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The Business Case for Model Informed Drug Development

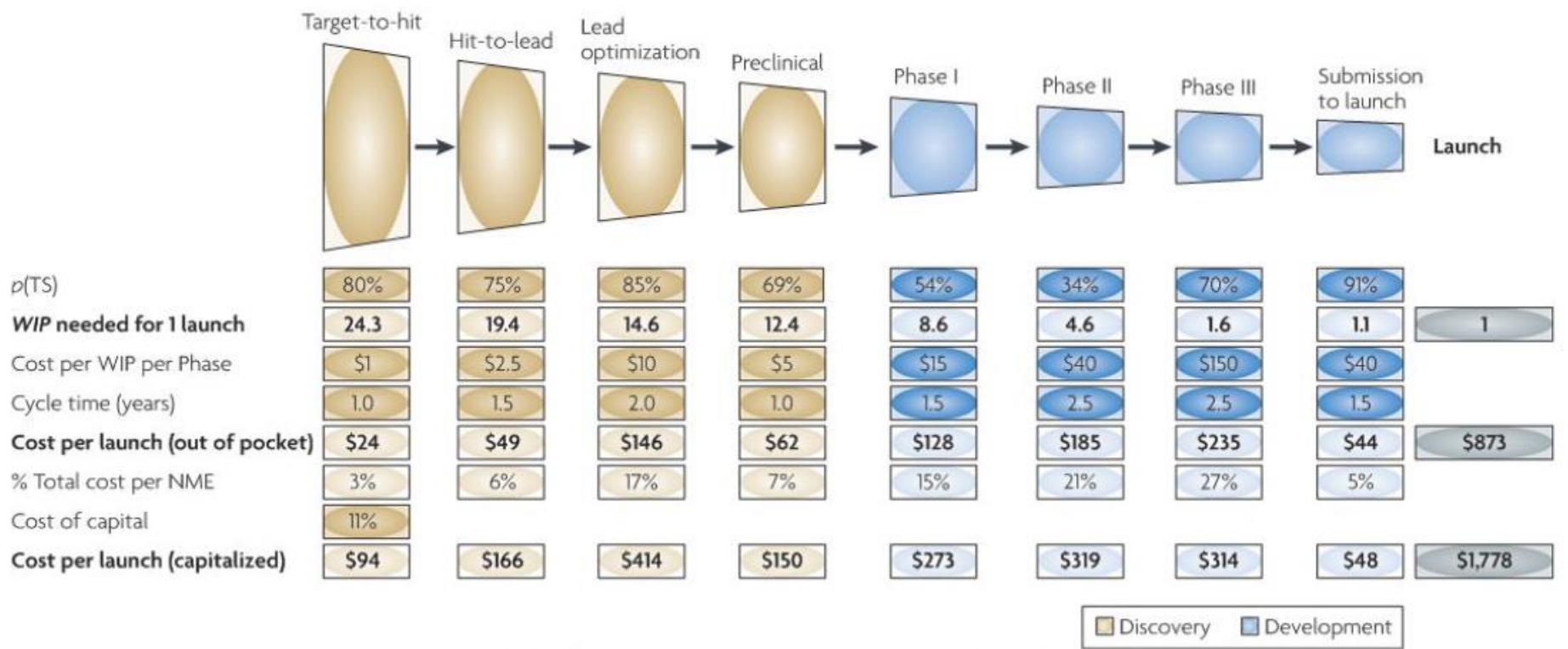
Patrick F. Smith

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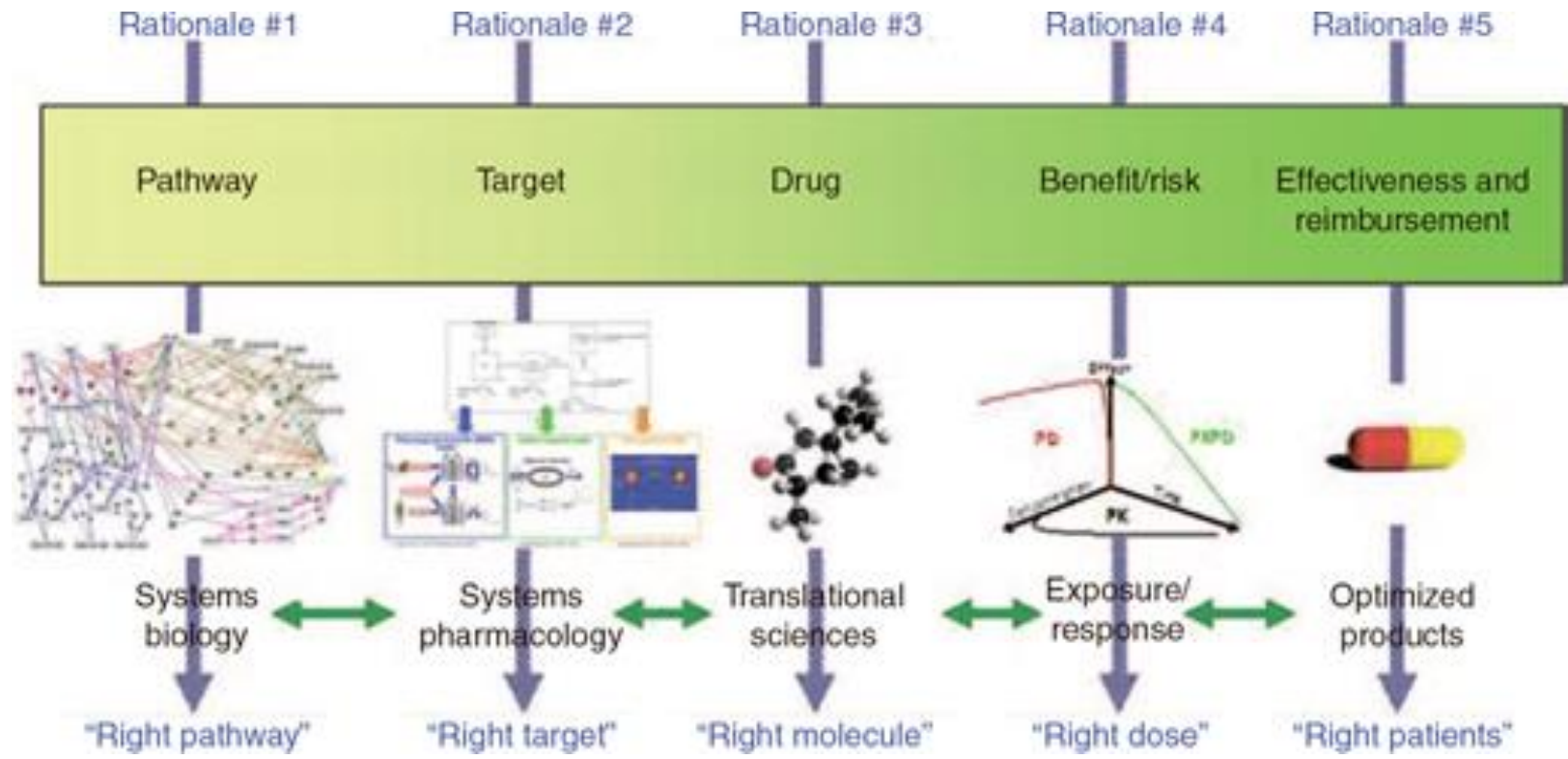
d3 Medicine

Research and Development Productivity

$$\text{Productivity} \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$$



Model-Informed Drug Development: A Rational Approach to Efficiently Accelerate Drug Development



Regulators Affirm Importance of MIDD

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

We're at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.

