Quantitative Decision Making by Drug Regulators

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Roche Shanghai

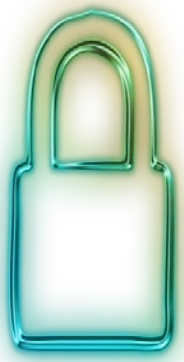
john.powell@roche.com

My many conflicts- I'm guilty of…

- **Employer: Roche**
- **Prior work: FDA, Pfizer, Parke Davis, Glaxo, UNC**
- **Nationality: American**
- **State: West Virginia** ***'Country roads, take me home….West Virgina-Mountain mama'***
- **Gender: Male**
- **Age: 62 years**
- **Profession: Clinical pharmacology**
- **Choice: to work in China**

Pharma Company-Regulatory Relationship
(my mental model)







Pharma Company

- Health opportunity
- Innovation
- Science

Regulatory (FDA-SFDA)

- Protect & promote public health
- Facilitate innovation
- Science basis (receptor)

People-Families

- ↑ Health
- ↑ Life quality
- ↑ Productivity

Outline

- Decision making & bias
- Cases
  - Drug interaction- safety
  - NDA approval
  - Pediatric exclusivity approval
  - Conflict resolution- safety
- Prior to decisions
  - Guidances
  - Research
    - Biomarkers
    - Disease models & clinical trial simulation
- Next steps
  - Informatics
  - Predicting safety

Reasons for Poor Decisions

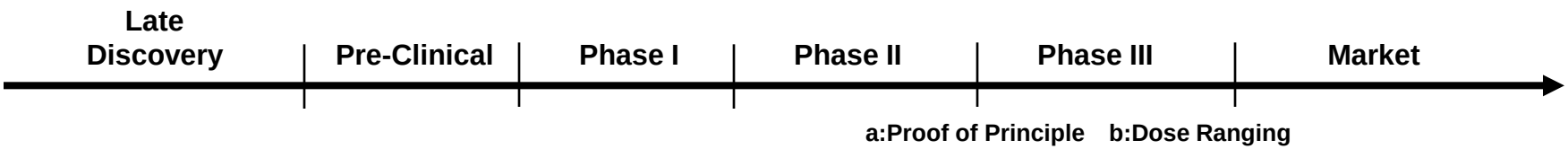
(Definition: an outcome which should/could have been anticipated)

- **Conspiracy of optimism**
- **Framing the problem too narrowly to bring it inside my own comfort zone**
- **Not involving the right people**
- **Avoiding uncertainty**
- **Ignoring information I do not understand**
- **Being attached to 'sunk costs' – high spent development costs**
- **Ignoring risks**
- **Assuming no uncertainty in potential outcomes**
- **Making decision alone**

BIAS

Hammond, Keeney, Raiffa. Smart Choices Harvard Business School Press, 1999

FDA (CDER) Decisions



Concerns

- Safe for humans
- Dosing
- Safety & Efficacy Develmt Strategy

- Sufficient Benefit-Risk
- Efficacy in whom
- Safety in whom
- Dosing

- Post-market safety strategy & assessment
- Comparative efficacy

Decisions

Go

IND
'safety to go into humans'

End Ph 2-
Special Protocol Assessment
'trial design'

Go-Stop

NDA
'go to market'

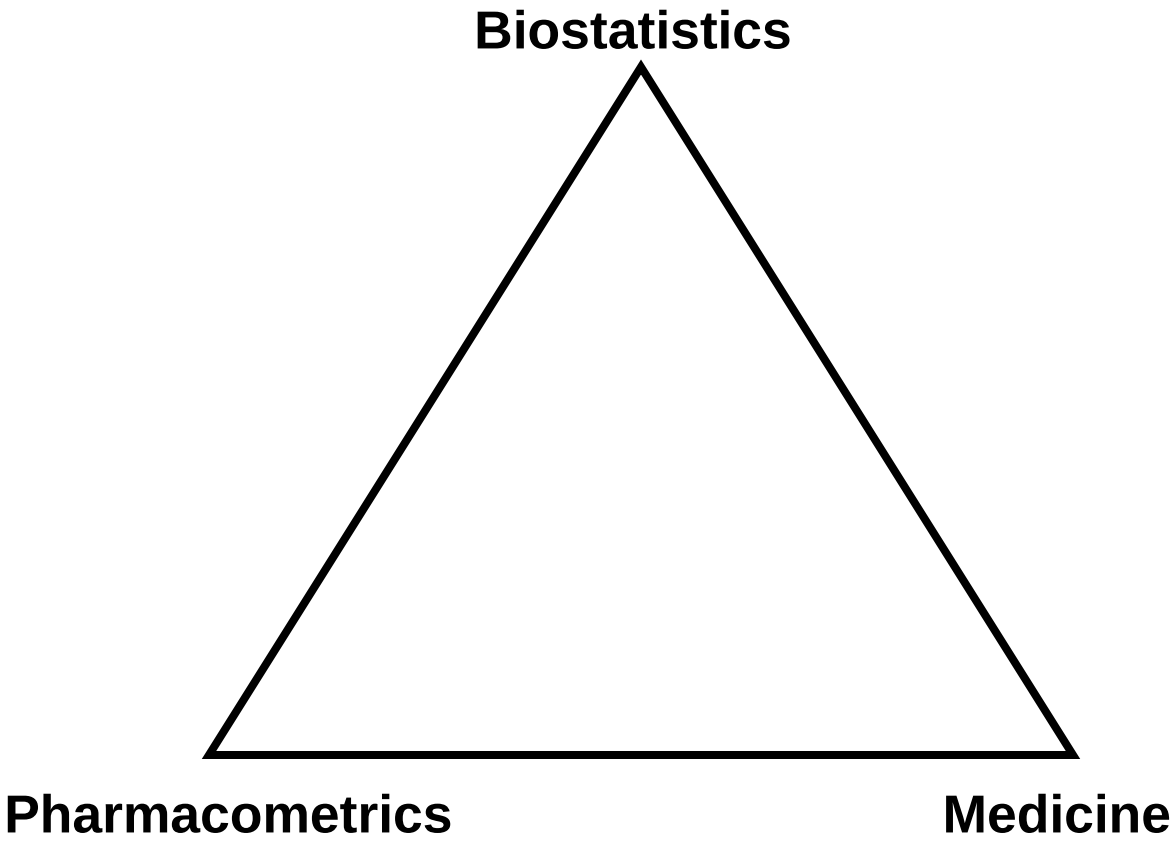
Go-Stop

Safety emergency

Steps to ↓ Bias

- Rapid access to necessary data to decide
  - Prior to key decisions
  - Prior knowledge (eg, prior NDAs, literature)
- Tools for common data analysis (eg, meta-analysis cross trial efficacy-safety)
- Quantitatively skilled scientists (eg, biostatisticians, pharmacometricians, epidemiologists)
- Decision process enhancing needed perspectives & skills. Minimizing bias
- Development & selection of decision makers based on science, skills, behaviors

Key Quantitative Skills



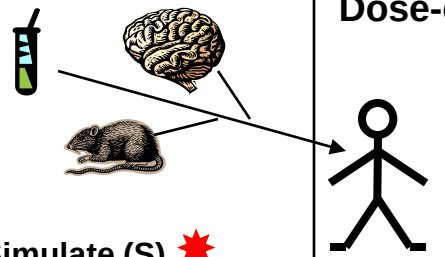
Quantitative People

- Biostatistics
- Pharmacometrics
- Epidemiology
- Experimental medicine
- Decision analysis
- Chemistry (QSAR)
- Systems biology

