Impact of Pharmacometric Analysis on Drug Approvals and Therapeutics

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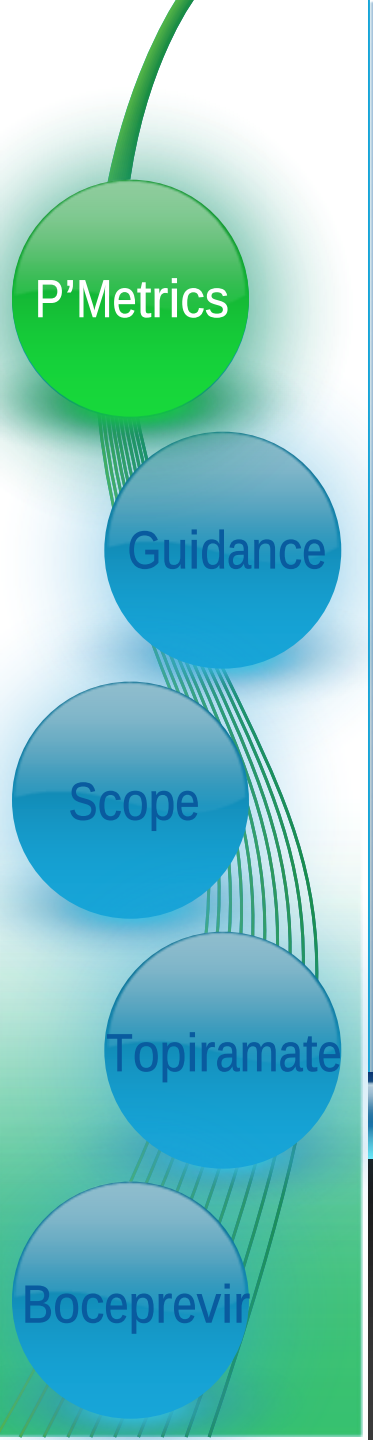
The opinions expressed in this presentation do not represent official FDA policy

Today's Objectives

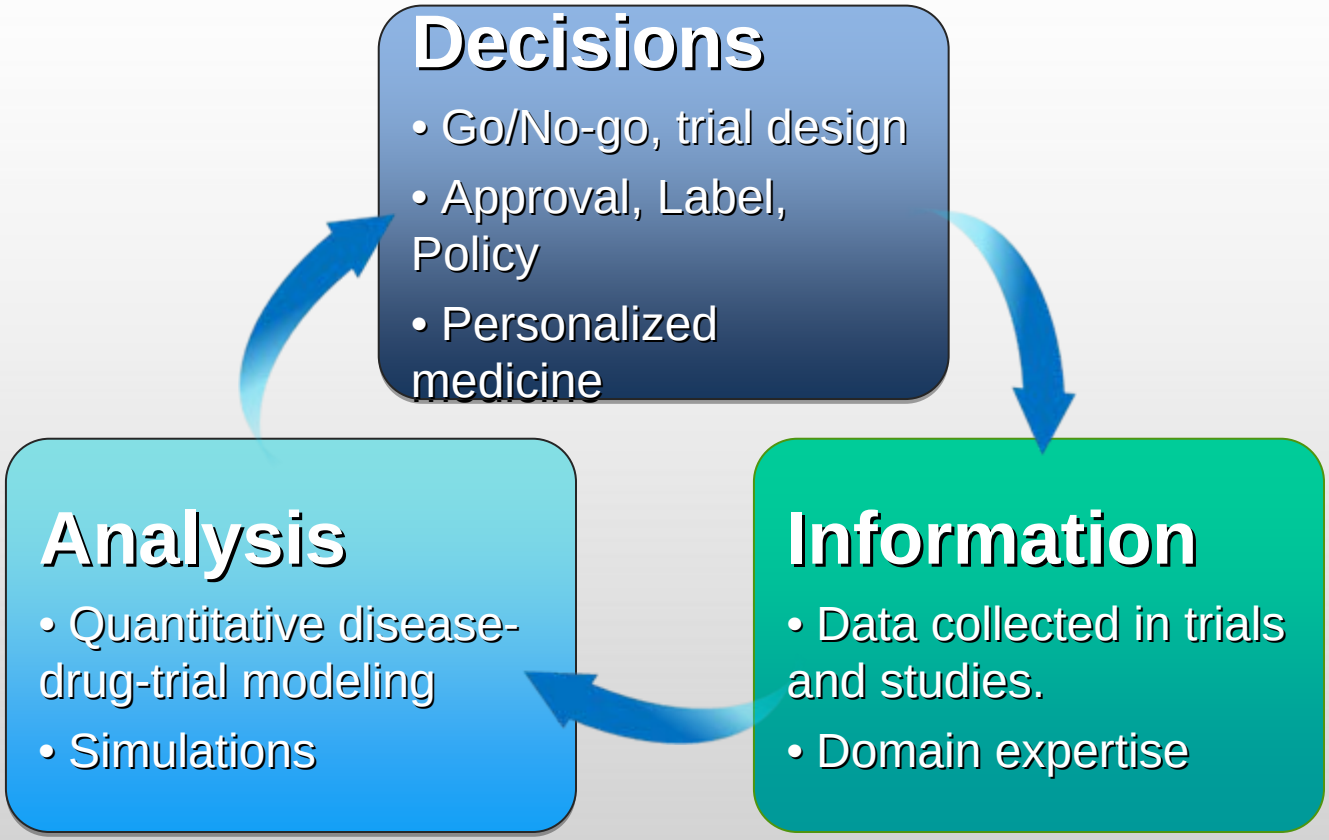
1. Highlight Growth of Pharmacometrics at FDA

2. Describe Scope of Pharmacometrics at FDA

3. Discuss Impact on Drug Development and Therapeutics



What is Pharmacometrics?



