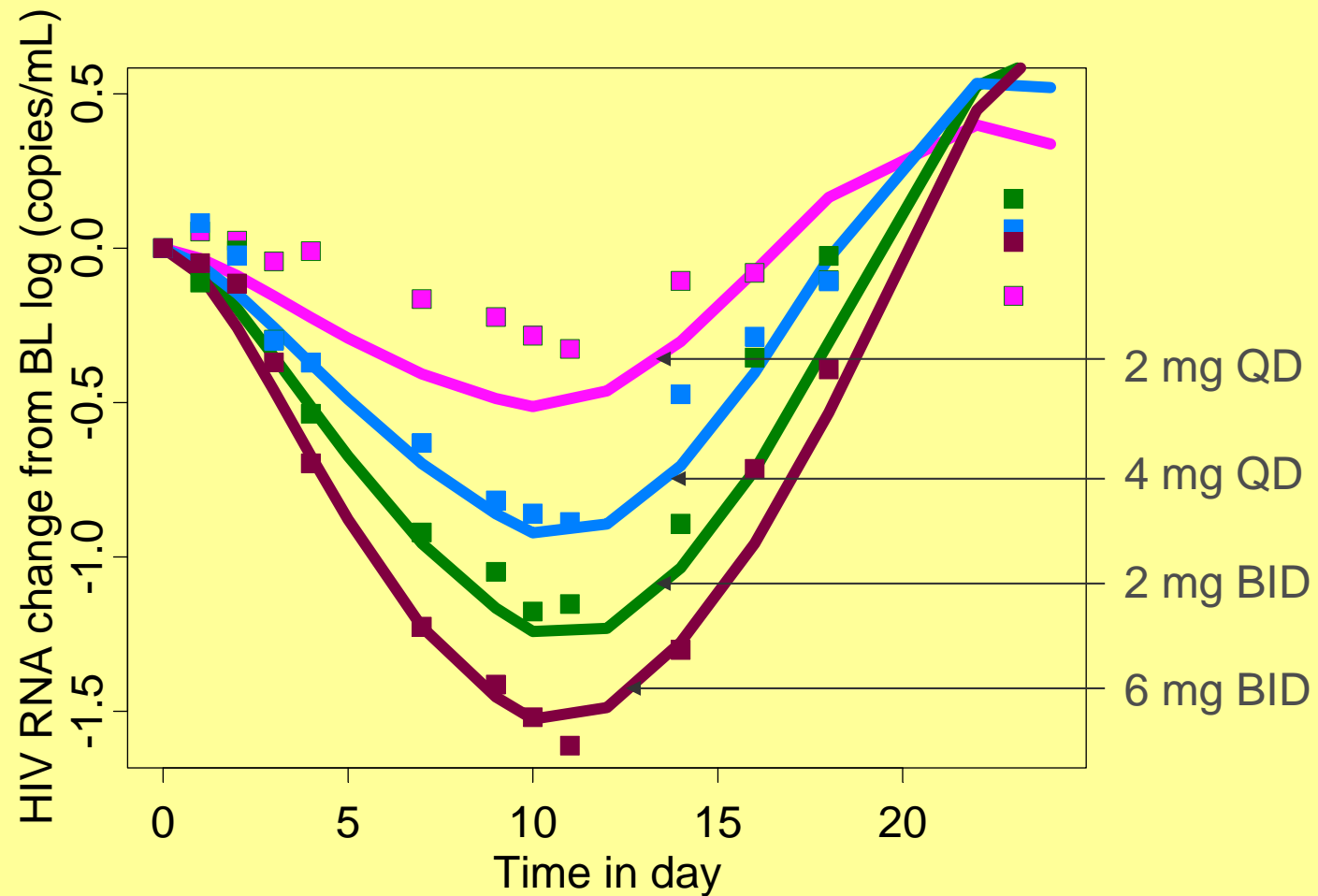
- D/R for efficacy from 0.5 to 6 mg BID
 - Co-administered with Kaletra 400 mg/100 mg
- Risk
 - Severe GI events increased at higher doses
- Benefit
 - Patient co-variates, resistance, drop-outs, non-compliance
- Question to be asked
 - How can optimal dosing and study design be determined after 4 weeks in order to predict phase 2B trial outcome at 48 weeks?