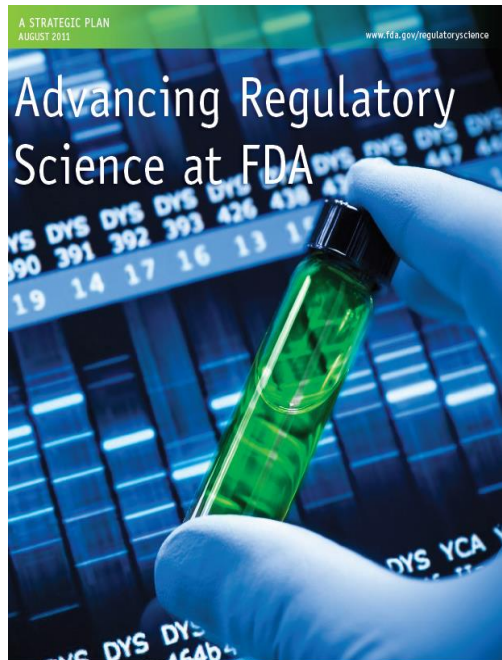


To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.

"I want to highlight one example of these steps, which we're investing in, and will be expanding on, as part of our broader Innovation Initiative. It's the use of in silico tools in clinical trials for improving drug development and making regulation more efficient."

FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms."

50% of FDA Scientific Priority Areas include MIDD



- 1. Modernize toxicology to enhance product safety**
- 2. Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcome**
- 3. Accelerate development of novel drugs, biologics, and medical devices to improve patient health**
- 4. Increase transparency and accountability in regulatory decision-making**
- 5. Harness diverse data through information sciences to improve health outcomes**
- 6. Increase the efficiency of regulatory processes**
- 7. Facilitate development of MCM to protect against threats to health**

<https://www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/ucm268225.pdf>

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology – March 2012

- Should modeling and simulation methods be considered in **all** pediatric drug development programs? - **(VOTE) YES: 13; NO: 0; ABSTAIN: 0**
- Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study? – **(VOTE) YES: 12; NO: 1**
- Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time? – **(VOTE) YES: 7; NO: 6**

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm>

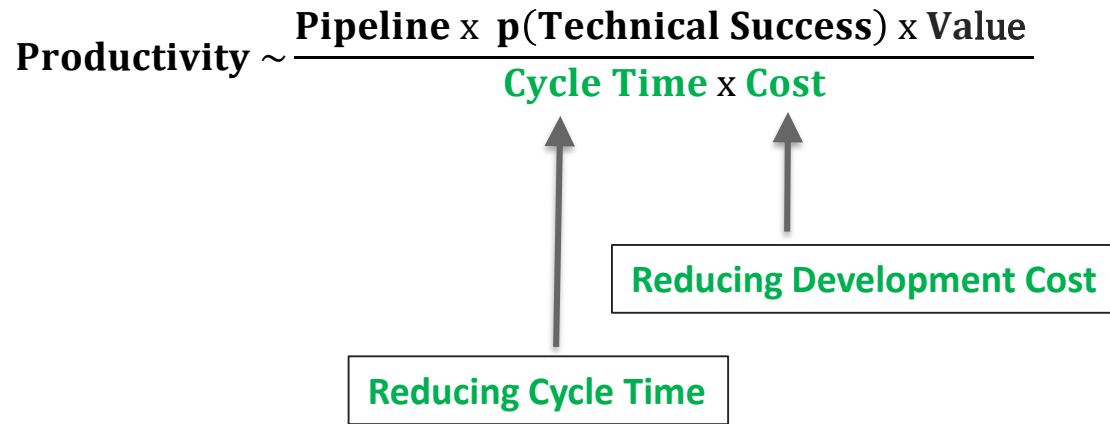
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Research and Development Productivity

$$\text{Productivity} \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$$

M&S Impacts 4 of the 5 Key Drivers of Productivity

Reducing Development Costs and Cycle Time



Financial Impact of Earlier Market Entry

Table 2: Increase in NPV of a new drug from an earlier approval and launch

Expected Market Uptake	Percent Increase				Dollar Value (\$mil) of NPV Improvement for \$500 million Peak Annual Sales Drug			
	Calendar Quarters Saved				Calendar Quarters Saved			
	1	2	3	4	1	2	3	4
Most Rapid	4.0%	8.2%	12.4%	16.7%	\$88	\$178	\$270	\$364
Rapid	4.3%	8.7%	13.2%	17.8%	\$82	\$167	\$253	\$341
Average	4.9%	10.0%	15.1%	20.3%	\$74	\$150	\$228	\$307
Slower	6.1%	12.5%	19.1%	26.0%	\$64	\$130	\$198	\$267
Slowest	6.3%	12.7%	19.2%	25.9%	\$14	\$30	\$46	\$62

Published Examples of Financial Impact

MERCK

- >\$500M in costs avoided over 3-yr period
- Enables ~10 critical development decisions annually

VERTEX

- \$30-40M saved in the development of HCV PI telaprevir using MIDD due to shorter trial durations

PFIZER

- \$100M reduction in annual clinical trial budgets

TUFTS

- Adaptive Designs could save companies \$100 - 200M annually

Allerheiligen, CPT 2014

<http://www.bio-itworld.com/issues/2008/june/boger-keynote.html>

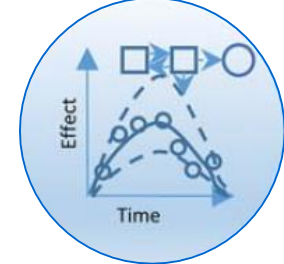
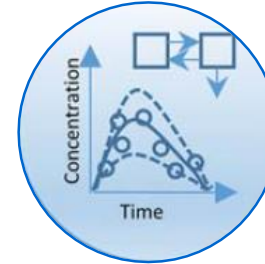
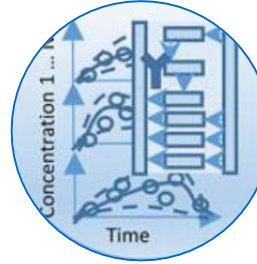
Lamberti and Getz Tufts CSDD Whitepaper, May 2015

