

Biomarkers in Model Based Drug Development

CV Biomarker Symposium

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Donald Rumsfeld on Knowledge

**As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.**



Feb. 12, 2002, Department of Defense news briefing

Don's and my thoughts on Model Based Drug Development and the Critical Path

As we know,

There are known knowns.

There are things we know we know **and this knowledge is available in the form of public data and models that are used to simulate next steps.** We also know

There are known unknowns.

That is to say

We know there are some things We do not know **and we invest and do research to understand the known unknowns that influence outcome. Then we change our practices.**

But there are also unknown unknowns,

The ones we don't know

We don't know **and these become evident as we create new knowledge.**

Model Based Drug Development

FDA's Critical Path

Biomarker Model

The Ultimate in Personalized Medicine?

Patient Drug Response



Demographics



Disease, Drug

Disease Gene Marker



**Cell, protein, antibody,
small molecule**

**Biological Markers
(Efficacy, Toxicity)**

N1+N2



Gene, Drug Conc, Activity

Drug Markers

**Gene Conc
 IC₉₅**

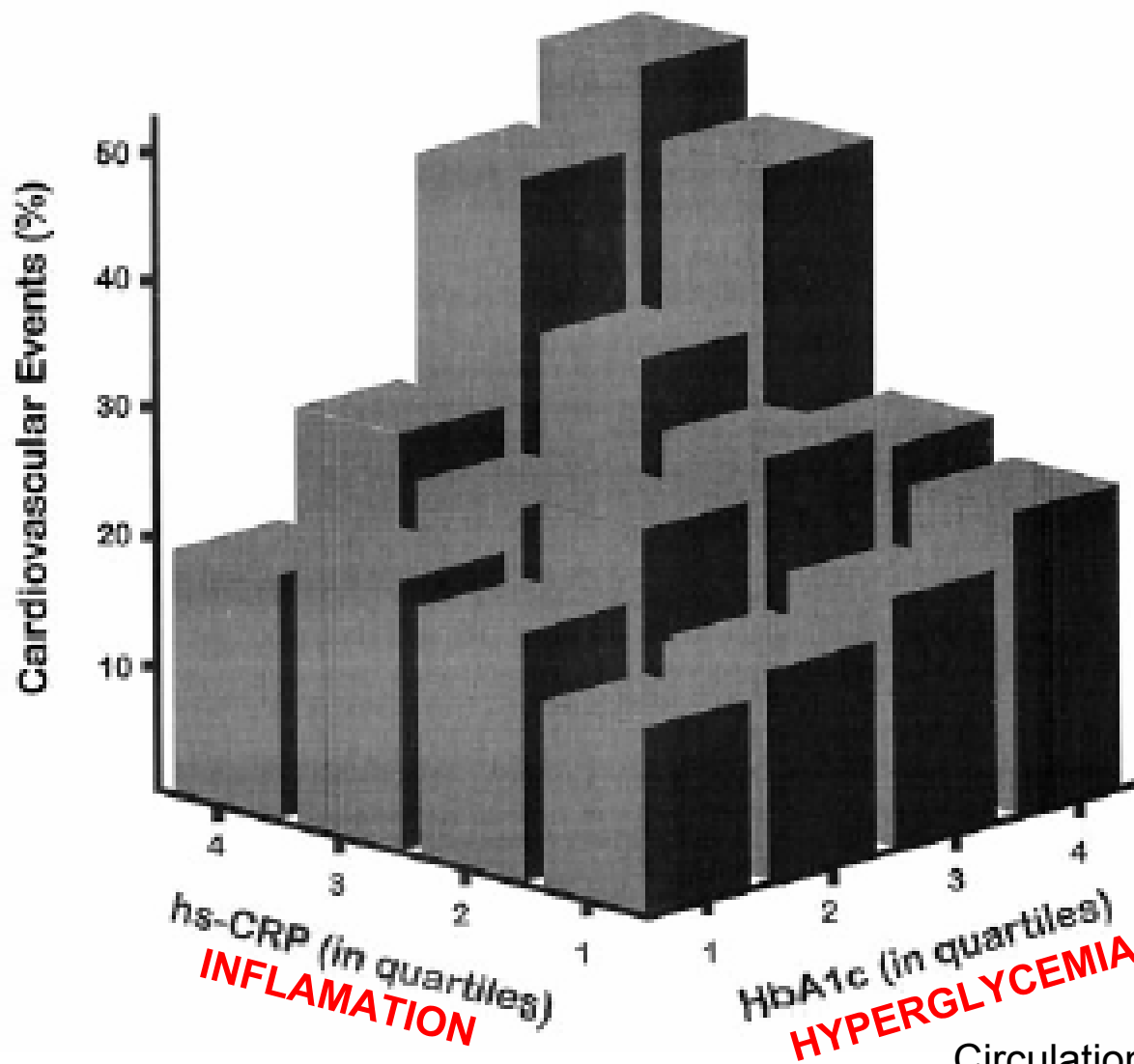


PET, MRI

**Imaging
Marker**

OUTCOME
Morbidity, Mortality

Combination of Two Biomarkers May Be More Predictive of Outcome than One in Advanced Atherosclerosis



Model Based Drug Development

Utility

- **Patient Decision Tools** (diabetes, breast & prostate CA, CV risk)
(How can I decrease my risk of developing disease or treat it by changing diet, drug Rx, surgery,.....?)
- **Drug development decisions** (Pfizer, Lilly, Novartis, GSK,.....)
(Go/No Go, trial design, dose-response, dosage form design,.....)
- **Regulatory decisions** (FDA)
(Approve/not approve/remove), dose-response, labeling, trial design, endpoints-biomarker utility, QT studies, pediatric written requests,.....)

Cardiovascular Risk in Women

...model

- 24,558 initially healthy women \geq 45 years followed median 10.2 years for incident CV events.
- 2/3 (16,400) randomly assigned to model development
- 1/3 (8,158) tested to compare observed vs. prediction (validation cohort)

	Simplified Model B, β (SE)	χ^2	P value
Age	0.080 (0.006)	193.5	<.001
HbA _{1c} % with diabetes	0.134 (0.017)	62.3	<.001
Current smoking	0.818 (0.109)	55.9	<.001
Natural logarithm			
Systolic blood pressure	3.137 (0.423)	55.1	<.001
HDL-C	-1.172 (0.172)	46.2	<.001
Total cholesterol	1.382 (0.239)	33.3	<.001
hsCRP	0.180 (0.043)	17.5	<.001
Parental history of MI <age 60 y	0.438 (0.118)	13.7	<.001

Cardiovascular Risk in Women

...model

$$10 \text{ year CV Risk (\%)} = [1 - 0.98634^{\exp[B - 22.325]}] \times 100\%$$



B = 0.0799 × age + 3.137 × natural logarithm (systolic blood pressure) + 0.180 × natural logarithm (high-sensitivity C-reactive protein) + 1.382 × natural logarithm (total cholesterol) - 1.172 × natural logarithm (high-density lipoprotein cholesterol) + 0.134 × hemoglobin A1c (%) (if diabetic) + 0.818 (if current smoker) + 0.438 (if family history of premature myocardial infarction)