Model Based Drug Development

eIND preIND IND VGDS EOP2a EOP2 NDA 6 mo safety

Human PK/PD Prediction



Simulate (S)

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

Target Product Profile

PK/PD Dose-escalation → S → POP → S → Dose Ranging → S → Confirming

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

Approval
- Drug
- Label

Individual Dosing



Label Update

Benefit
Risk

PK/PD Bridging
- Pediatrics
- Elderly
- Ethnic- Countries
- Dosage forms

Quantitative Analysis &/or Simulation

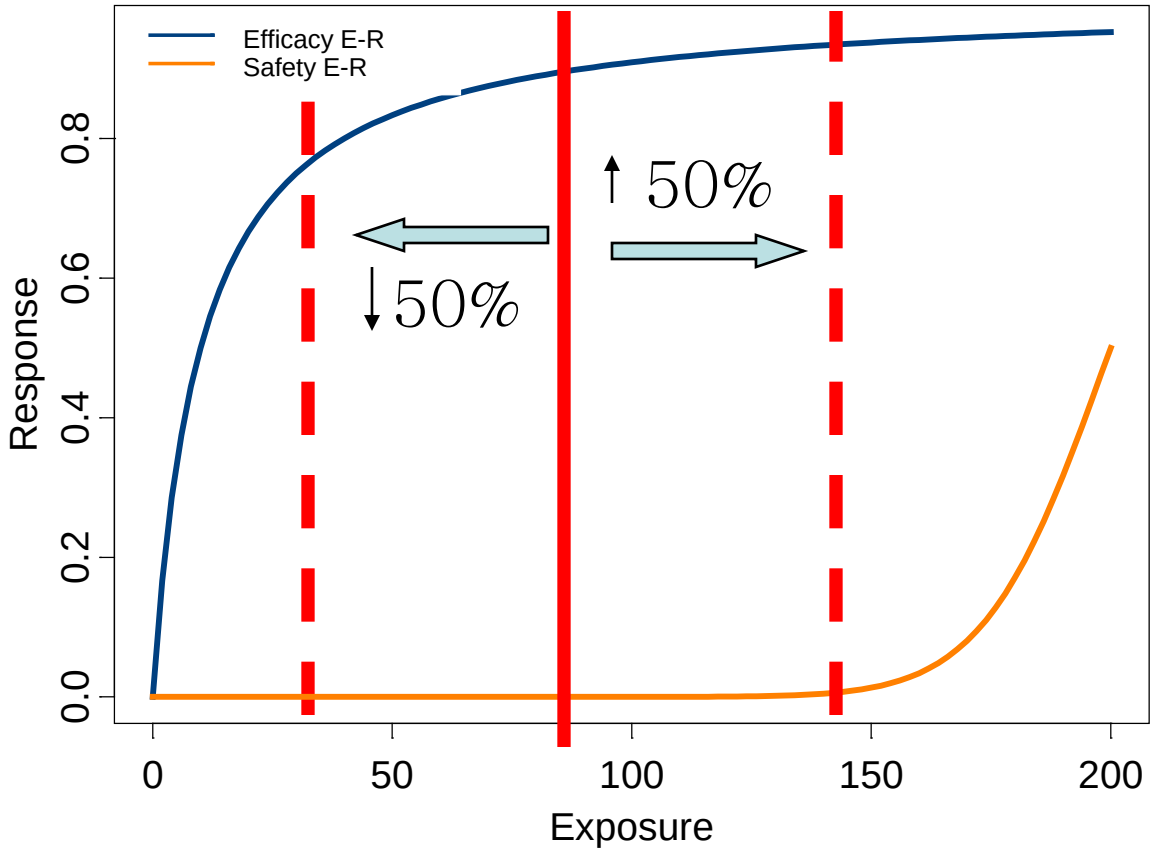
Drug Model: Mechanistic → PK/PD → Efficacy/Safety → Benefit/Risk →

Safety Model: mechanistic toxicity (liver, kidney, MI/stroke, bone marrow, immune, …)

Disease Model: Mechanistic/empiric, detect change, qualify biomarkers, simulate trial design

Dose (concentration)-Response

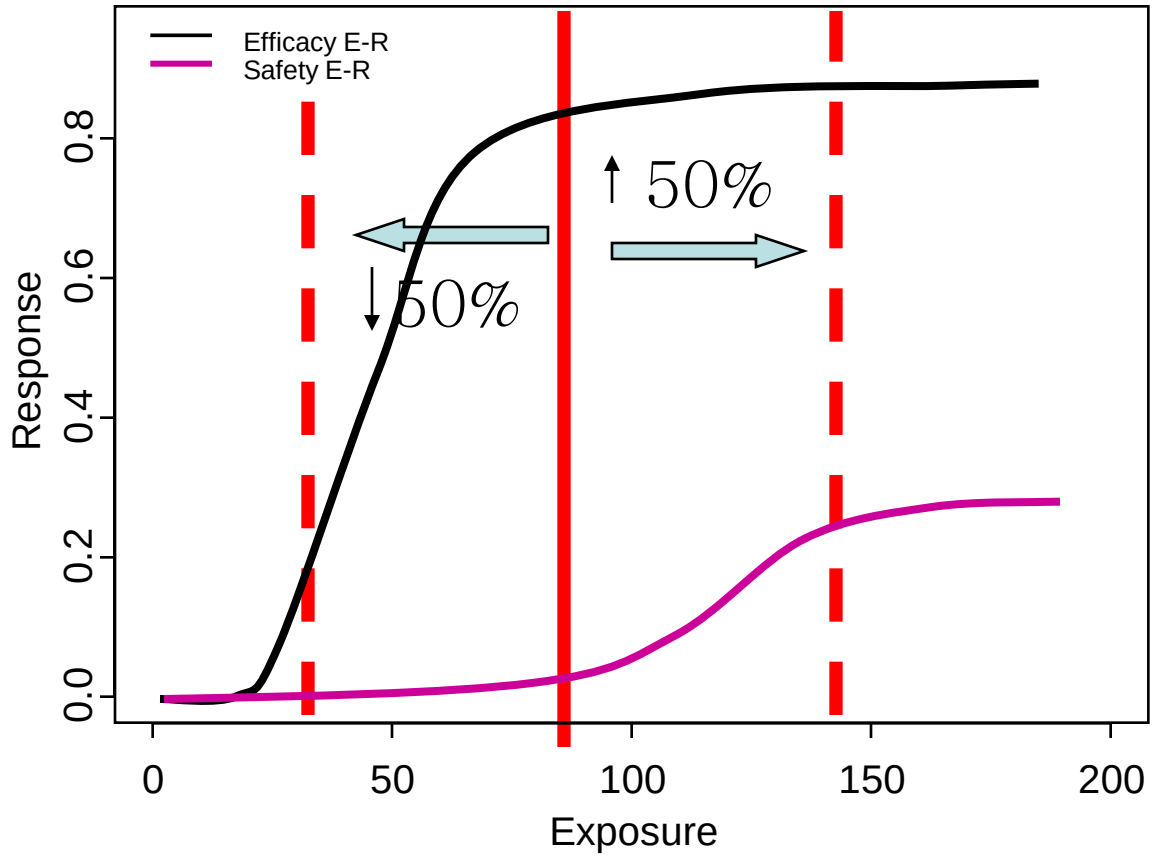
A Foundation of Regulatory Decision-Making