Milligan et al, CPT 2013

Case: RSV - MIDD

- Tools

- PBPK, POPPK, PK/PD

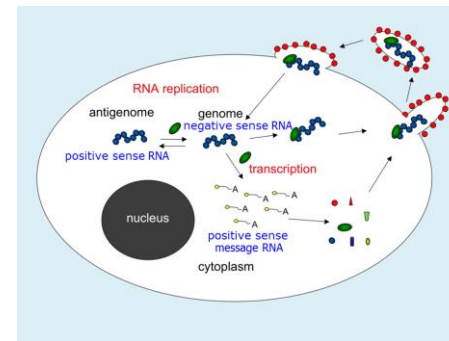


- Application

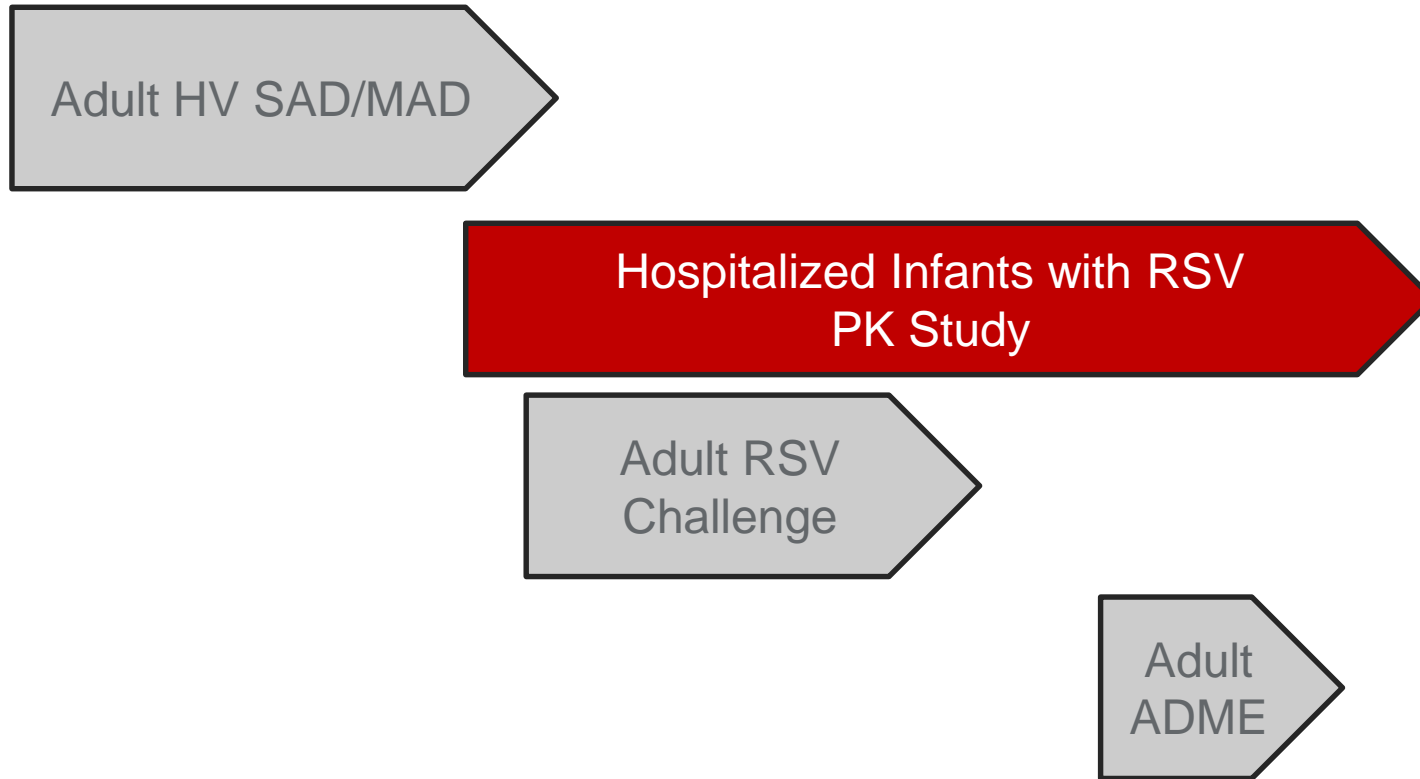
- Early development
 - MIDD embedded in Development Plans
 - Clinical Trial Optimization
 - Informing regulatory pathway

Respiratory Syncytial Virus (RSV) Background

- Most children have been infected while an infant
- Majority of severe infections occur in children < 2 years of age
 - 40% develop lower RTI; 2-5% require mechanical ventilation
 - Mortality 1-3% in hospitalized patients
- No approved drugs for treatment of infection (supportive care)
- ALS-8176: Novel, potent nucleoside analogue prodrug being developed as a potential treatment for RSV in children

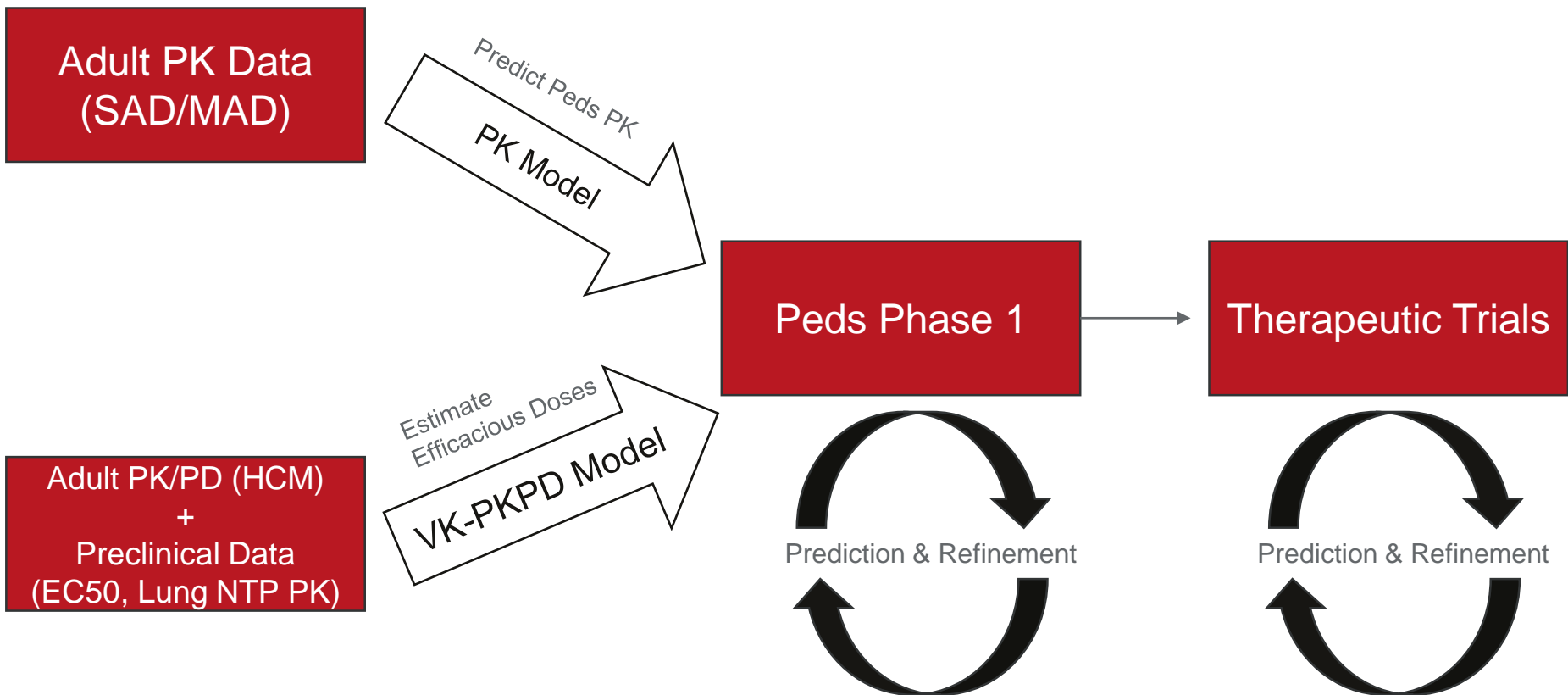


ALS-8176 Early Development Plan



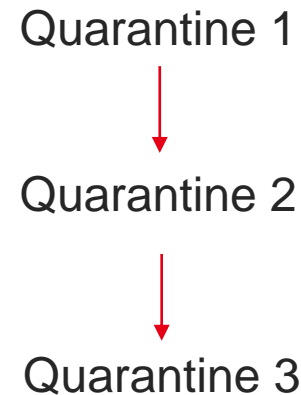
N Engl J Med 2015; 373:2048-2058
<https://clinicaltrials.gov/ct2/show/NCT02202356?term=ALS-008176&rank=4>
<https://clinicaltrials.gov/ct2/show/NCT01906164?term=ALS-008176&rank=5>
<https://clinicaltrials.gov/ct2/show/NCT02231671?term=als-008176&rank=7>
McClure M, et al. ID Week 2015