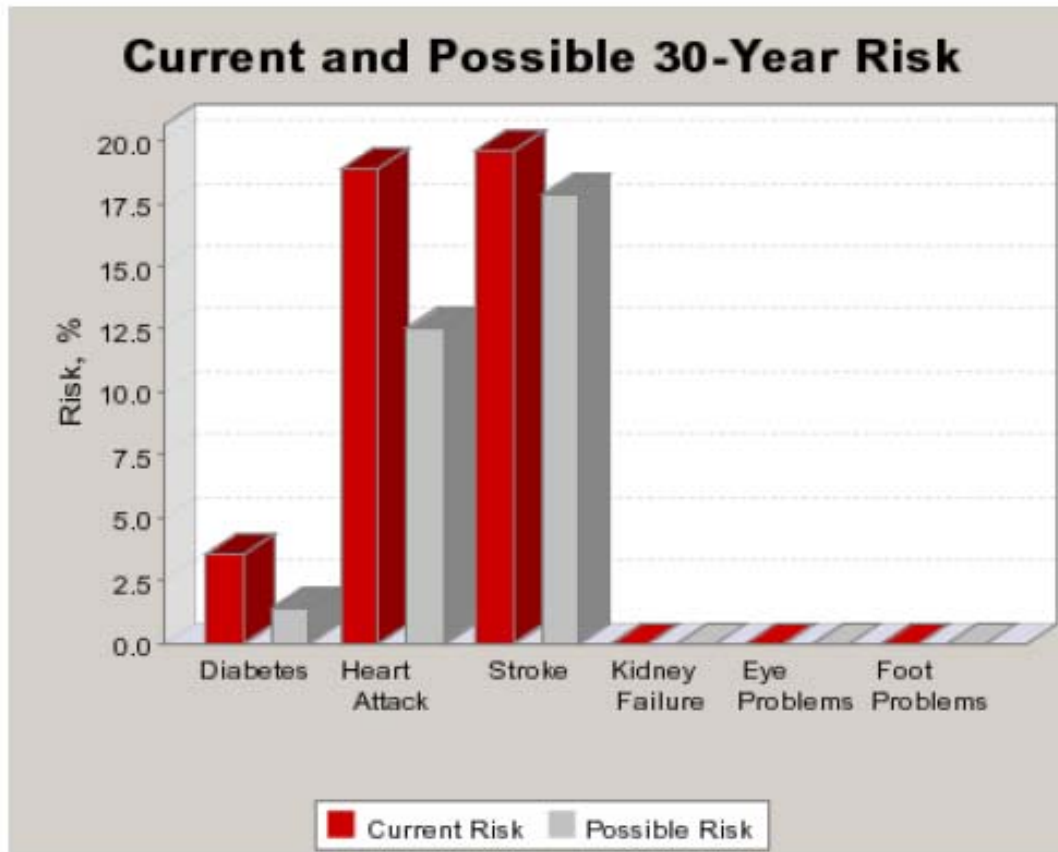
RESULTS OVERVIEW

www.diabetes.org/diabetesphd

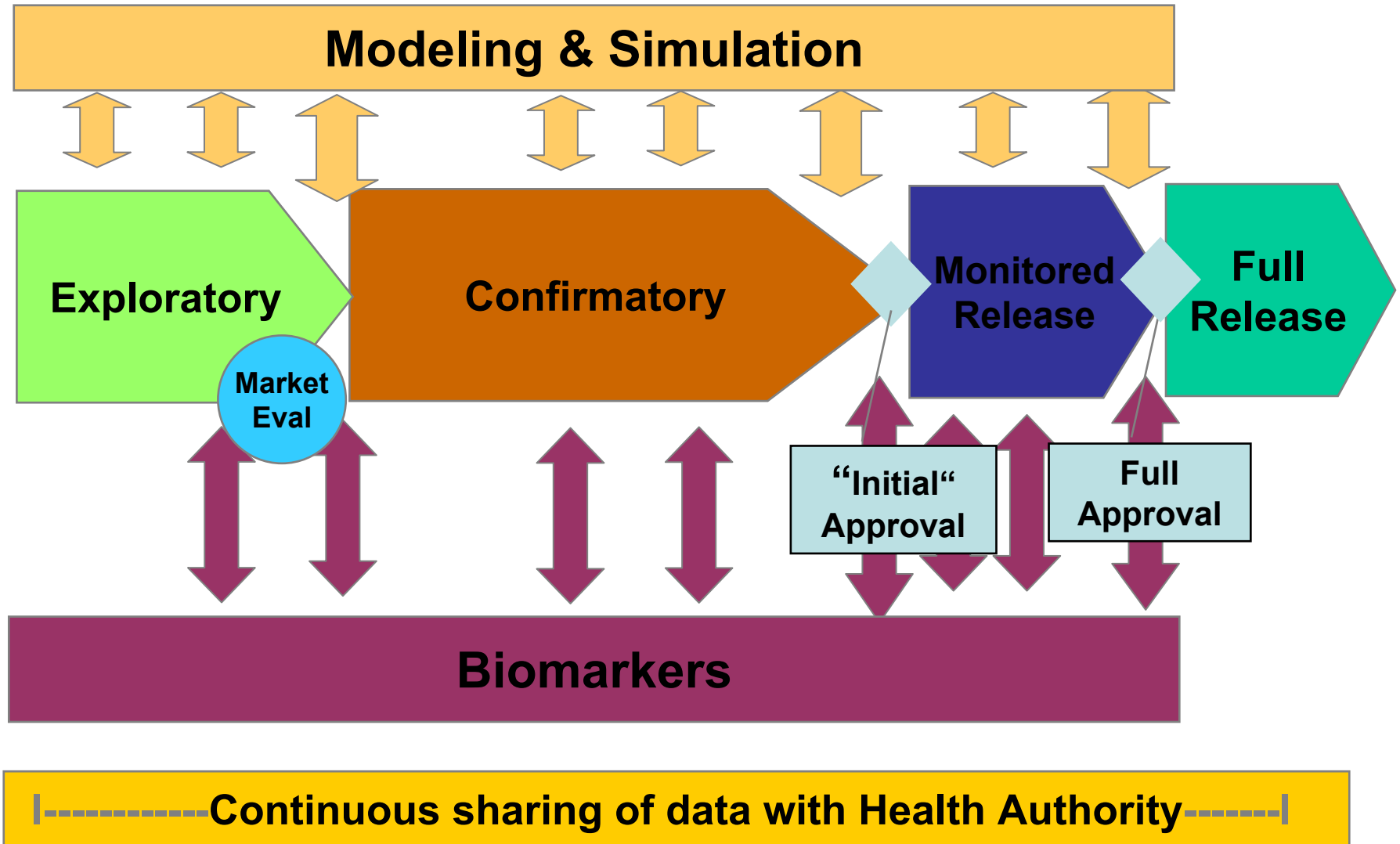
Profile Name: bobpowell

The chart below presents your customized health risk profile. The red bar shows your risk for diabetes and its complications; the gray bar shows your risk after modifying any of the modifiable health factors.

Health Factors		
	Current	Possible
Weight	215	180
Cholesterol (LDL)	130	90
A1C	0.0	0.0
Systolic BP	115	115
Not Smoking	X	X
Regular Foot Exams		
Regular Eye Exams		
Taking Aspirin	X	X
Taking Beta Blockers		
Taking Ace Inhibitors		