50% Exposure change may not be significant with a broad safety-efficacy margin

Dose (concentration)-Response

A Foundation of Regulatory Decision-Making



50% Exposure change with different curves and narrower therapeutic index may lead to loss of efficacy or unacceptable toxicity

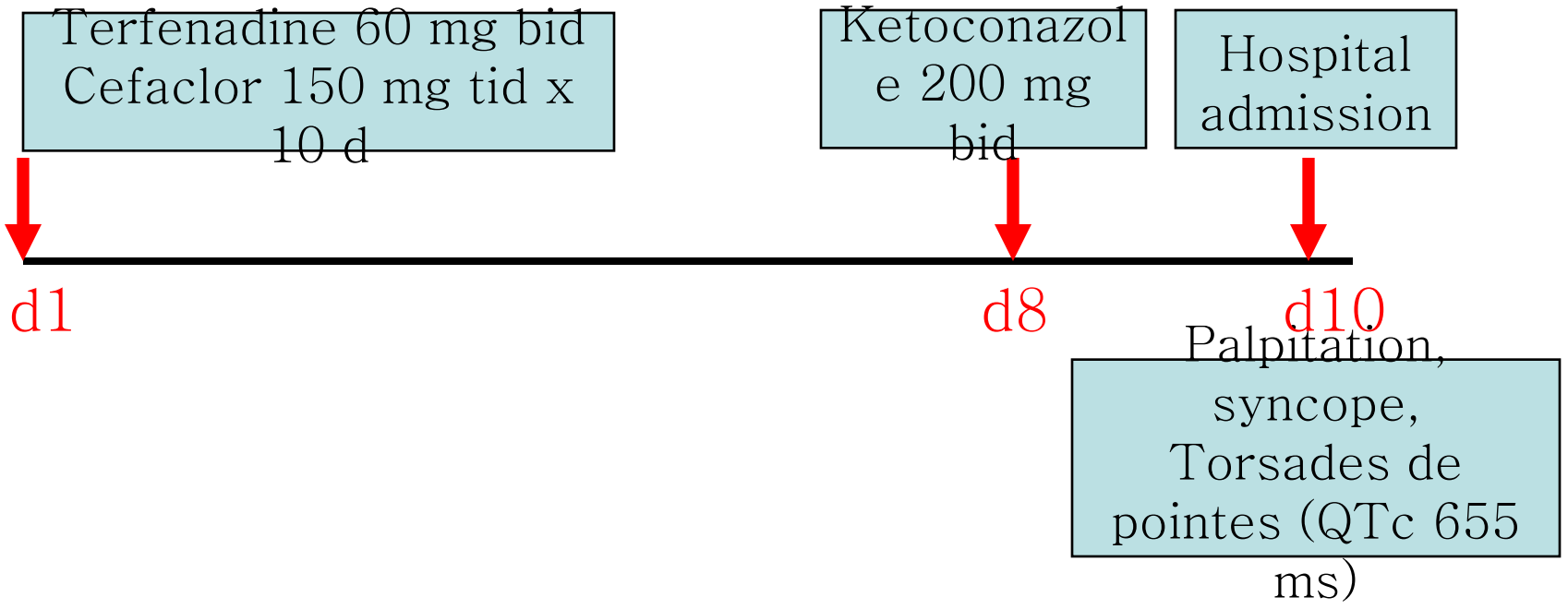
Terfenadine Case

- Non-sedating antihistamine approved in 1985 for relieving symptoms of seasonal allergies or hay fever
- Withdrawn from market in 1998 due to the cardiac toxicity (Torsades de Pointes)

- PK properties:
  - Terfenadine rapidly metabolized to its active acid metabolite by first pass effect (99%)
  - No parent terfenadine was detectable at BLQ of 10 ng/mL

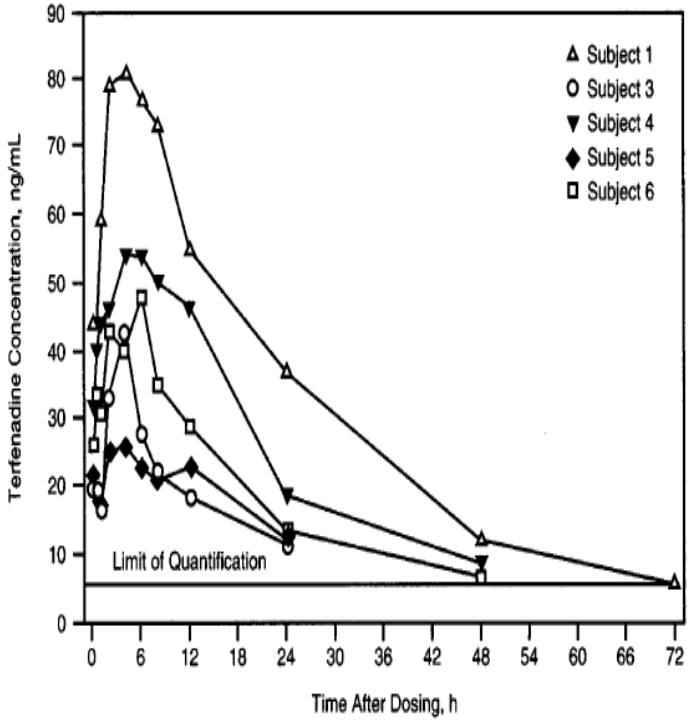
1st ventricular arrhythmia (Torsades de Pointes) case of terfenadine

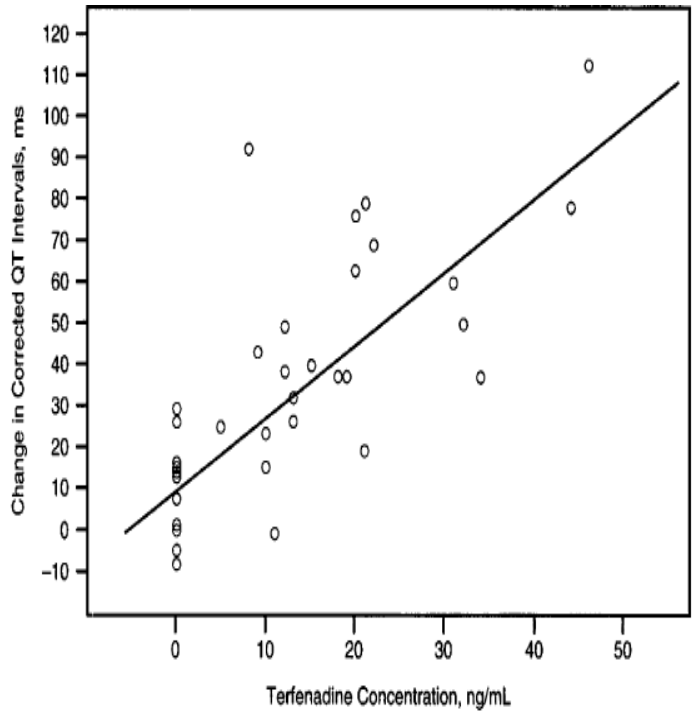
- 39 years/F



Monahan BP et al JAMA 1990,264: 2788-2790

What happened?