Quantitative Pharmacology Approach to Support Early Entry into Infants

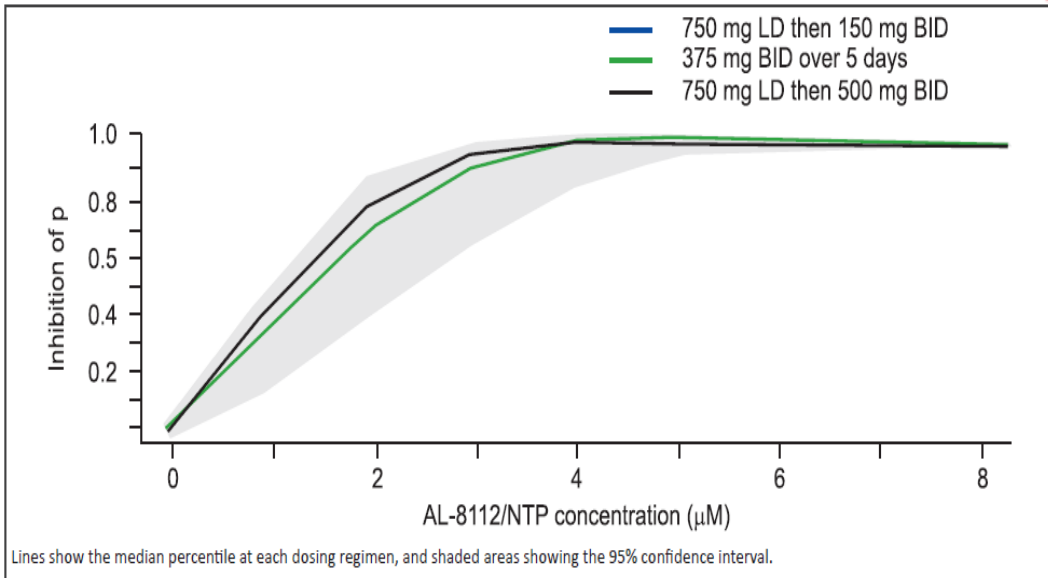
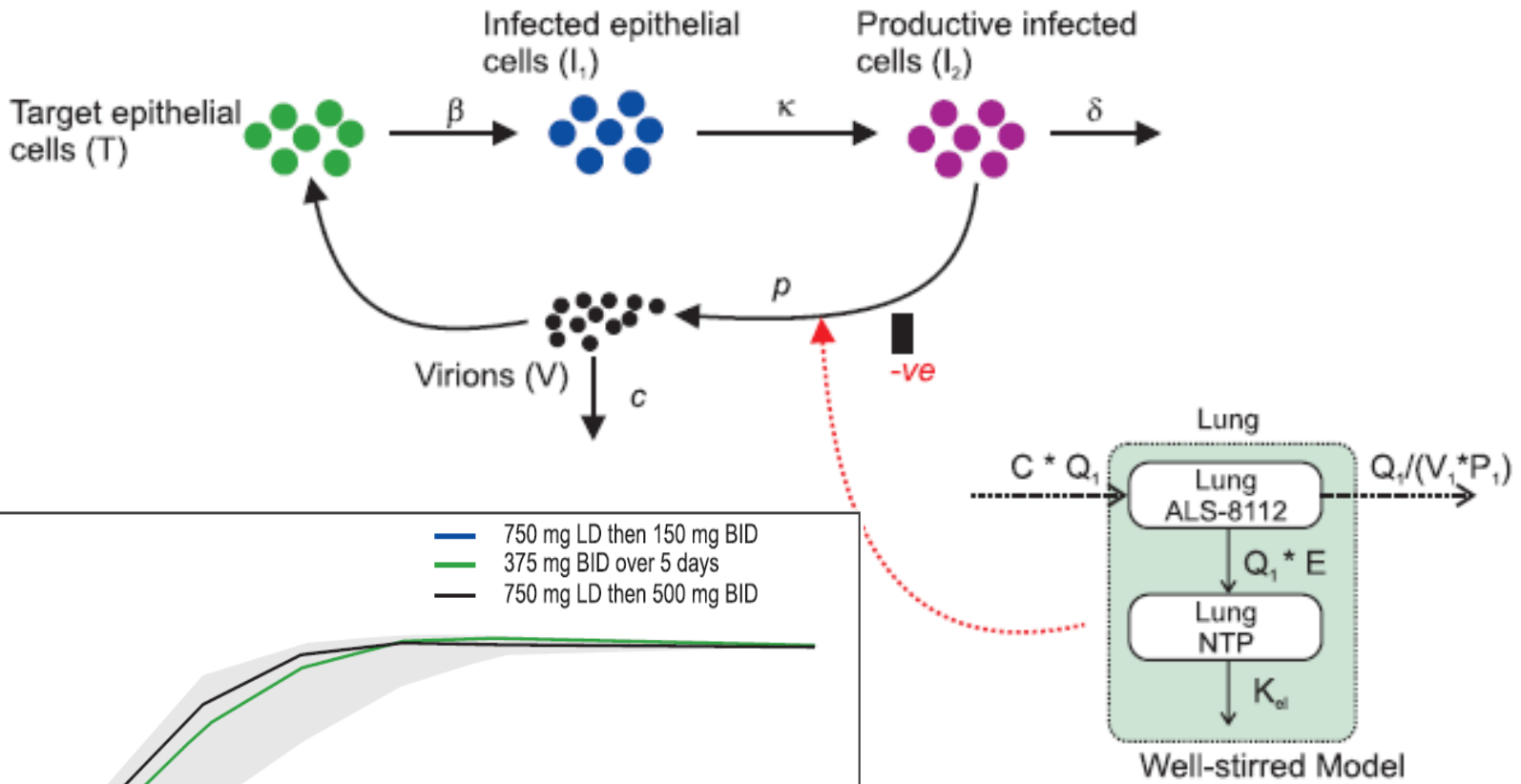


RSV Human Challenge Model Adaptive Design

- Traditional HCM designs: few doses, pairwise comparison of dose vs. placebo
- Study Objectives
 - Demonstrate POC that ALS-8176 has antiviral activity
 - Characterize exposure-response relationship to guide further studies in pediatrics
- PK and PD data examined between each cohort to determine dose levels for subsequent quarantine
 - Could utilize any mix of placebos and doses (N=22 per group, 70% infection rate)



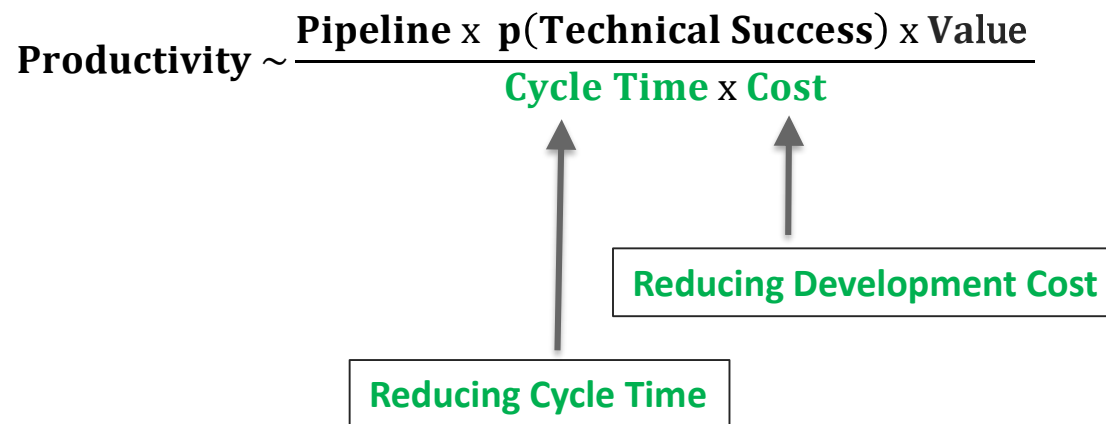
Defining PK/PD Targets for Antiviral Efficacy from the HCM