Pharmacometrics is the science of quantifying disease, drug and trial characteristics with the goal to influence drug development, regulatory and

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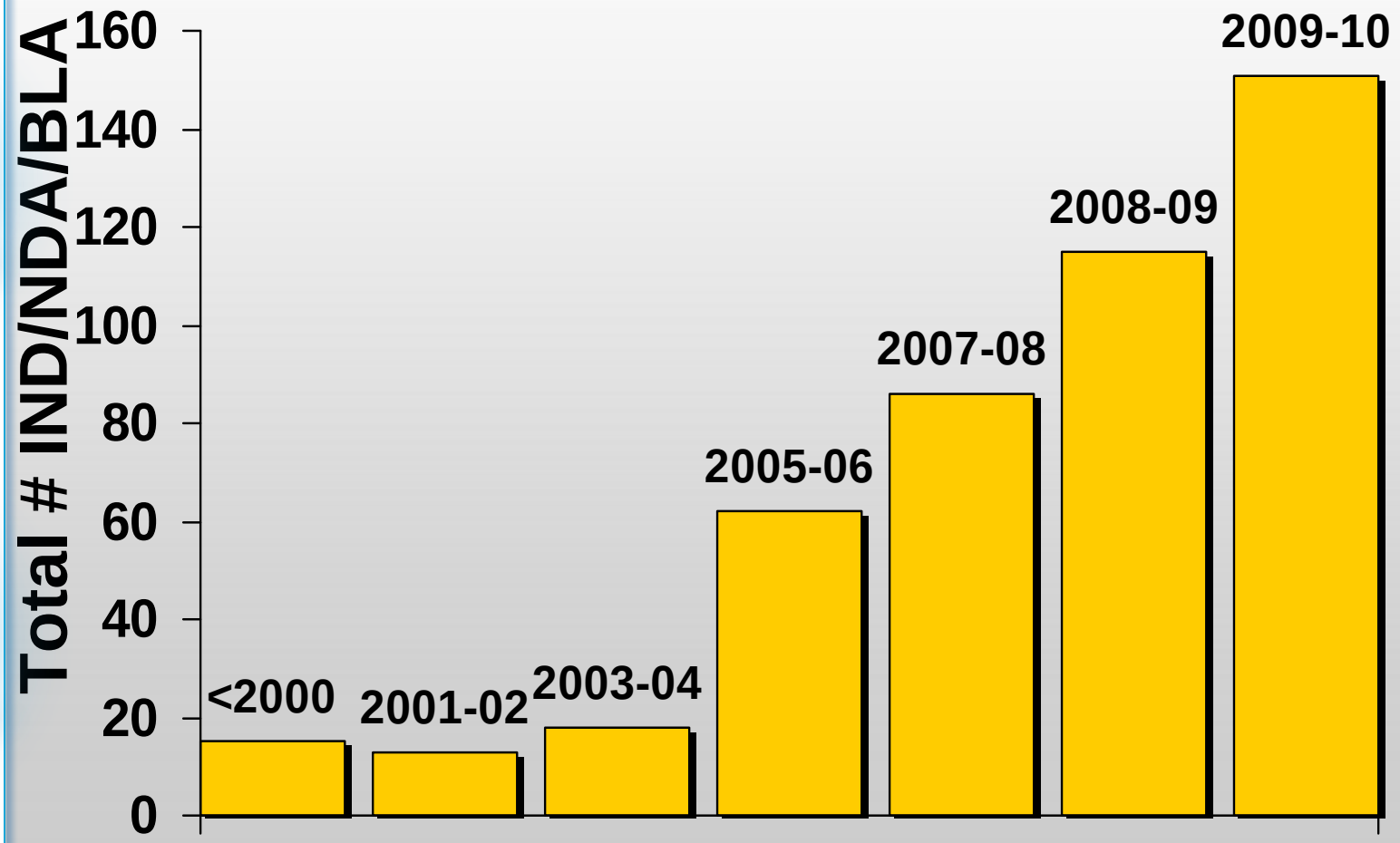
Guidance