1. Co-administration of terfenadine and ketoconazole results in significant increase in terfenadine conc.
2. Terfenadine caused QT prolongation

P Honig et al: JAMA, 1993, 269:1513-18

How it happened?

- Terfenadine causes QT prolongation
- It is a CYP3A substrate
- 99% of terfenadine was metabolized by first pass effect
- The plasma terfenadine concs are below quantitative level (approx. 10 ng/mL)
- Ketoconazole is CYP3A inhibitor
- Terfenadine concs increased when terfenadine was co-administered with ketoconazole
- Increased terfenadine concs cause QT interval prolongation, consequently, Torsade de pointes.

PK DDI could result severe AE, even death. Consequently, the drug was withdraw from market.

P Honig et al: JAMA, 1993, 269:1513-18

Drugs Withdrawn from Market Due to Interactions

Withdraw	Approved	Drug	Risk
1998	1997	Mibefradil	Torsades de Pointes
1998	1985	Terfenadine	Torsades de Pointes
1999	1988	Astemizole	Torsades de Pointes
2000	1993	Cisapride	Torsades de Pointes
2001	1997	cerivastatin	Rhabdomyolysis

NDA Case Study

(Gobburu)

- Drug is proposed for a 'rare' debilitating, fatal disease with no approved treatment.
- One trial successful and other ***failed***
  - *Failure* likely due to trial execution errors
    - Potential miscommunication about dose timing
  - Primary variable: Change in symptom score

- **Key question**
  - **Is there adequate evidence for the effectiveness?**

Equivocal Evidence of Effectiveness Pivotal Studies

Tetrabenazine for Huntington's Chorea

DB#1
Dbl-blind (DB)
Randomized
PBO Controlled
Dose Titration
N=75
P<0.05[1]
(withdrawal)

DB#2
Dbl-blind (DB)
Randomized
PBO Controlled
Dose Withdrawal
N=30
P>0.05[1]

Agency at this point can ask for more evidence (one or more studies)

OR

Investigate further across the clinical trial database whether there is a consistent signal of effectiveness or not

[1]change in score at the end of study

Equivocal Evidence of Effectiveness
Pivotal + Other Studies

DB#1
Dbl-blind (DB)
Randomized
PBO Controlled
Dose Titration
N=75
P<0.05
(withdrawal)

OL-1
Open label (OL)
Withdrawal
Dose Titration
N=75

DB#2
Dbl-blind (DB)
Randomized
PBO Controlled
Dose Withdrawal
N=30
P>0.05

OL-2
Open label (OL)
Continue 'old' dose
N=30

Significant Dose-Response Relationship – DB1, OL1

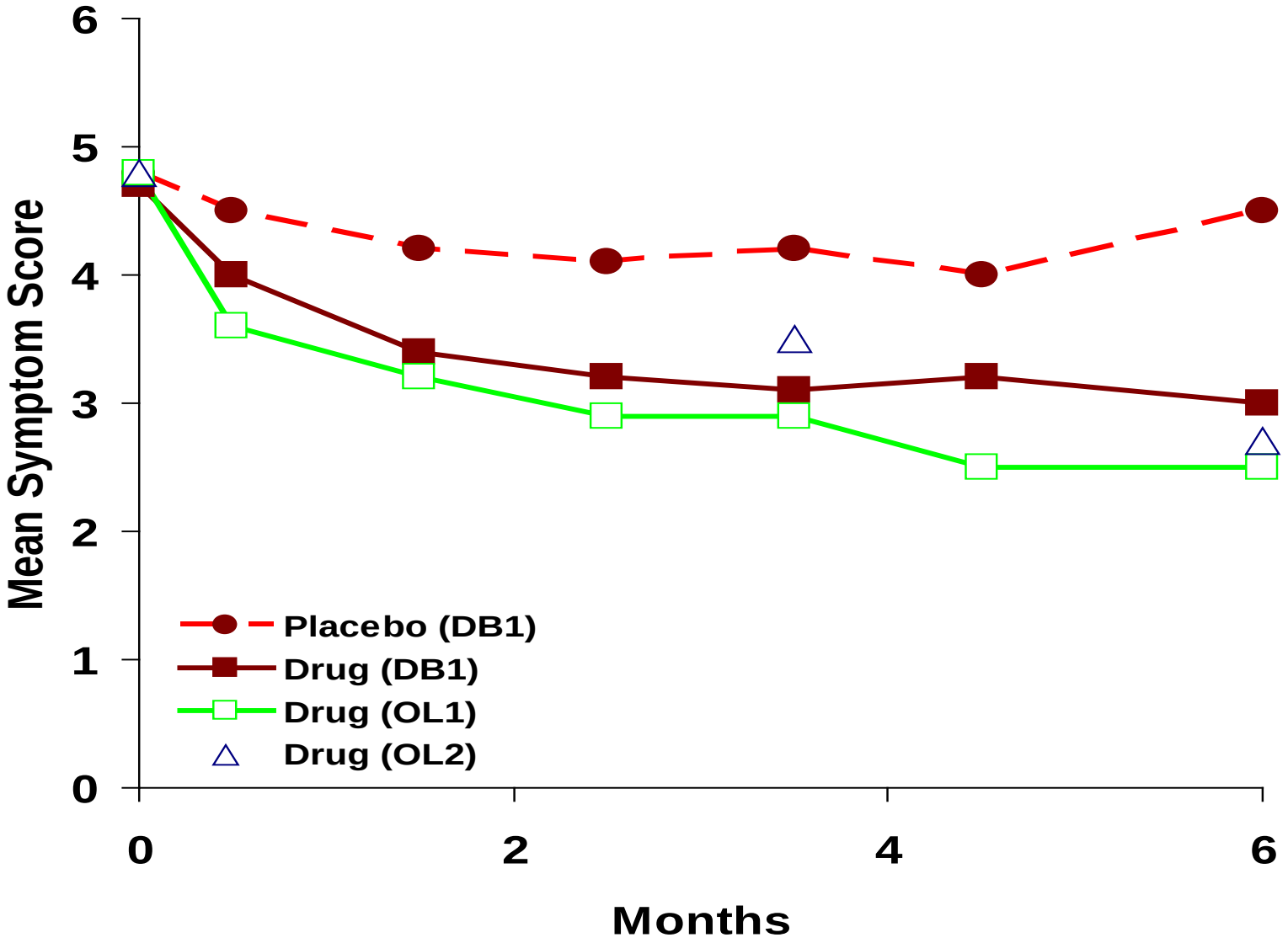
Parameter	Mean (Confidence Interval)	Between-Patient Variability (CI)
Slope of dose-response, % per mg	4.3* (3.7, 4.6)	**56% (46%, 66%)**
Within-Patient Variability	**26% (23%, 29%)**	