Impact of RSV Model Informed Development Program

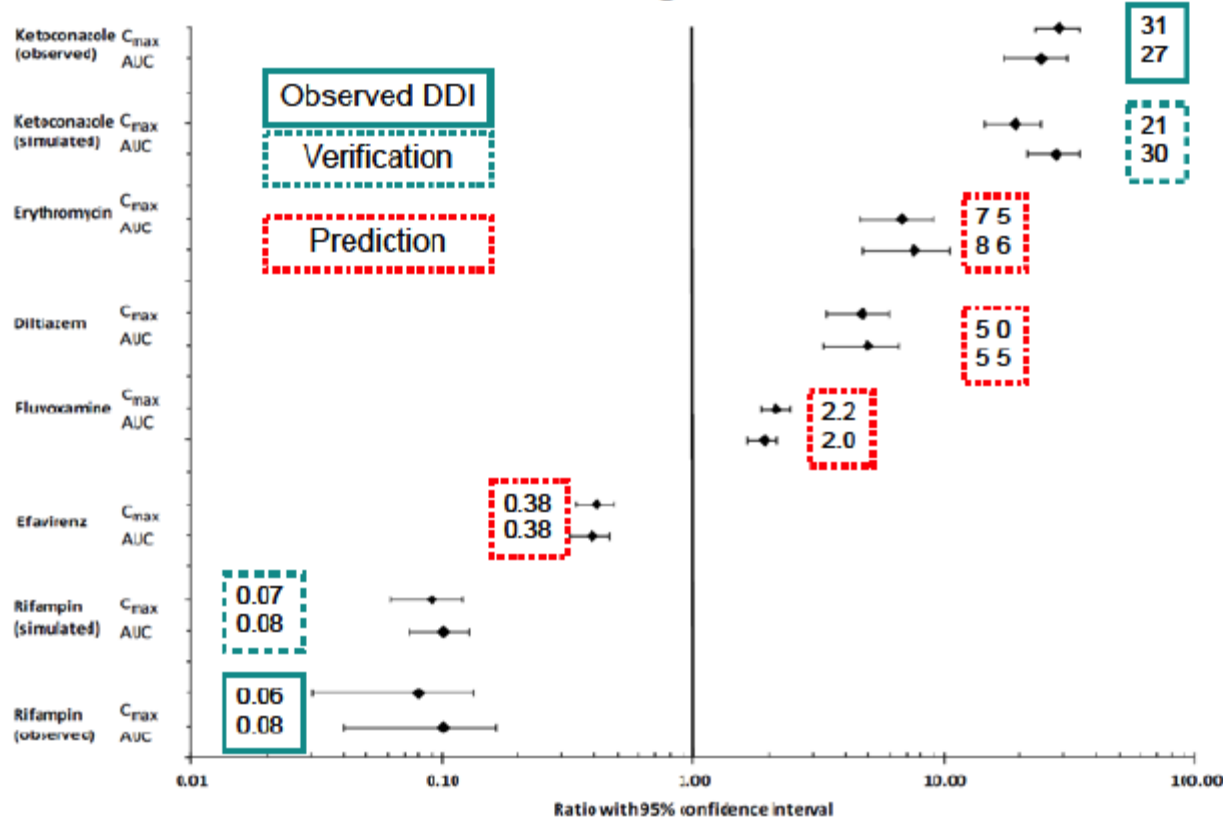
- Model based approach provided justification to move rapidly into the target patient population
- Adaptive HCM provided significant savings over traditional studies
 - Fewer subjects required, more informative dataset for exposure-response modeling
 - ~6 months and >\$5 million saved in trial costs compared to competitors using more traditional approach
- Alios acquired for \$1.75B based on results of the HCM

Avoiding Clinical Trials



















Ibrutinib – DDI Susceptibility

Figure 16: Simulated and Observed Ibrutinib C_{max} Ratios and AUC Ratios with 95% Confidence Intervals of Weak, Moderate and Strong Inhibitors and Moderate and Strong Inducers of CYP3A4



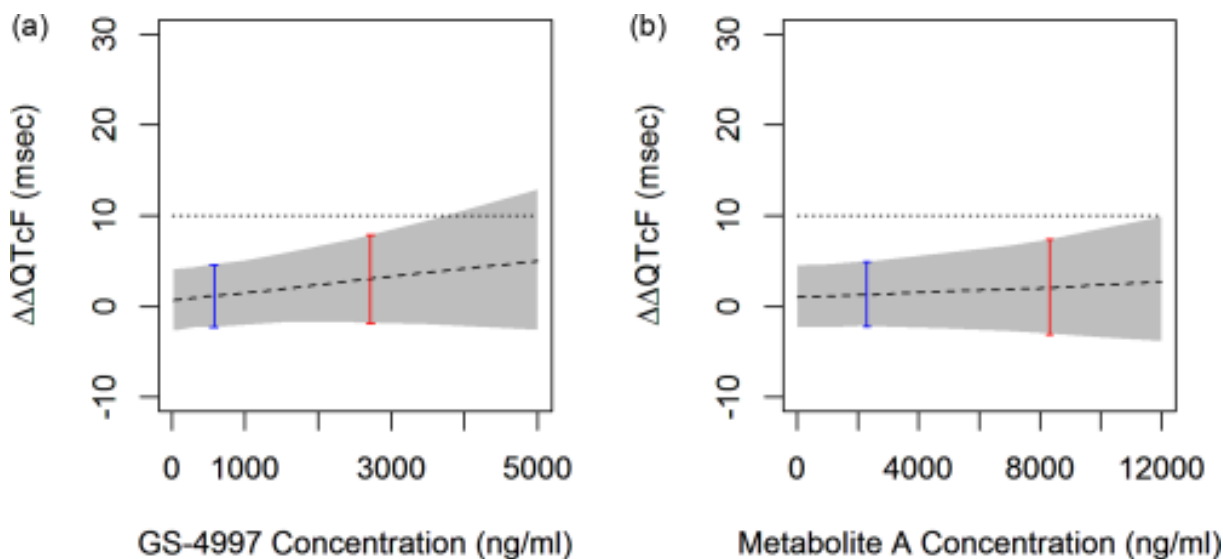
Impact of PBPK Modeling: Trials Not Conducted

Company	Drug Name	Indication	No Clinical Studies
 Johnson & Johnson	Xarelto (Rivaroxaban)	Deep Vein Thrombosis - Pulmonary Embolism – hip/knee replacement and surgery	4
 ACTELION	Opsumit (Macitentan)	Pulmonary Arterial Hypertension	2
 tibotec	Edurant (Rilpivirine)	HIV infection	1
 janssen	Olysio (Simeprevir)	Hepatitis C	7
 pharmacyclics	Imbruvica (Ibrutinib)	Mantle cell lymphoma & chronic lymphocytic leukemia	24
 AstraZeneca	Movantik (Naloxegol)	Opioid Induced Constipation	10
 genzyme A SANOFI COMPANY	Cerdelga (Eliglustat)	Gaucher Disease	12
 NOVARTIS	Zykadia (Certinib)	Metastatic Non-Small Cell Lung Cancer	2
 SANOFI	Jevtana (Cabazitaxel)	Metastatic hormone refractory prostate cancer	1
 AMGEN	Blinicyto (Blinatumomab)	Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	1
 NOVARTIS	Farydak (Panobinostat)	Myeloma	2
 Eisai	Lenvima (Lenvatinib)	Metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer	1
 NOVARTIS	Odomzos (onidegib)	Adult patients with locally advanced basal cell carcinoma (BCC)	3
 Genentech A Member of the Roche Group	Alecensa (Alectinib)	Non Small Cell Lung Cancer	1
 Alkermes Patient inspired	Aristada ((Aripiprazolel)	Schizophrenia	5
 Genentech A Member of the Roche Group	Cotellic (Cobimetinib)	Metastatic Melanoma	16

Exposure-Response Modelling Is Now Being Used to Avoid Costly Dedicated TQT Trials

A Quantitative Framework to Evaluate Proarrhythmic Risk in a First-in-Human Study to Support Waiver of a Thorough QT Study

CH Nelson^{1*}, L Wang^{1*}, L Fang¹, W Weng¹, F Cheng¹, M Hepner¹, J Lin¹, C Garnett² and S Ramanathan¹



Enhancing Probability of Success

Enhancing P(Technical Success)