Built Dynamic Viral Disease Model Using Literature, In-House Data, Information Provided Voluntarily by Companies



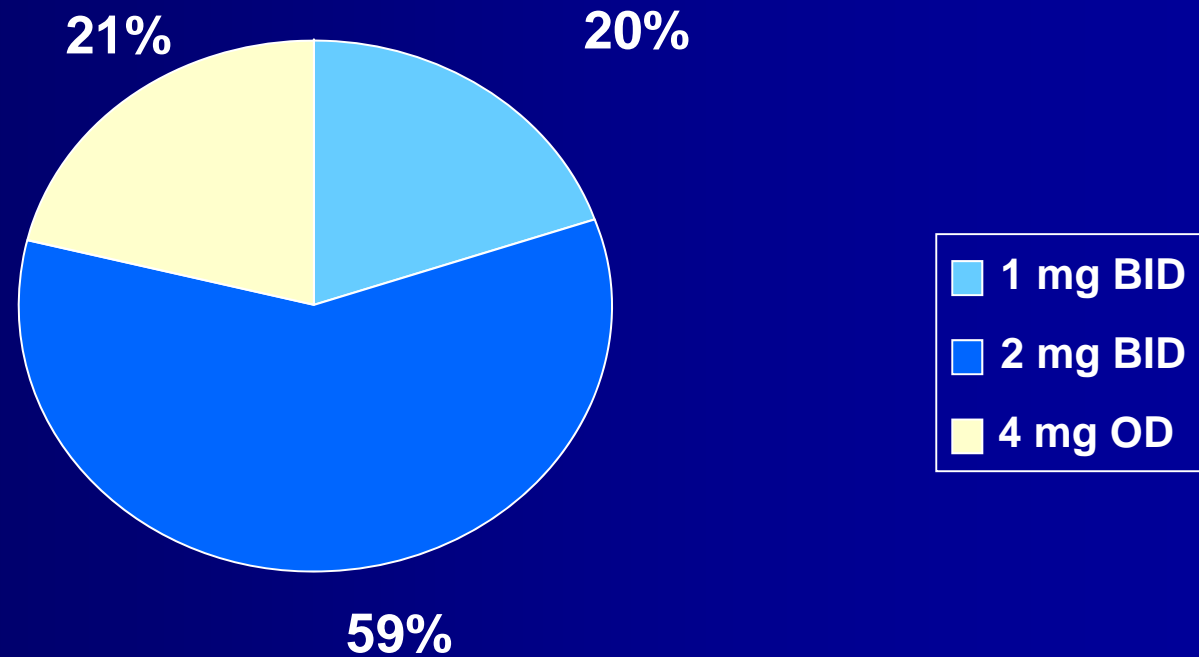
- λ : production rate of target cell
- d_1 : dying rate of target cell
- c : dying rate of virus
- β : infection rate constant
- d_2 : dying rate of active cells
- d_3 : dying rate of latent cells
- p : production rate of virus

Differentiated Dosing and Study Designs by Simulating Viral Load Over Time



Simulating 20 Clinical Trials with 50 Patients per Group to Estimate Probability of “Picking the “Winner””*