**** p<0.001***

Linear mixed effects model employed

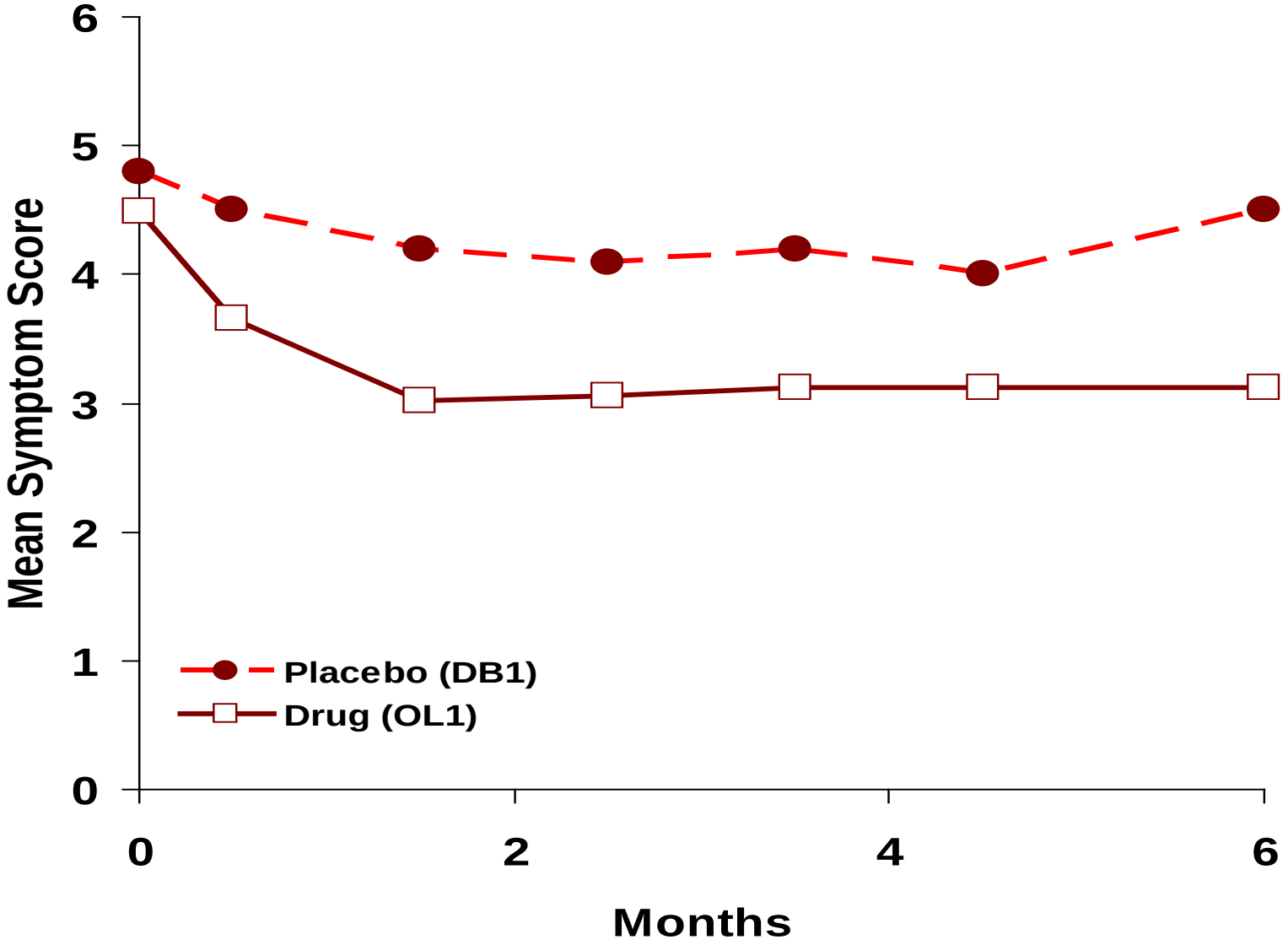
Estimate of dose-response slope is similar for individual and combined analyses. Results from combined shown here.

Significant and Consistent Drug Effects Across Studies



Drug in OL1 beat Placebo in DB1

Cross-over comparison



Value of Exploratory Analysis

- **To Patients/FDA**
  - **Availability of drug sooner, especially given no approved treatments (debilitating disease)**
  - **Efficient solution to challenging patient enrollment**
  - **Fewer review cycles (because of this issue alone)**
  - **Ultimately might lead to lower drug costs**
- **To Sponsor**
  - **Alleviated the need for additional trial(s) to demonstrate effectiveness**
  - **Save $$ and time**

Pediatric Written Requests

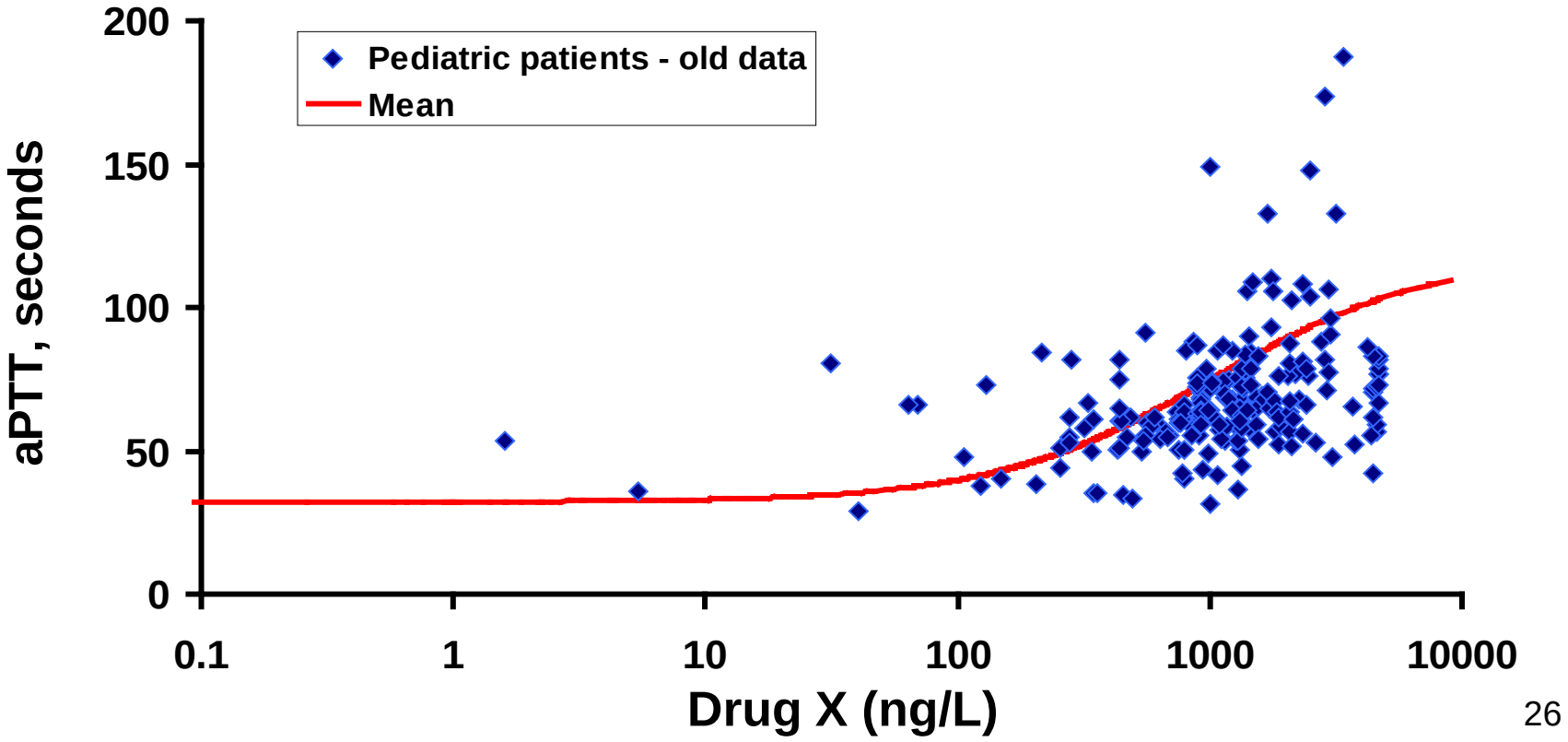
- **FDA invites sponsor to prepare a written request for pediatric submission detailing efficacy, safety, dosing**
- **FDA agrees the protocol**
- **If sponsor complies with protocol & studies requisite patient #, 6 months additional patent exclusivity granted**
- **Too often trials fail and limited or no information gets to label even though exclusivity granted**