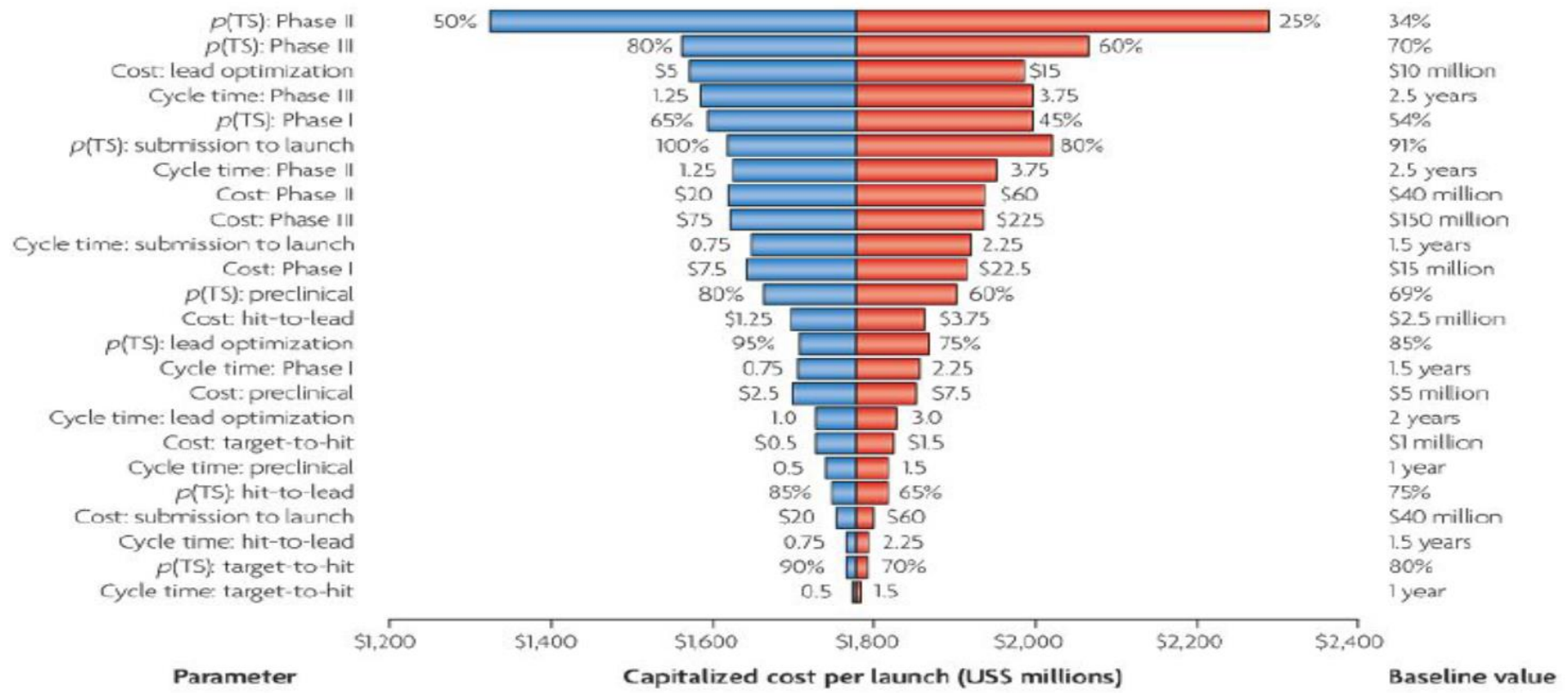


$$\text{Productivity} \sim \frac{\text{Pipeline} \times \mathbf{p(\text{Technical Success})} \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$$

Enhancing Success Rates by Reducing Failure

Enhancing the Probability of Technical Success

$$\text{Productivity} \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$$



Enhancing Success Rates by Reducing Failure

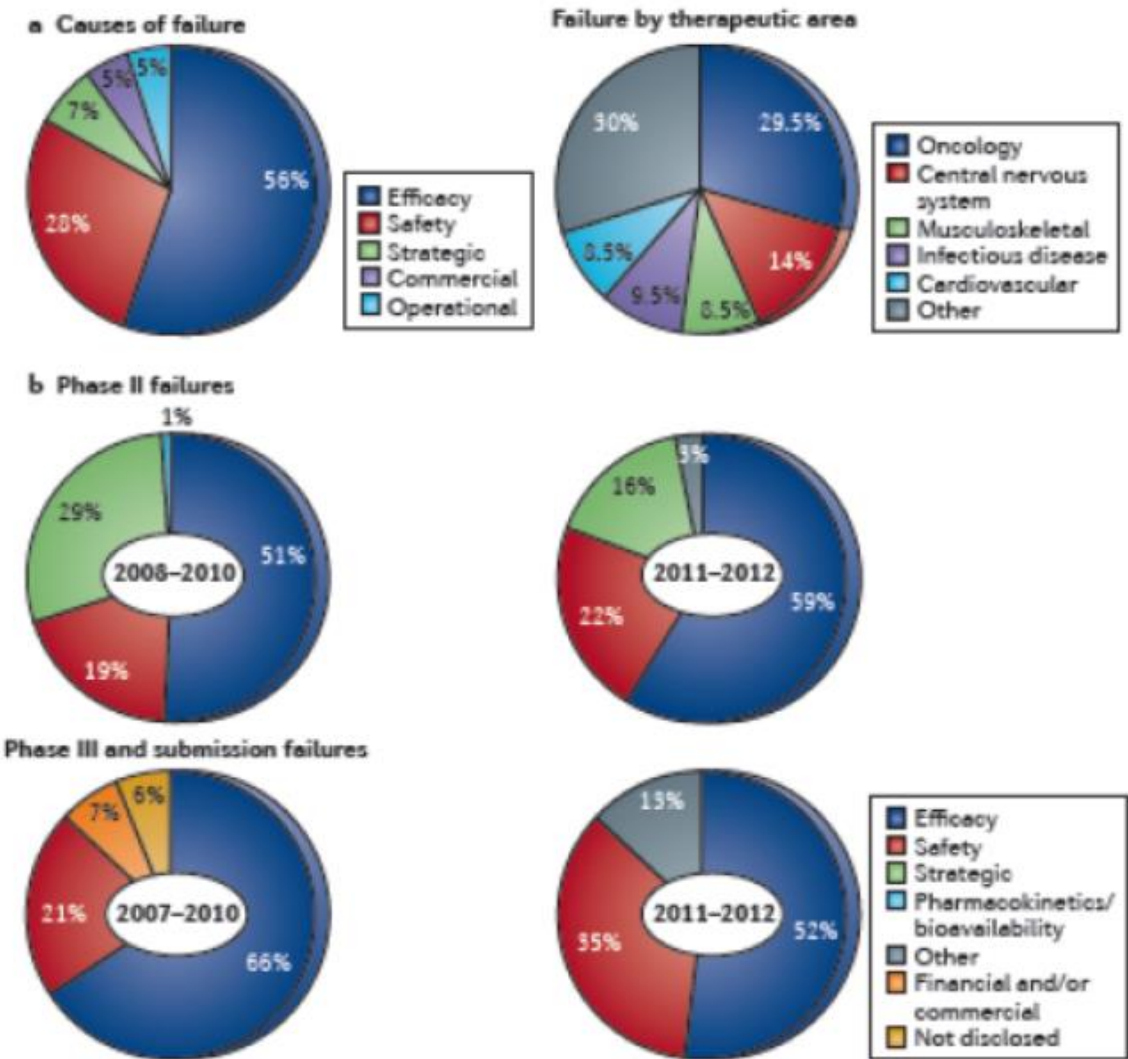
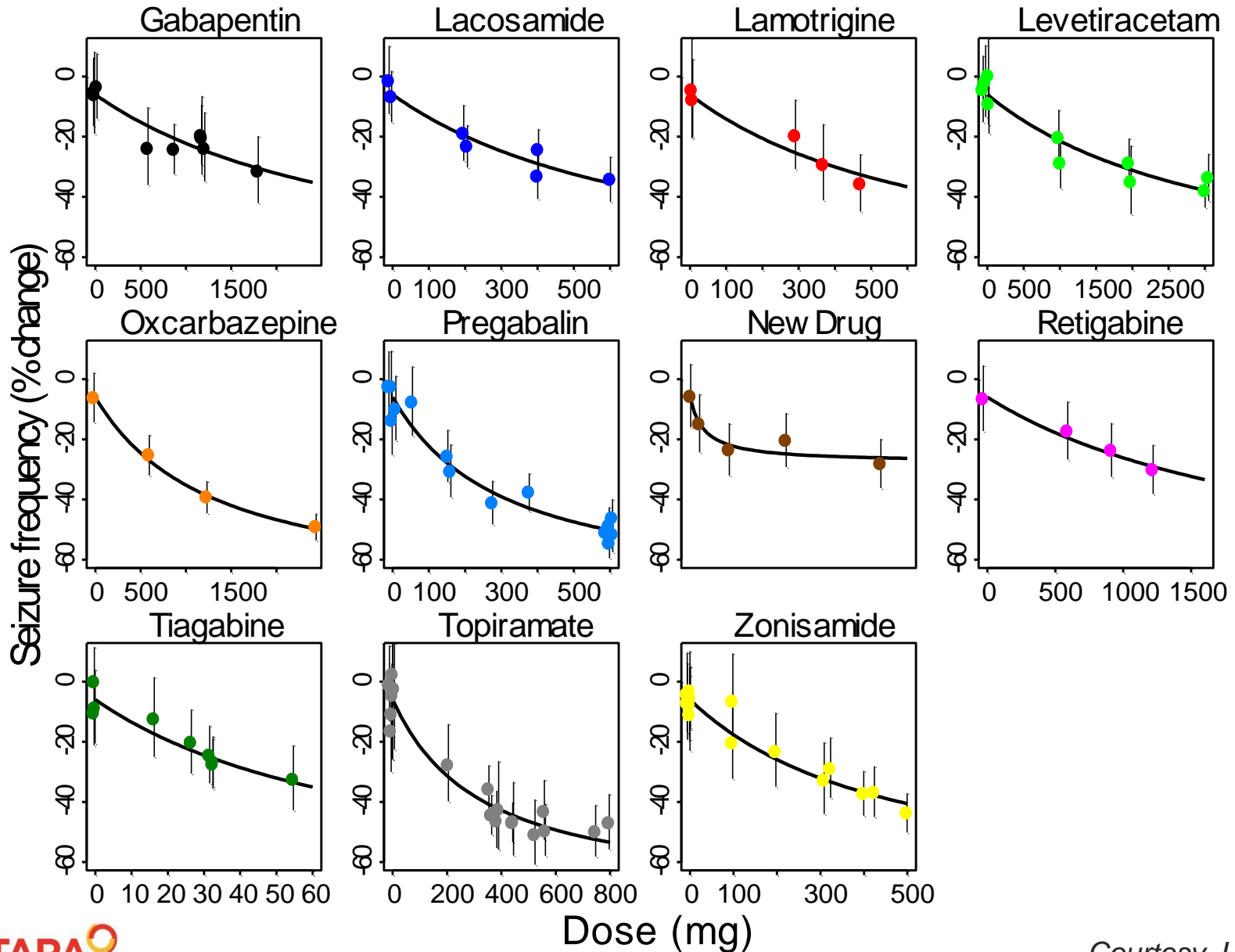