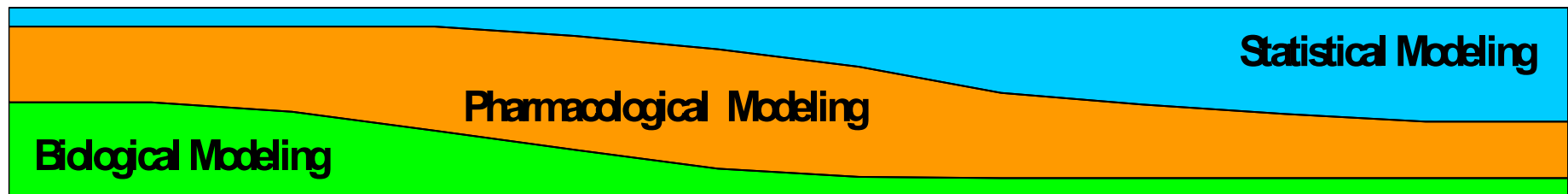
Future Development Vision: Novartis



Integrating Knowledge for Model-based Drug Development

Genes...Cells...Tissues...Systems...Patients...Populations

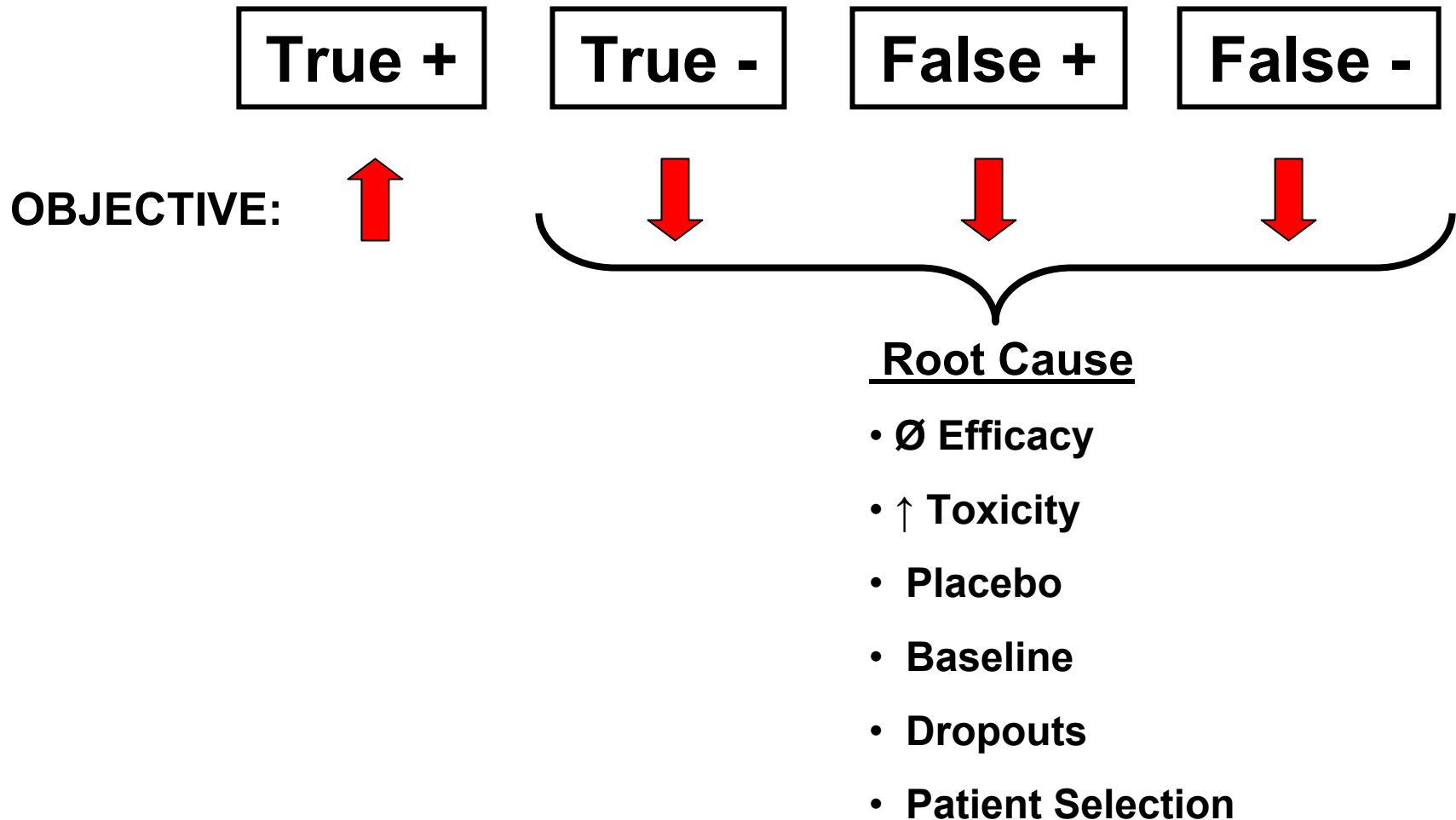
Development time axis



Integrated approach to Modeling & Simulation:

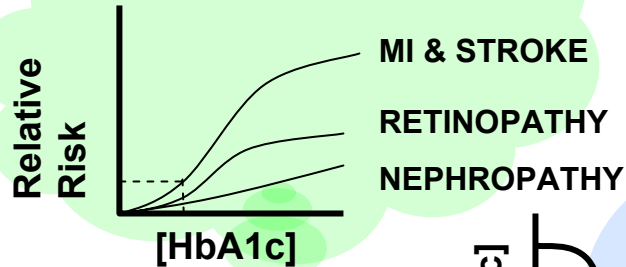
- **Biological modeling** – model pathways of disease as targets of intervention