Pediatric Case - 'blood thinner'

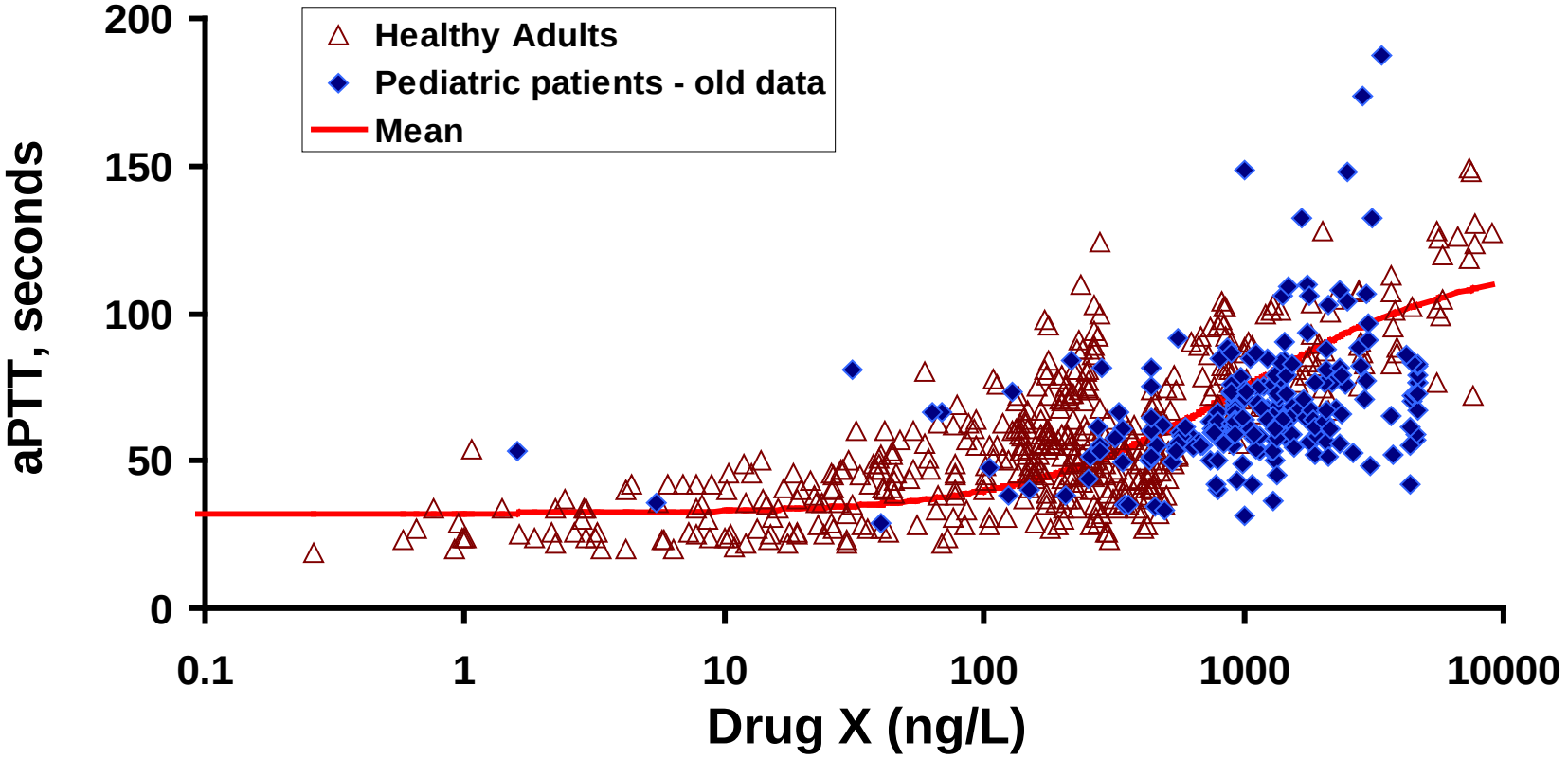
(Raj Madabushi-FDA)

- **Sponsor required to study efficacy, safety & pk/pd in 24 patients (0-2 , 2-8, 8-16 years)**
- **Completed 12, internal recommendation to deny. Data not reviewed. No information would be in label**
- **Reviewed data**
- **Difficult internal negotiation**
- **Sponsor had additional 4 patients, requested data**
- **Labeling and exclusivity granted**

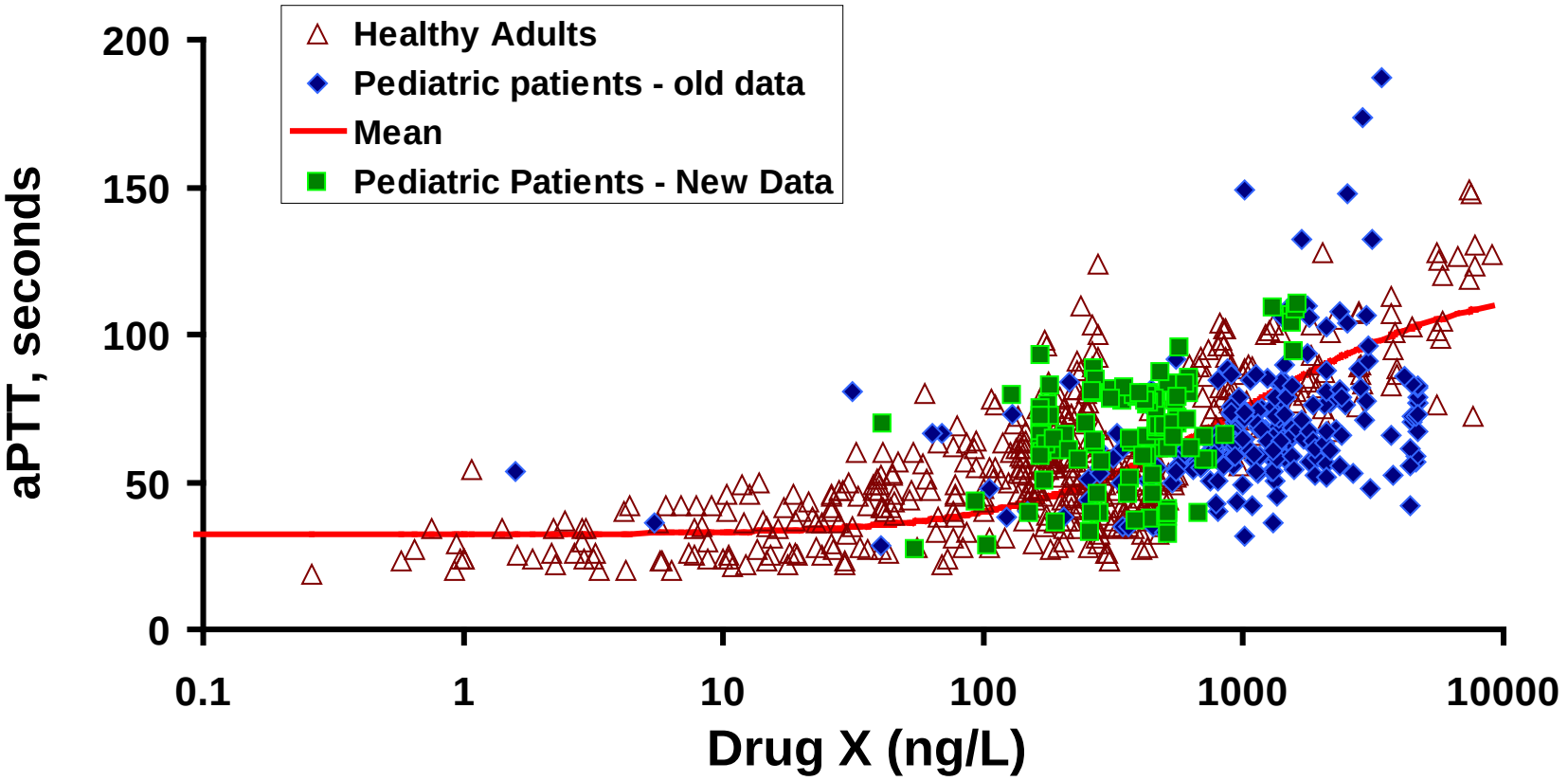
Effect on aPTT is concentration dependent