% of Simulated Trials Achieving Target Efficacy Outcome



* 2 log drop in viral RNA

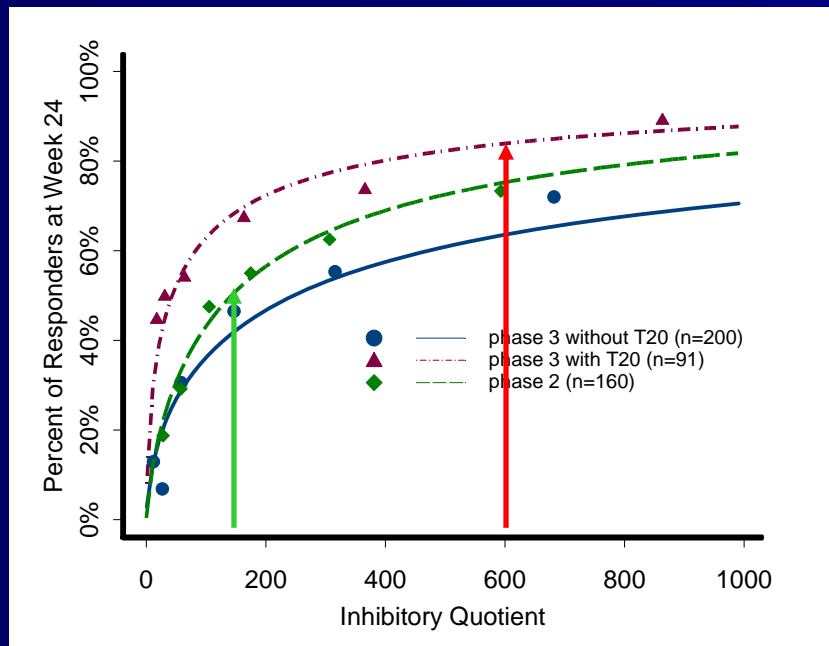
Tipranavir: Good Biomarker Work Informs Drug Development and Therapeutics

- Non-peptidic protease inhibitor for experienced patients or patients with virus resistance to other PIs
- Plasma TPV levels ~ major driver of efficacy and toxicity, boosted with ritonavir (RTV)
- HIV-1 protease mutations ~ major driver of resistance and decreased efficacy
- 500/200 TPV/RTV dose selected for phase III
 - Plasma TPV levels $> IC_{50}$ to suppress viral load and avoid development of resistance
- Inhibitory quotient, IQ, predicts responders after 24 weeks
 - $IQ = C_{min} / [Wild\ Type\ IC_{50} \times 3.75]$

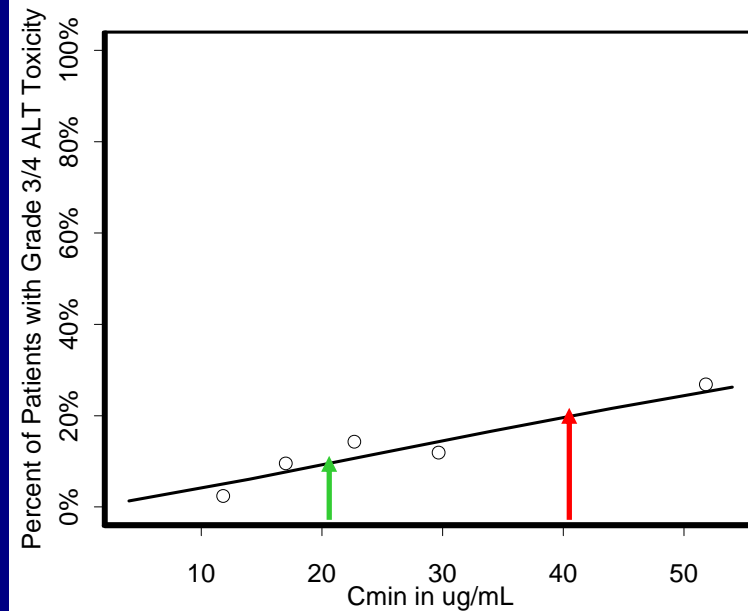
See The Pink Sheet, June 30, 2005

Impact of IQ on 24-Week Viral Load Response and C_{min} on Liver Toxicity

Benefit: Viral Load Change From Baseline (\log_{10})