- **Pharmacological modeling** – determine relationships for dose, exposure, response
- **Statistical modeling** – assesses development strategies and trial designs in populations

50% Clinical Trial Failure Rate: ***What to do?***

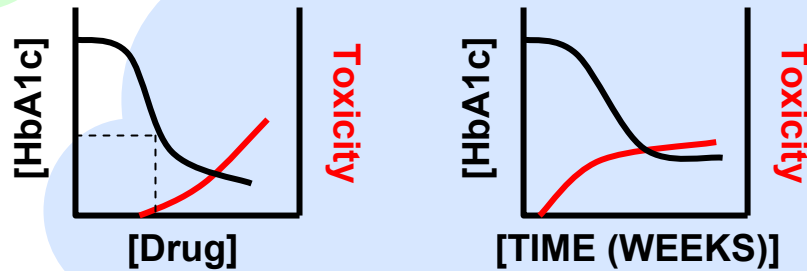


Model Based Drug Development

DISEASE MODEL

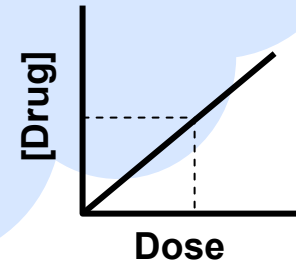
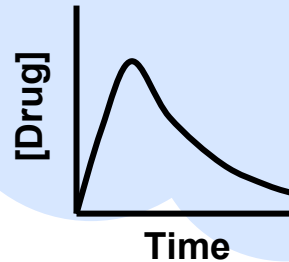