Scope

Topiramate

Boceprevir

10- fold Increase in Demand



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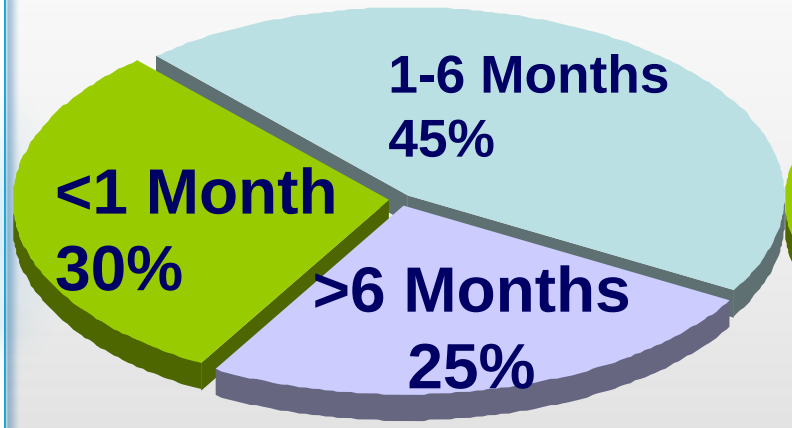
FDA Pharmacometrics: Return on Investment

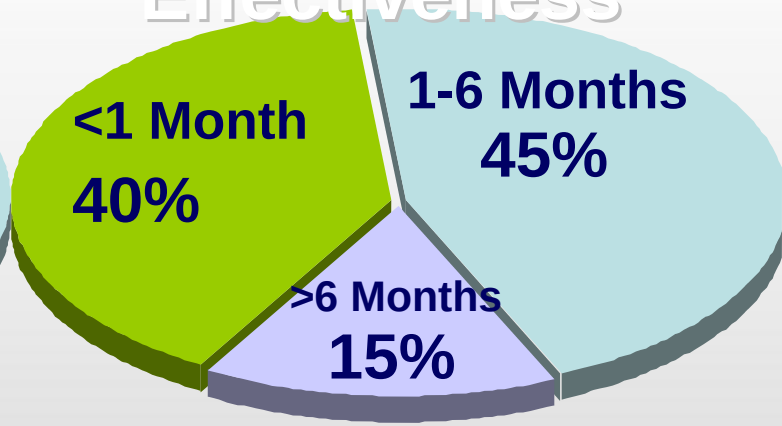
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm167032.htm

Based on 2007-08 reviews

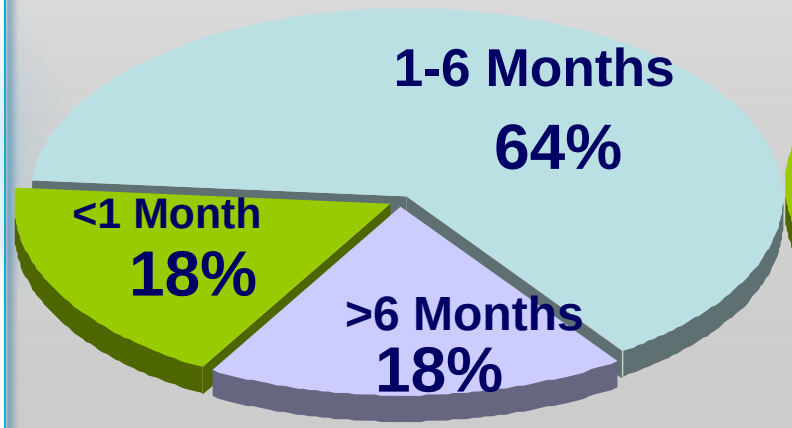
Approved Dose

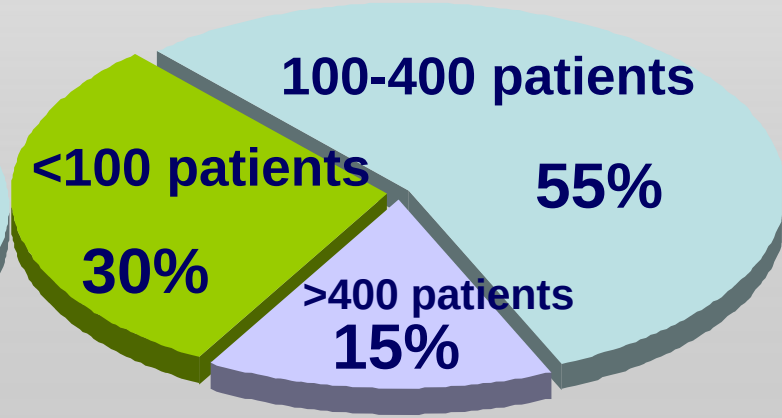


Evidence of Effectiveness



Safety





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Several Guidance Documents Illustrate Application of Modeling and Simulation

Population Pharmacokinetics

Exposure-Response

Evidence of Effectiveness

Combination Drugs

Drug-Drug Interaction

Hepatitis C Drug Dev

320 n. We recommend that sponsors conduct mechanistic modeling of the
321 concentration-viral kinetics and the concentration-safety profile from phase 1 trials to
322 predict the most active and tolerable doses for study in phase 2. The mechanistic viral

Diabetes Drug Dev

447 pulation. We recommend that exposure-response data be obtained during the phase 2
448 dose-finding studies. (See the guidance for industry *Exposure-Response Relationships: Study*
449 *Design, Data Analysis, and Regulatory Applications*.)