Risk: Grade 3-4 ALT, AST or Bilirubin



From Dr. Jenny Zheng (OCPB), FDA Antiviral Drug AC Meeting, May 19, 2005

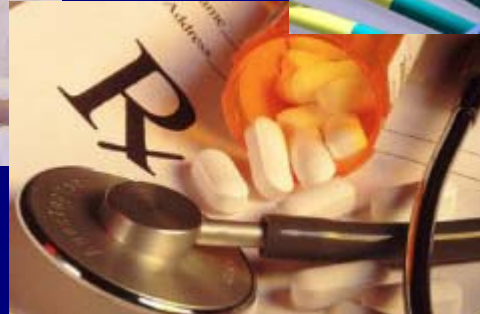
Translation of Information to Approved Label

“Among the 206 patients receiving APTIVUS-ritonavir without enfuvirtide.....*the response rate was 23% in those with an IQ value < 75 and 55% with an IQ value > 75.*”

“Among the 95 patients receiving APTIVUS-ritonavir with enfuvirtide, *the response rate in patients with an IQ < 75 vs. those with IQ > 75 was 43% and 84% respectively.*”

Critical Path Opportunity for Innovative Adaptive Trial Design

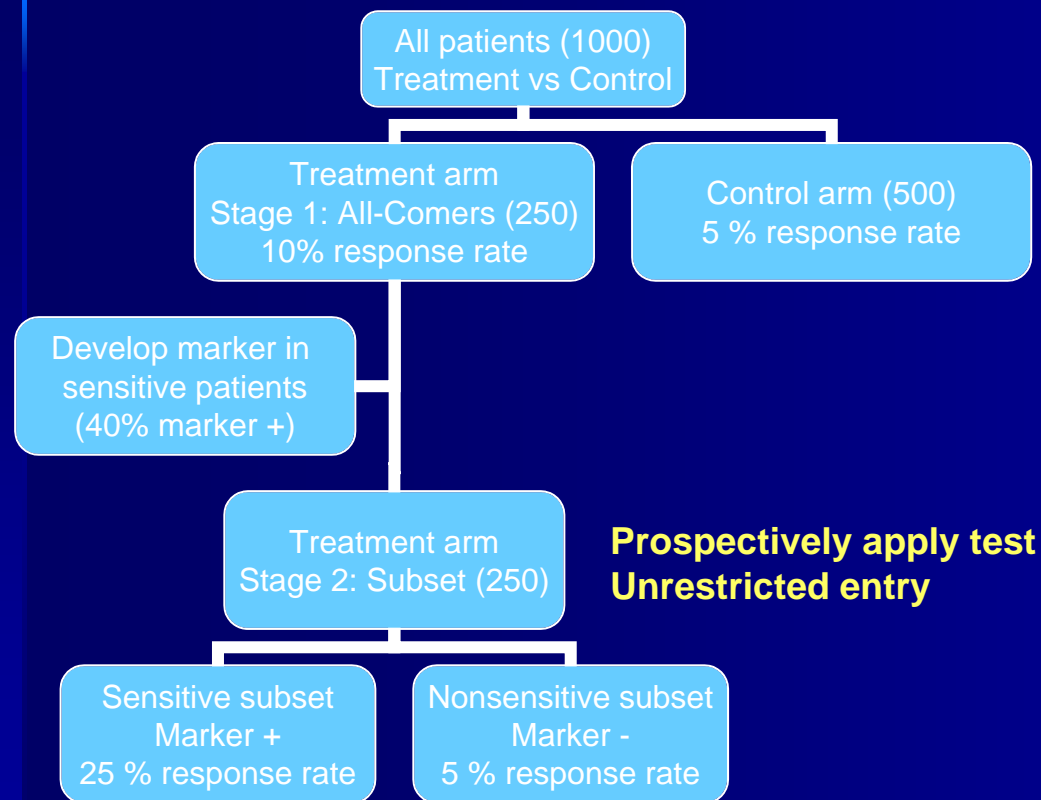
Pharmacogenomics



Focus on Phase II/III Randomized Controlled Trials of Targeted Medicines

- Several innovative clinical trial designs and statistical methodologies that increase efficiency ~ focus on “right patients”
 - adaptive
 - Predictive assay to identify binary outcomes (e.g., response) not available before trial
 - enrichment
 - Predictive assay to identify binary outcomes (e.g., response) known before trial (*a priori*)
 - stratification
 - Predictive assay to identify a range of outcomes (e.g., response) known before trial