DRUG MODEL



CLINICAL TRIAL INFO

- BASELINE
- PLACEBO EFFECT
- DROP-OUT RATE
- ADHERENCE



MODEL & SIMULATE KEY DECISIONS

Preclinical Phase

Clinical Phase

Post-NDA Phase

eIND

preIND

IND

VGDS

EOP2a

EOP2

NDA

6 mo safety

Drug Model: measure change in disease & safety over time

Predict, Learn

Confirm, Save

Disease Model: detect change, qualify new biomarkers, simulate trial design

Predict, Learn

Confirm, Save

Safety Model: learn 'at risk' population, detect early or avoid risk

Predict, Learn

Confirm, Save

Preclinical Phase

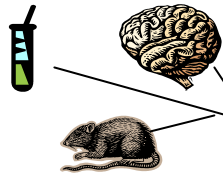
Clinical Phase

Post-NDA Phase

eIND preIND IND VGDS EOP2a EOP2 NDA 6 mo safety

Drug Model:

Human PK/PD Prediction



PK/PD Dose-escalation

S*

POP

S*

Dose Ranging

S*

Confirming

Cross-trial analysis:
dose-response
(efficacy/safety)

Approval
• Drug
• Label

Label Update*



Individual Dosing



PK/PD Bridging*

- Pediatrics
- Elderly
- Dosage forms

Simulate (S) *

- Dosing
- Human proof of principle
- Phase 3 trial design
- Value

Target Product Profile

*Quantitative Analysis &/or Simulation

*Disease Model: detect change, qualify new biomarkers, simulate trial design

Predict, Learn

Confirm, Save

*Safety Model: learn 'at risk' population, detect early or avoid risk

Predict, Learn

Confirm, Save

PK/PD Efficacy/Safety Benefit/Risk

Disease Models

(trial design & endpoints)

- **Objectives**
 - Use prior data plus statistical analysis & simulation to solve regulatory problems
 - Share solution + models of prior data publicly
- **Collaboration: Clinical (OND), Biostatistics (OB), OCP**
- **Projects**
 - **Parkinson's disease:** trial design to detect disease progression change
<http://www.fda.gov/ohrms/dockets/ac/cder06.html#PharmScience>
 - Critical to understand disease/baseline characteristics, disease progression, placebo/drug effects, and statistical issues (Missing data, etc)
 - **Non-small cell lung cancer:** predictive value in 2D imaging for disease progression-8 NDAs
 - **Osteoarthritis:** predictive value of 2D imaging for disease progression. Large failed phase 3 trial
 -