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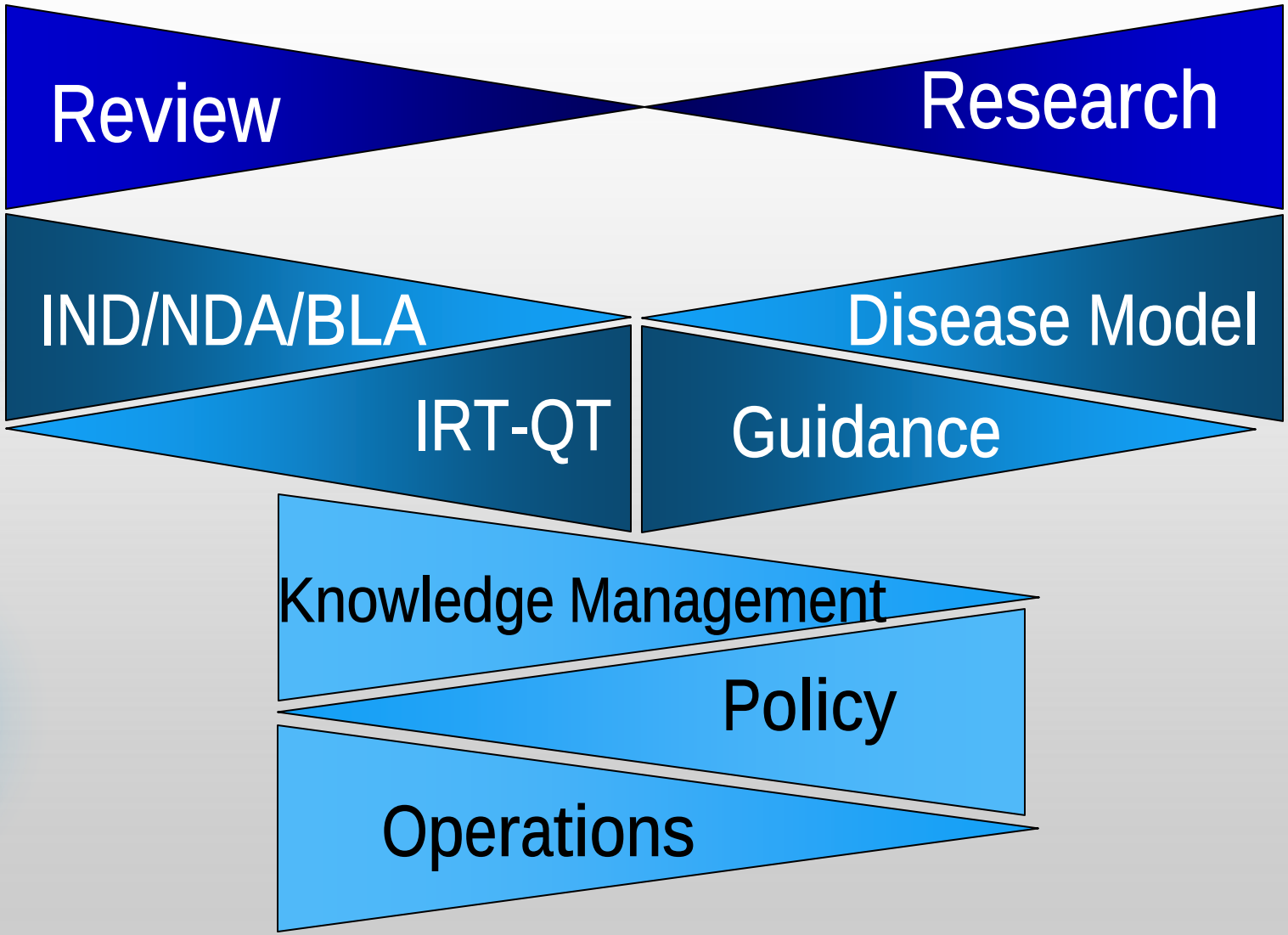
Pharmacometrics Scope