Figure 1 | Trends in attrition rates. a | Of the 148 failures between Phase II and submission in 2011 and 2012, reasons were reported for 105; the majority of failures were due to lack of efficacy, as shown on the left. On the right, the 105 reported failures are broken down according to therapeutic area. b | Comparison of the reasons for failures in Phase II and Phase III trials in 2011 and 2012 with those in earlier periods that we reported previously (see main text for details). Data are from Thomson Reuters, *Drugs of Today* © Prous Science S.A.

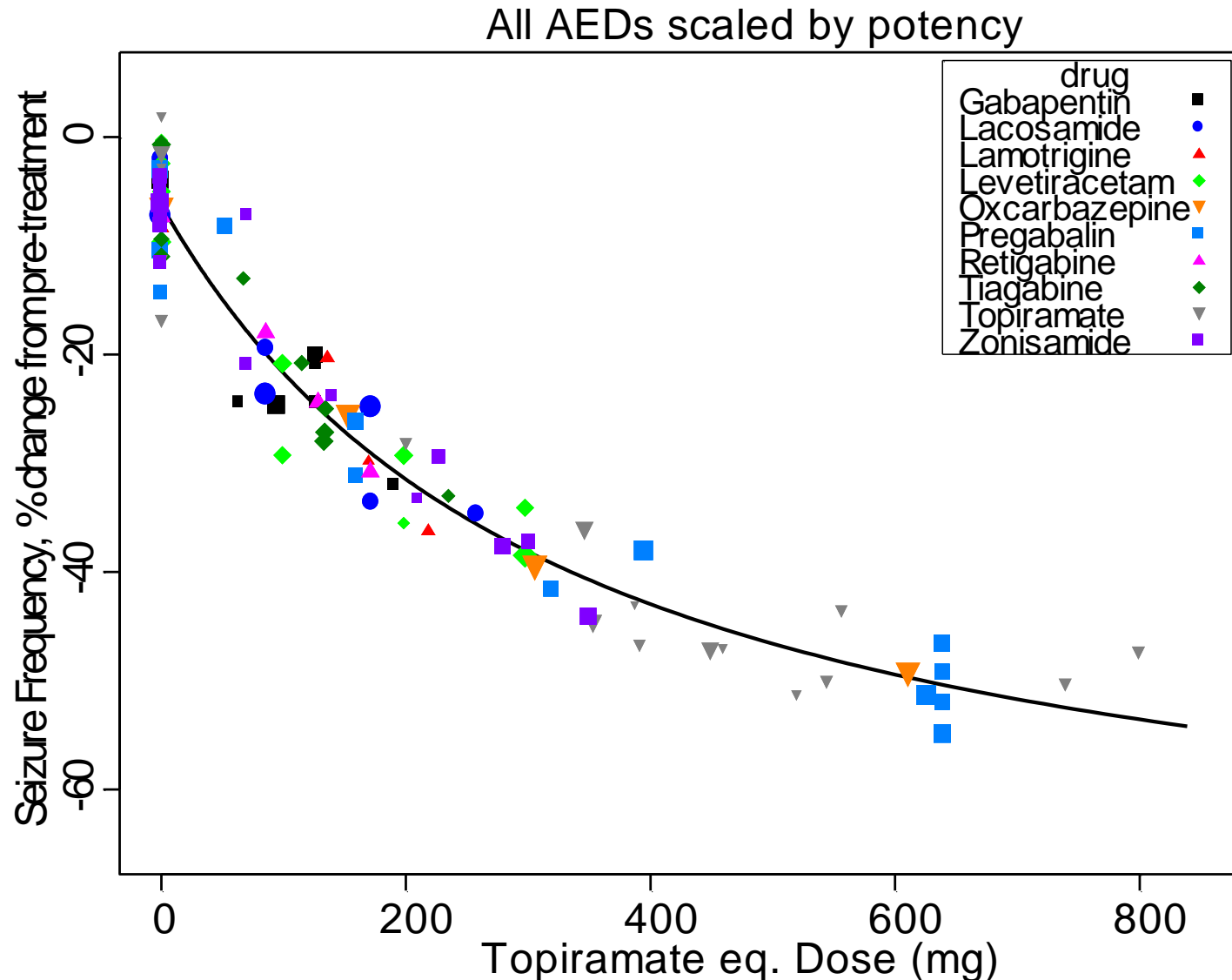
Arrowsmith et al, Nature Rev Drug Disc 2013