Parkinson's Disease Database

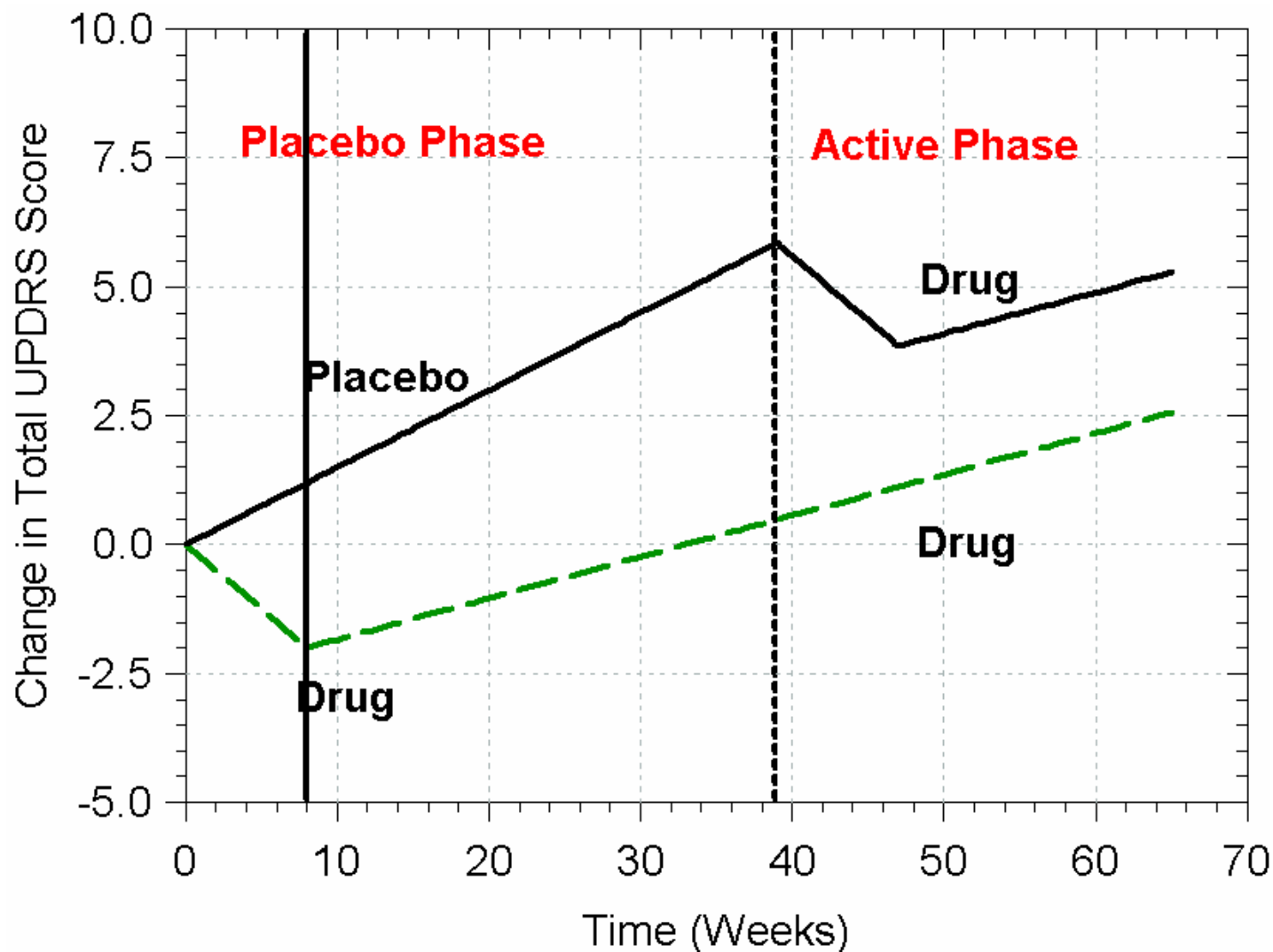
Data	Source	#Patients	Trial Duration
Trial#1	NDA	400	1yr + 3yr follow-up
Trial#2	External	400	1yr + follow-up
Trial#3	NDA	900	9mo + follow-up
Trial#4	NDA	200	9mo + follow-up
Trial#5	External	300	1.5yr

<http://www.fda.gov/ohrms/dockets/ac/cder06.html#PharmScience>

Parkinson's Disease Progression & Clinical Trial Models

(drug, placebo, drop-outs, baseline)

Objective: to simulate trial design able to detect a change in disease progression for drugs currently in pipeline



Similar information can be used to answer questions from different perspectives

Perspective	Questions
Patient- customer	<ul style="list-style-type: none"> • Which Rx • How to use
Clinician	<ul style="list-style-type: none"> • Which Rx • How to use
Provider- payer	<ul style="list-style-type: none"> • Relative cost/benefit • Price
FDA-decider	<ul style="list-style-type: none"> • Approve (Efficacy/Safety) • Label- how to use
Companies- drug, biologic, device	<ul style="list-style-type: none"> • Go/no go • Label • Other populations & indications



Decisions
Benefit/risk/ Cost
Benefit/risk
Cost/benefit
Efficacy/safety Dosing
Efficacy/safety Value Market

Further Reading

- Powell JR, Gobburu JVS. Pharmacometrics at FDA: Evolution and Impact on Decisions *Clin Pharmacol Ther* 82(1) 97-102, 2007. **FDA**
- Bhattaram, A.V. et al. Impact of pharmacokinetic review on new drug approval and labeling decisions-a survey of 31 new drug applications submitted between 2005 and 2006. *Clin Pharmacol Ther* **81**, 213-221 (2007). **FDA**
- Lalonde, RL et al. Model Based Drug Development. *Clin Pharmacol Ther* 82: 21-32, 2007. **Pfizer**
- Zhang, L et al. Model-based drug development: the road to quantitative pharmacology. *J Pharmacokinetic Pharmacodyn.* 33: 369-93, 2006. **Lilly**