Pivotal Role in Pediatric Applications

Case Study: Topiramate

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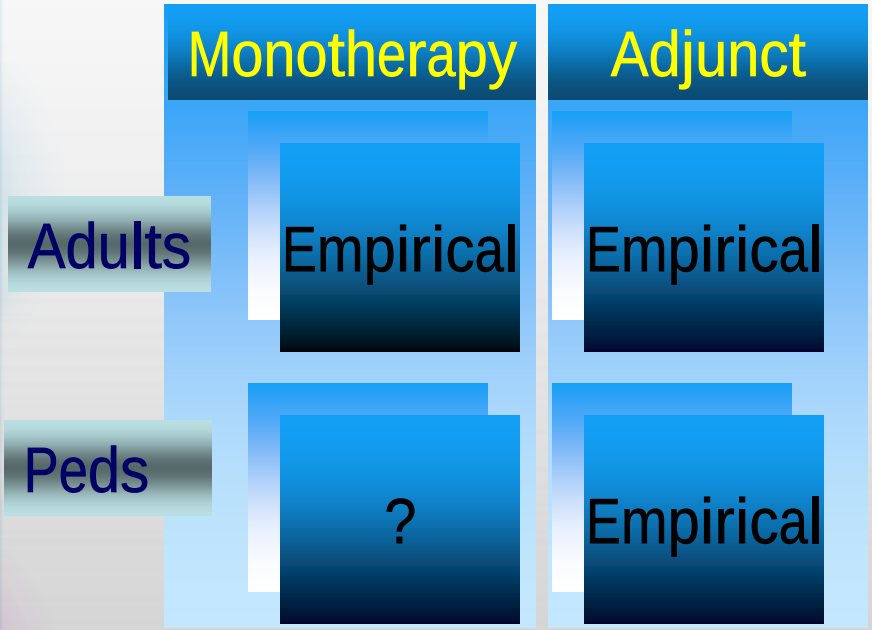
Model Based Extrapolation for All Monotherapy Approvals for Treatment of Epilepsy



Extrapolate Adjunct Therapy to Monotherapy

Is Exposure-Response Similar in Adults?

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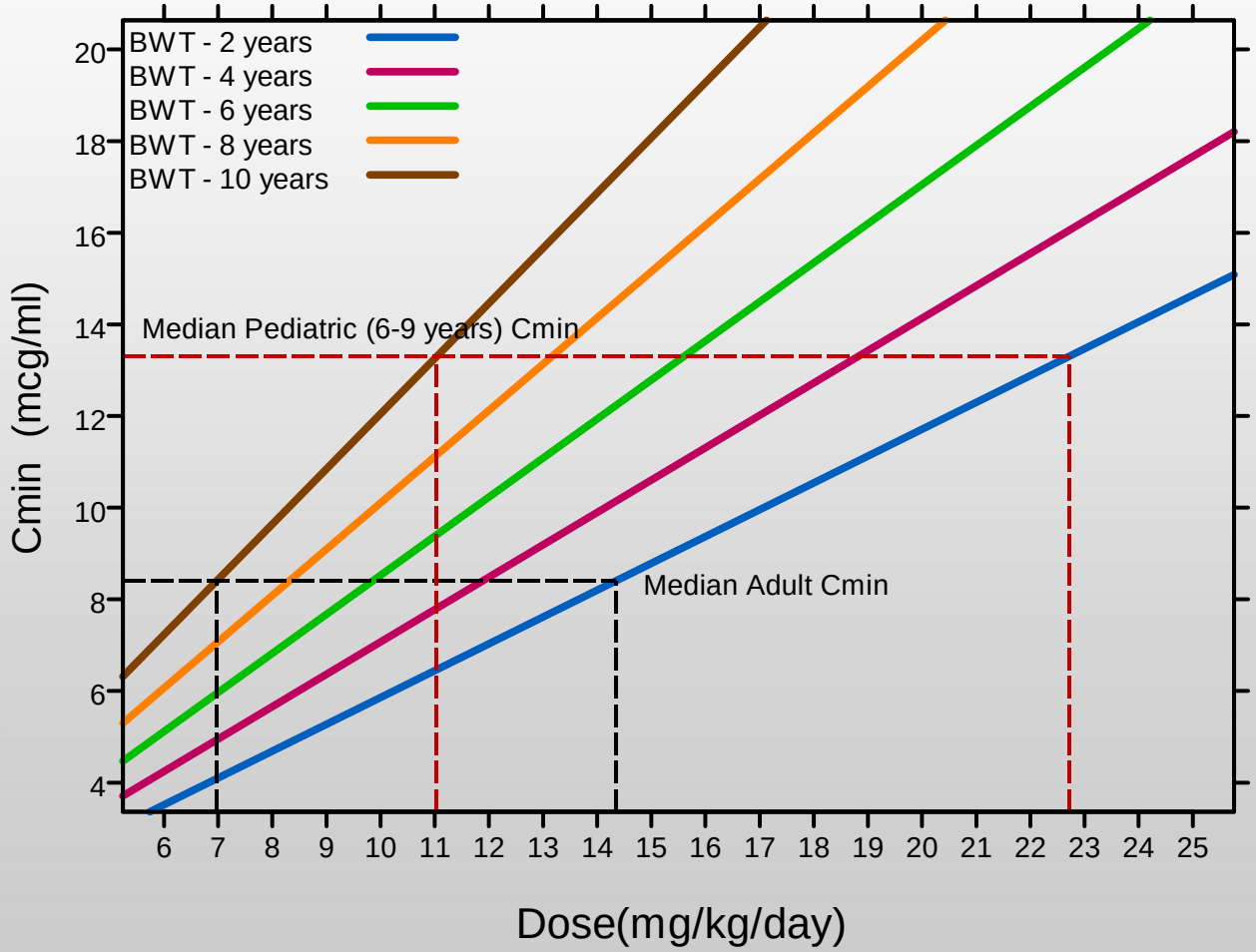
Topiramate Dosing Regimen was Derived by Matching Steady State Trough Concentrations (CMIN) for Different Age Groups