Improving Efficiency: Prospective Evaluation of a Predictive Biomarker in a Phase 3 RCT Without Compromising Evaluation of Overall Effect

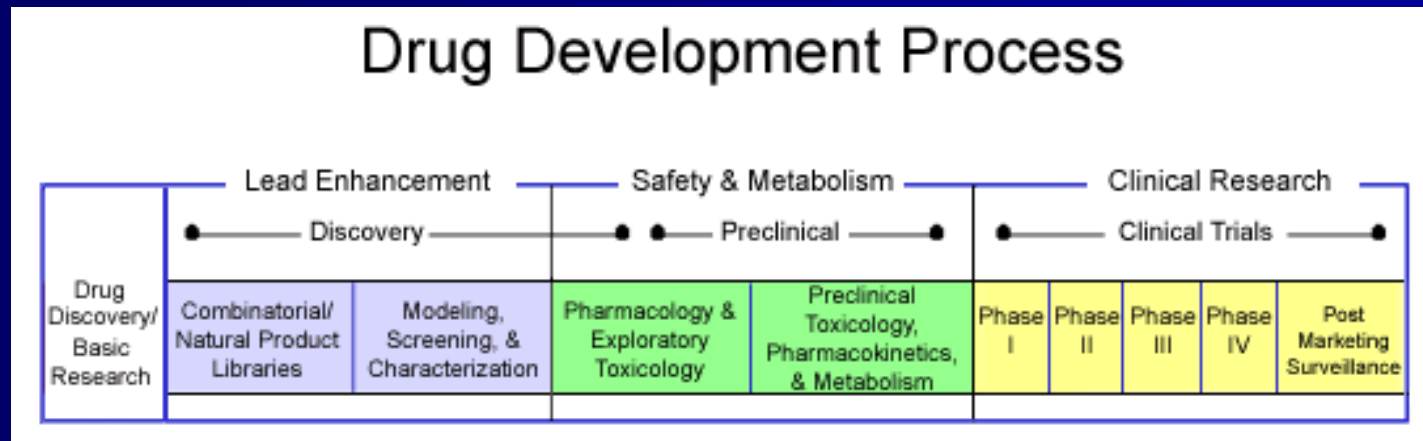


- Compare T vs C using data from all patients from Stage 1 at alpha = 0.04
- Compare T vs C using data from sensitive subset from Stage 2 at alpha = 0.01
- “Win” if either of two tests is positive
- 85% chance of finding overall effect or effect in sensitive subset

Confirmatory Adaptive Design: Features

- Prospectively define N in first and second stage
- Preserve ability to detect overall effect as well as effect in sensitive subset if overall effect is negative
- As efficient as traditional designs to detect overall benefit to all patients
- Reduce chance of rejecting an effective medicine if only effective in sensitive subset
- More stringent significance level at stage 1 (0.04 vs 0.05)
- Context for use is looking at anticancer drugs but applicability to other areas may be limited
- Examine timeframe for identifying test at Stage 1 (e.g. vs earlier biomarkers)
- Disease pathophysiology less established than tumor behavior

Summary: Integrating Use of Tools Along the Critical Path



➔ **Continual Reduction in Uncertainty in Benefit/Risk** ➔

Toolkit for Improving Success in Drug Development

Biomarkers: Prognostic, PD and Predictive

Patient Selection Criteria

Drug and Disease Modeling

Dose Response, PK-PD and Dosing

Targeted Label Information Optimal Use

Adaptive Trial Design

Thanks for your attention

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