Effect on aPTT is concentration dependent



Effect on aPTT is concentration dependent



Result

- Drug labeled for children with customized dosing
- Failure ➞ Success
- Empiric data mining…let the data speak

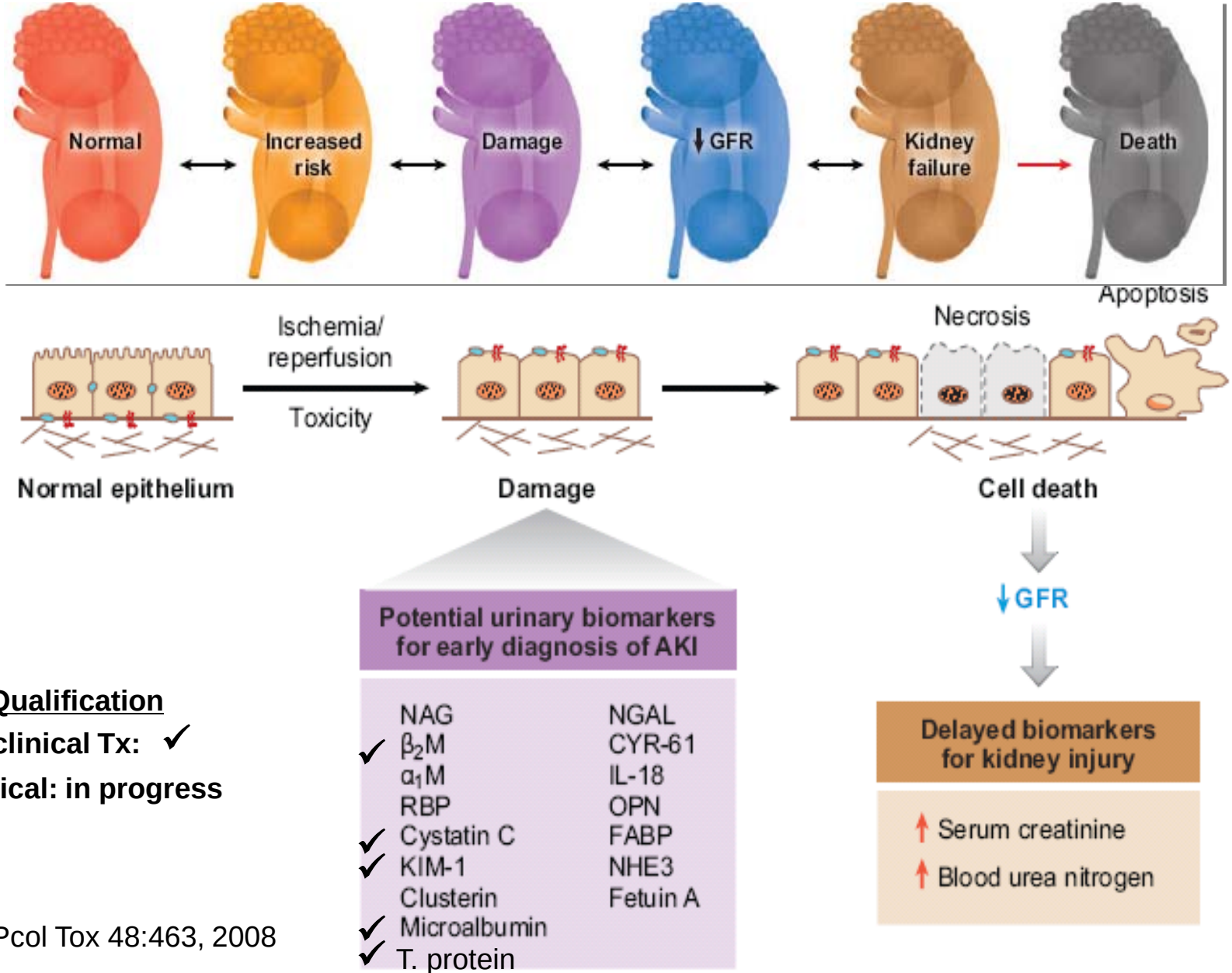
Prior to Decisions

(Clinical Pharmacology Guidances)

- Drug metabolism/drug interaction studies in the drug development process: studies in vitro (97); in vivo (99, 06)
- Pharmacokinetics in patients with impaired renal (10) & hepatic (03) function
- Pediatric pharmacokinetic studies for drugs (98)
- Pregnancy (04), Lactation (05)
- Population pharmacokinetics (99)
- Exposure-response (03)
- Exploratory IND studies (05)
- End of phase 2a meeting (09)
- Voluntary genomics data submission (05)

Regulatory Research

Kidney Failure: Biomarker Development



FDA Qualification

- **Preclinical Tx:** ✓
- **Clinical: in progress**

Ann Rev Pcol Tox 48:463, 2008

Parkinson's Disease

- All current drugs provide symptom relief
- No drug approved to ↓ disease progression rate
- Drugs in development pipeline for this indication
- No trial design available for this indication
- Regulatory uncertainty inhibits drug development
- Objectives:
  - Create a scientifically justifiable trial design
  - Share model publically
  - Encourage new designs using simulation

Parkinson's Disease

Database

(Bhattaram, Siddiqui)