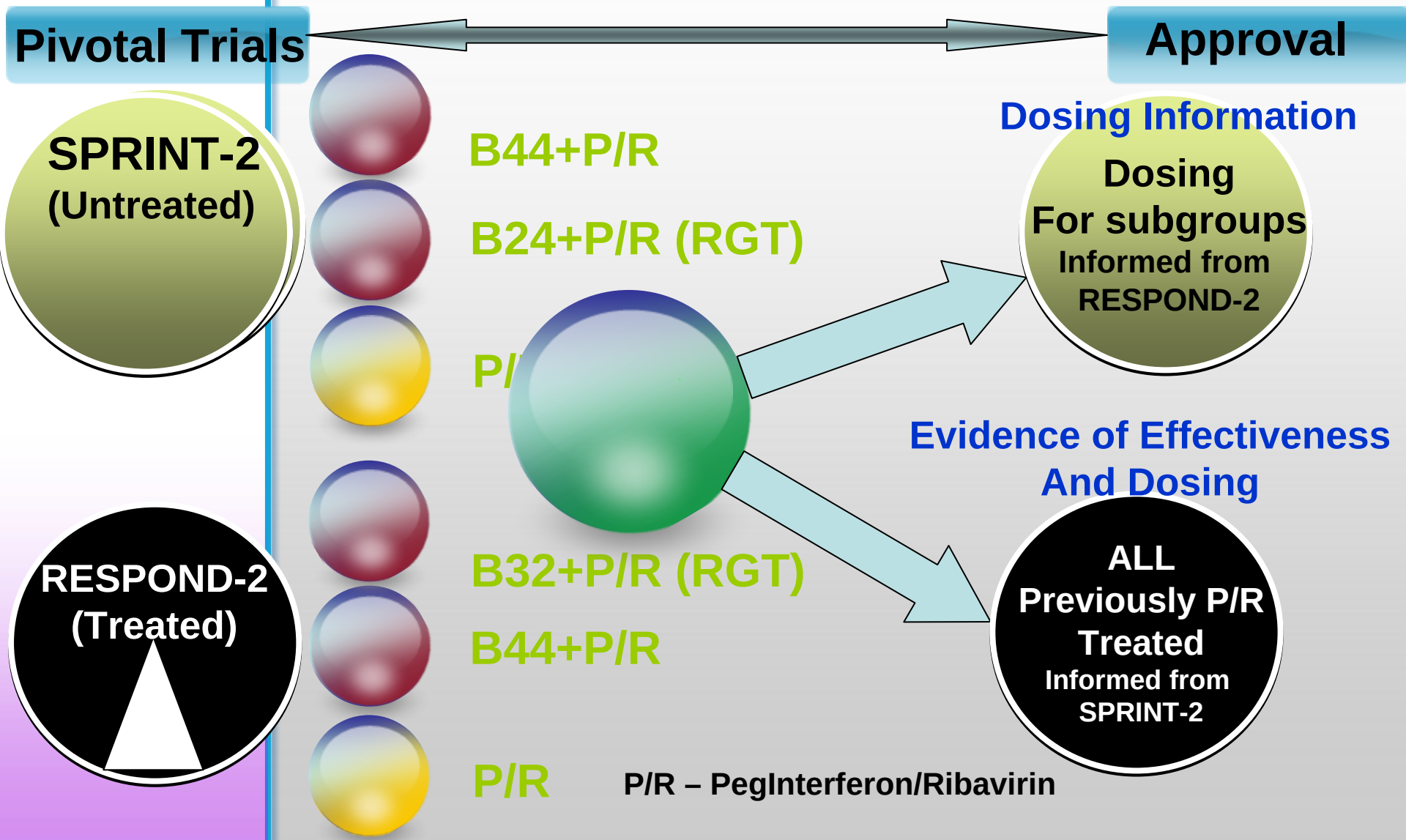
Pharmacokinetic Modeling and Simulation Based Approval



Pivotal Role in Dosing Recommendations After Pivotal Trials Are Completed

Case Study: Boceprevir

Null Responders were Excluded from Pivotal Trials but Pharmacometrics Bridging Approach Filled the Gap



P/R – PegInterferon/Ribavirin

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm254073.htm

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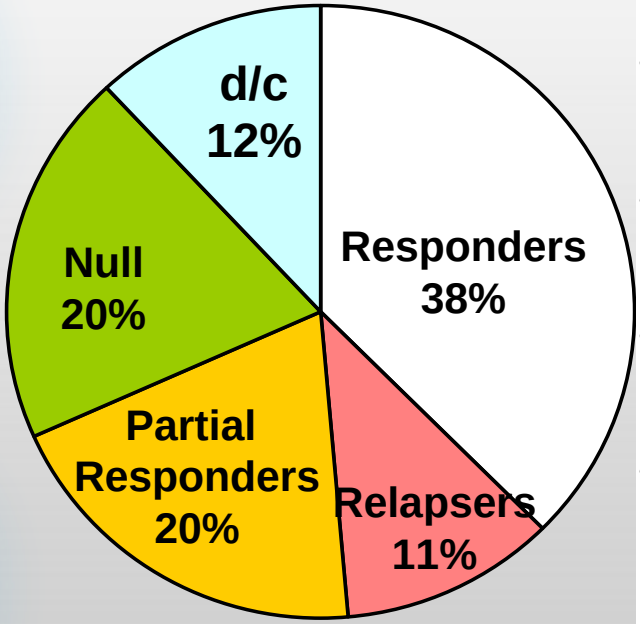
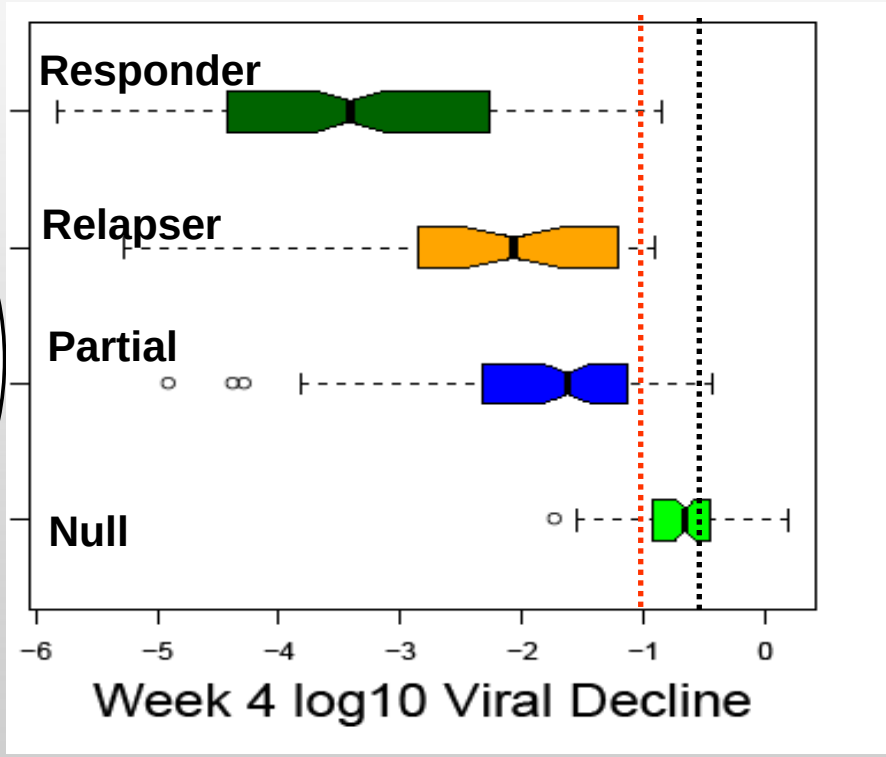
Null Responders can be identified based on Week 4 P/R response (<0.5 or <1 log decline) in untreated subjects

SOC outcome in untreated subjects





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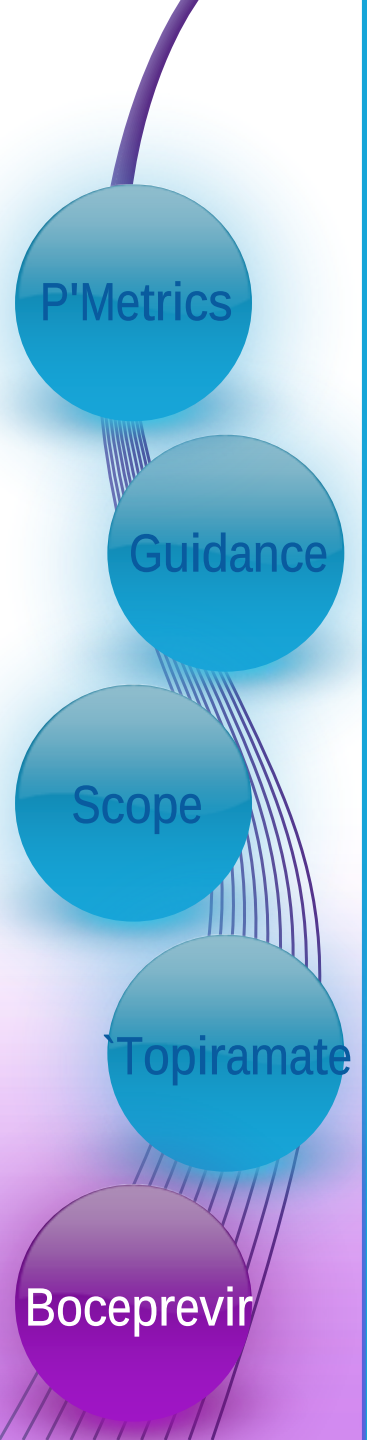
Higher SVR in Subjects with <0.5 or <1 log Week 4 P/R response with Boceprevir Compared to P/R Treatment

Week 4 Viral load decline	% null responders, (n/N)	Observed SVR in PR (Untreated Subjects)	Observed SVR in Boceprevir (Untreated Subjects)	
			RGT	PR4/BOC+PR44
<1.0	69% (57/83)	4%	28%	38%
<0.5	88% (22/25)	0%	28%	30%

- <1.0 $\log_{10}$ decline includes subjects who are not null responders and may over estimate SVR
- <0.5 $\log_{10}$ decline includes predominantly null responders and provides a more conservative estimate for SVR



Business and Public Health Impact

- Evidence of Effectiveness for Prior Null Responders
  - Estimated Sample Size for New Study

    200-300 patients studied over 72 weeks

- Dosing Recommendations for Untreated Late Responders
  - Impact on Healthcare Cost

    12 weeks of less therapy that costs $1100/week

These estimates are derived after regulatory review and were not considered during the review. The review focus was to scientifically justify the regulatory decision.