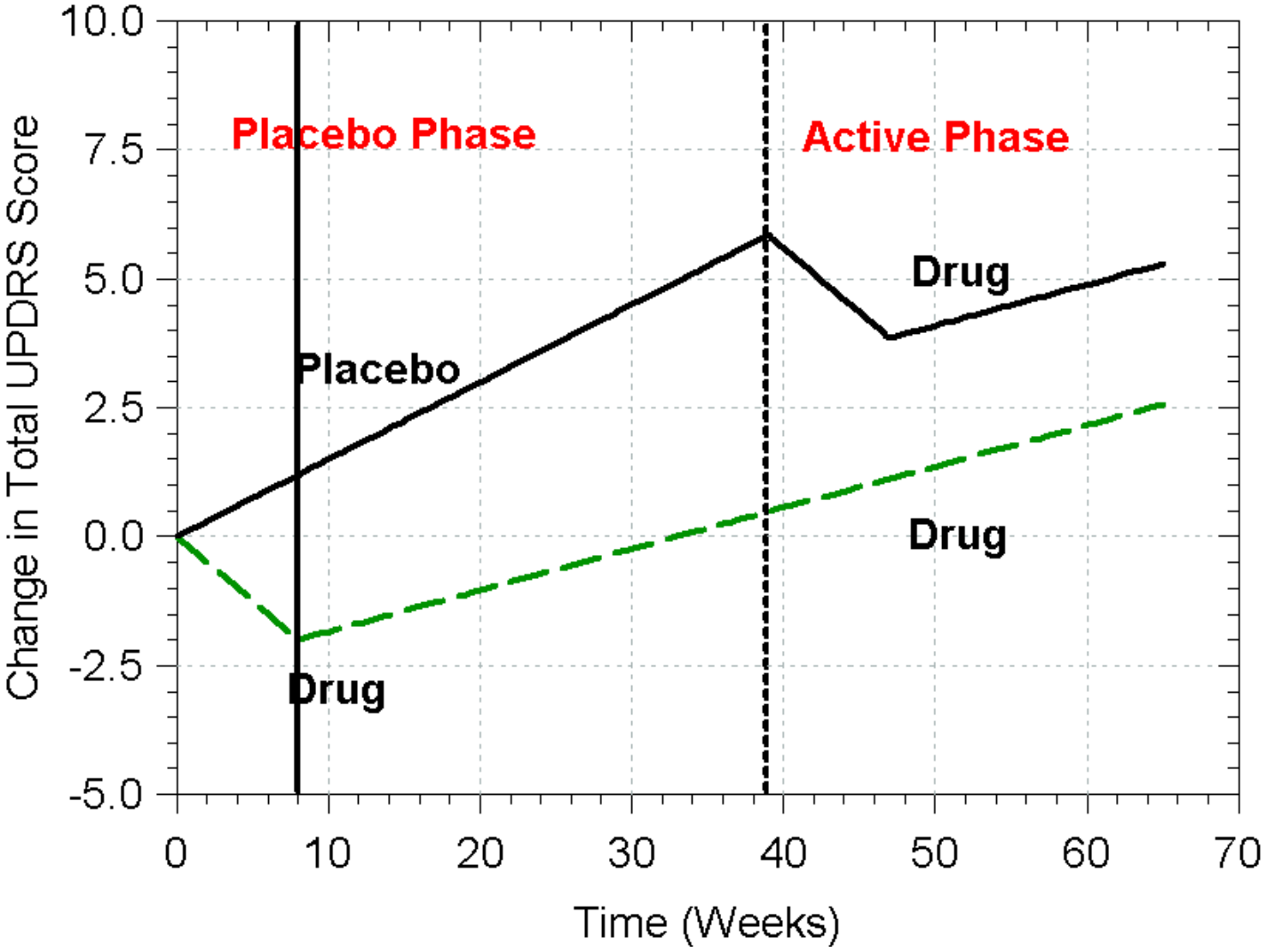
Data	Source	#Patients	Trial Duration
Trial#1	NDA	400	1yr + 3yr follow-up
Trial#2	External	400	1yr + follow-up
Trial#3	NDA	900	9mo + follow-up
Trial#4	NDA	200	9mo + follow-up
Trial#5	External	300	1.5yr

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



FDA Conflict Case

Zometa® (Zoledronic Acid)

- Indications
  - Hypercalcemia of malignancy
  - Multiple myeloma and bone metastasis of solid tumors (↓ bone fracture, radiation, surgery)
- Follow-on drug to pamidronate
- Regulatory history along with renal failure risk
  - **August 2001**
    - Drug approved. 97% eliminated in urine, hint of neprotoxicity, no dose reduction recommended **(inside FDA disagreement)**
  - **October 2003**
    - 72 AERS FDA renal failure case reports with Zometa (NEJM 349:1676-9, 2003 (~100 literature cases total) outcomes including dialysis, hospitalization, death
    - **Clinical pharmacology began negotiating with oncology on dose reduction in labeling**
  - **February 2004**
    - Re-labeled. Risk of renal failure enhanced in label. Not recommended in patients <30 ml/min GFR
    - Still no dose reduction
  - **January 2005**
    - 'The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over no less than 15 minutes every three to four weeks'

      Baseline Creatinine Clearance (mL/min) Zometa® Recommended Dose*

      > 60 mL/min 4.0 mg

      50 - 60 3.5 mg

      40 - 49 3.3 mg

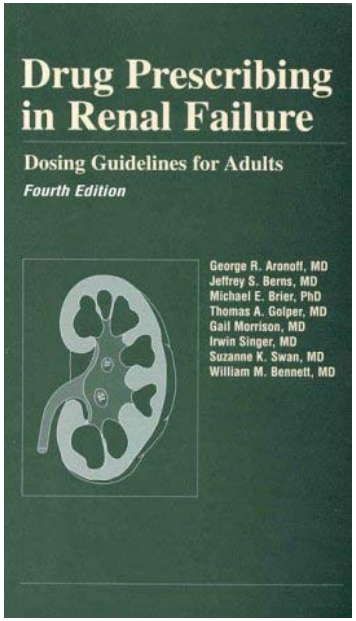
      30 - 39 3.0 mg

FDA Conflict Case

Zometa® (Zoledronic Acid)

- **Negotiation** did not succeed at reviewer-team leader level on several occasions over several years to adjust dose to GRF
- **Culture**. Oncologists all doses in label must be supported by phase 3 trials….even for palliative treatment
- **Solution**: moved negotiation up the management structure. Senior MD ‘decider’ explained pharmacokinetics to oncologists
- **Company**: Do not know why they did not take lead
- **Assessment**:
  - My principles ≠ your principles
  - Conflict worthwhile when outcome matters
  - Lack of diversity in ‘decision maker’ can produce bias

Reducing dose with ↓ GFR since 1970



Next!

(topics for future SFDA discussion?)

- **Informatics**
- **Simulation to justify complex decisions (eg, Phase 3 trial design)**
- **Predicting relatively rare, serious adverse events**
- **Bridging strategy: science based**
  - **US-EU → China**
  - **China → US-EU**
- **Quantitative Benefit-Risk**

In Summary

- **Minimize bias in decision making**
- **Let the data speak (quantitative decision making)**
- **Transparency in terms of prior decisions is helpful**
- **Research providing new tools and data on important issues is helpful. If not government, then who?**
- **Prediction is as important as confirmation**
- **Conflict is good and should be encouraged when constructive**
- **Decision-making process sets organization tone & culture. Culture precedes behavior**

Acknowledgements

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