Summary

Impact on Drug Development and Therapeutics

Herceptin® trastuzumab

- Identified an exploratory subgroup potentially lacking benefit
- Asked for new study

- Treatment of SEGA
- Pivotal Exposure-Response for evidence of effectiveness and TDM justification

AFINITOR® (everolimus) tablets

Celexa

- Concentration-QT analysis predicted QT effects at 40 mg/day to limit the dose

http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm

- Derived and recommended Pediatric Dosing Recommendations without any empirical data

Pralidoxime

Peramivir

Summary

Impact on Drug Development and Therapeutics

- Increased Demand for Pharmacometrics at FDA
- Several Pharmacometrics Applications in Review, Research, Official Guidance and Policy
- Pharmacometrics at FDA Plays Pivotal Role in Approval and Labeling

BACK UP

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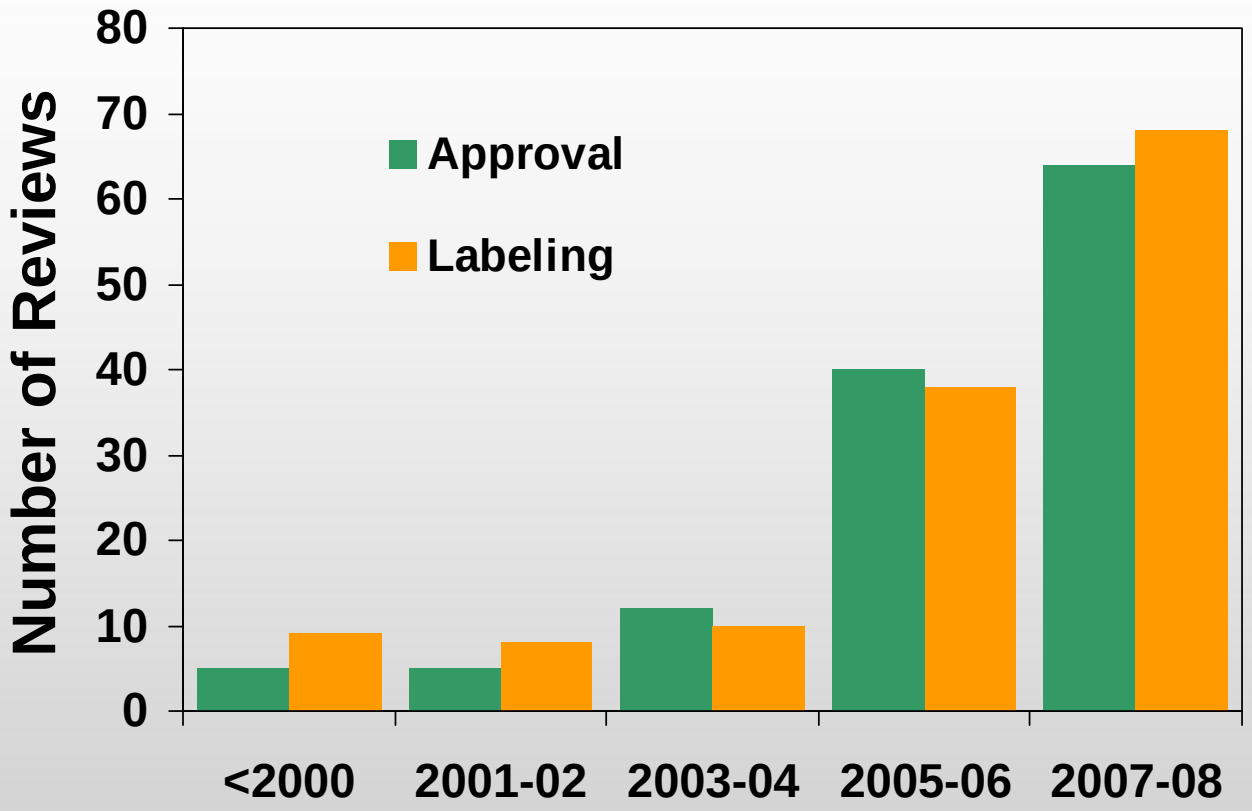
Boceprevir

Return on Investment – Drug Approval and Labeling



Impact on Approval-
ER analysis provided supportive or pivotal evidence of effectiveness.
Impact on labeling-ER analysis supported D&A, Warnings, Intrinsic/Extrinsic factors sections