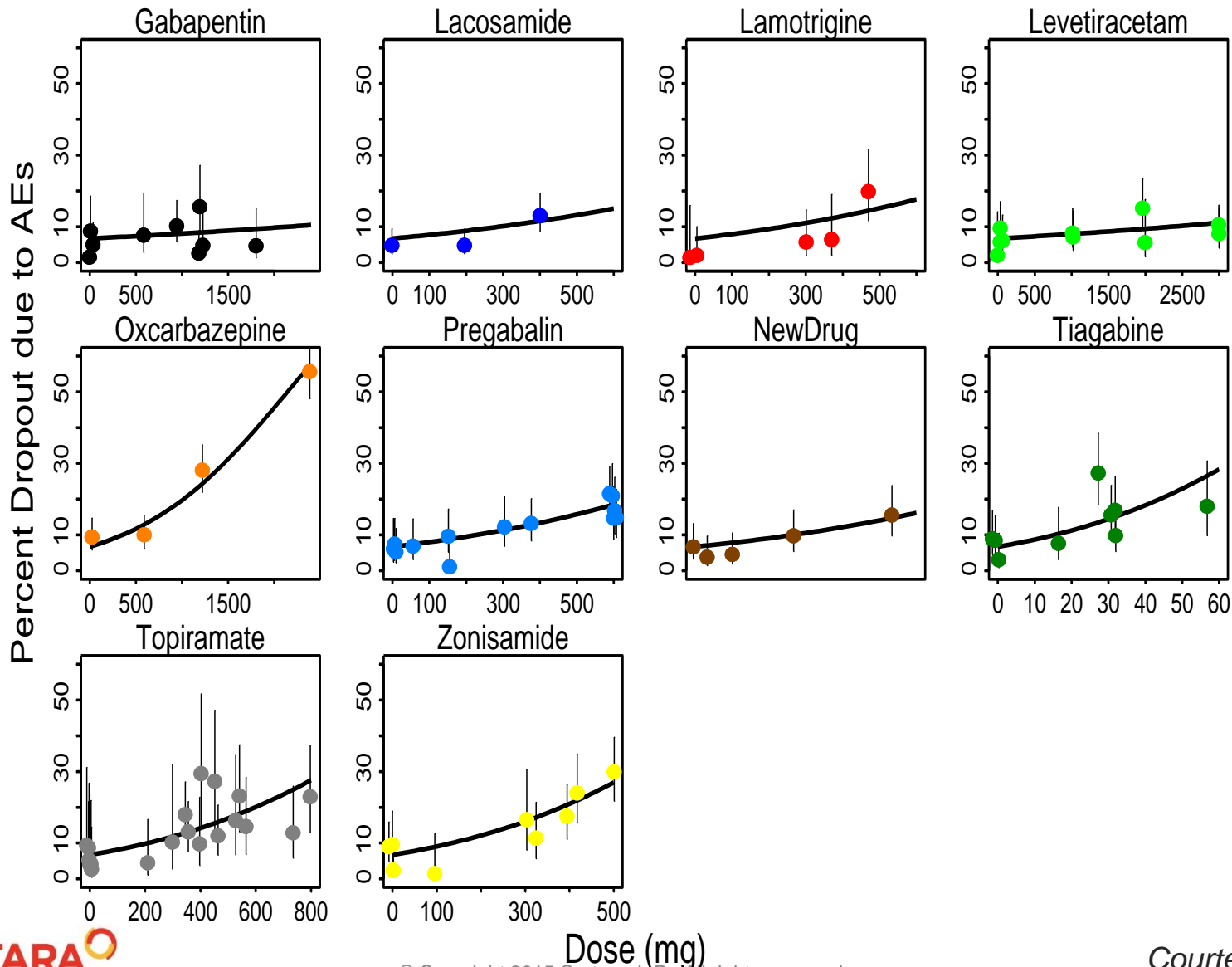
Dose response relationship for seizure frequency



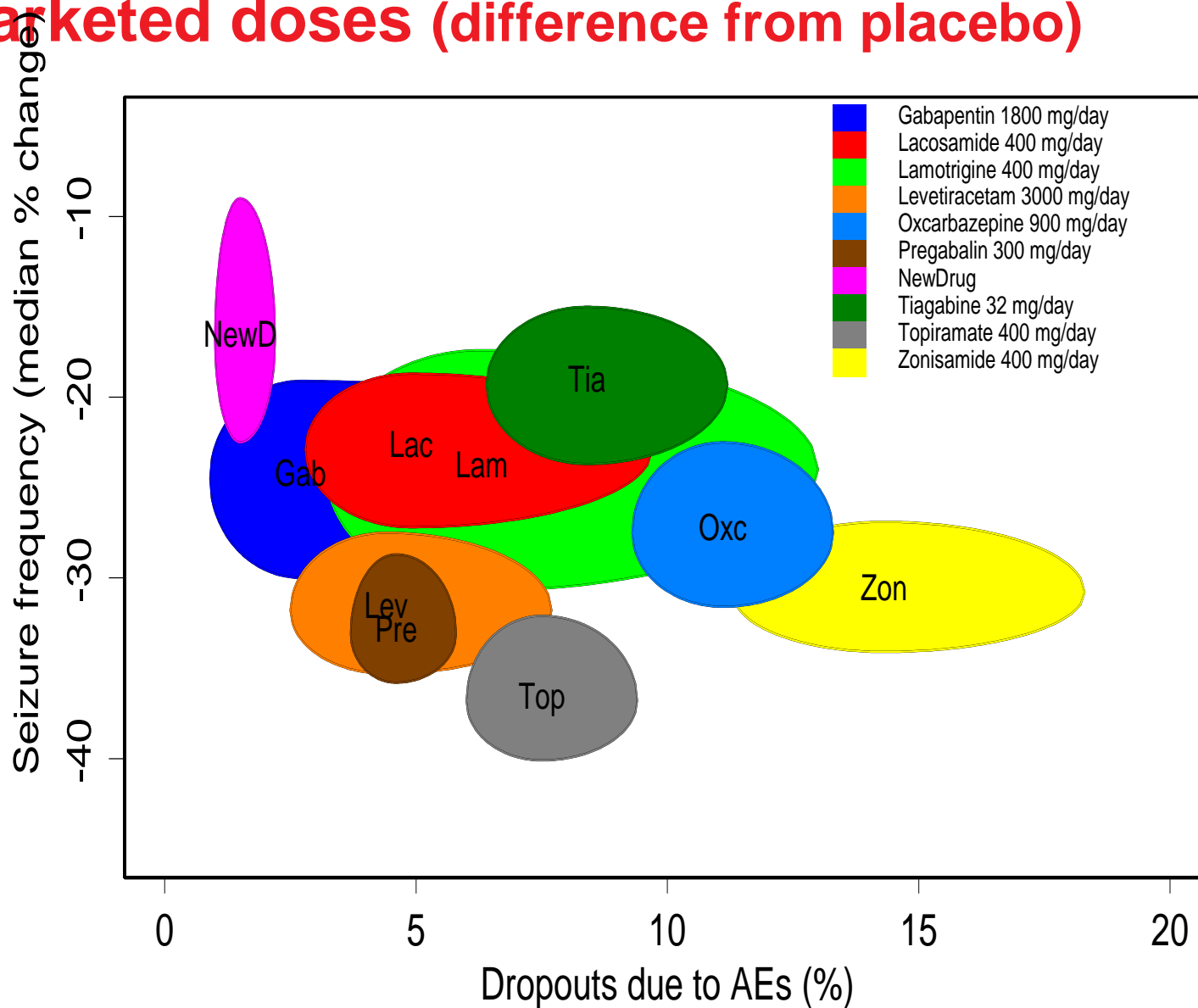
Since all compounds have the same maximum response, their Dose Response relationship can be scaled to that for Topiramate



In a similar way, the Dose Response for the AE drop out rate was quantified

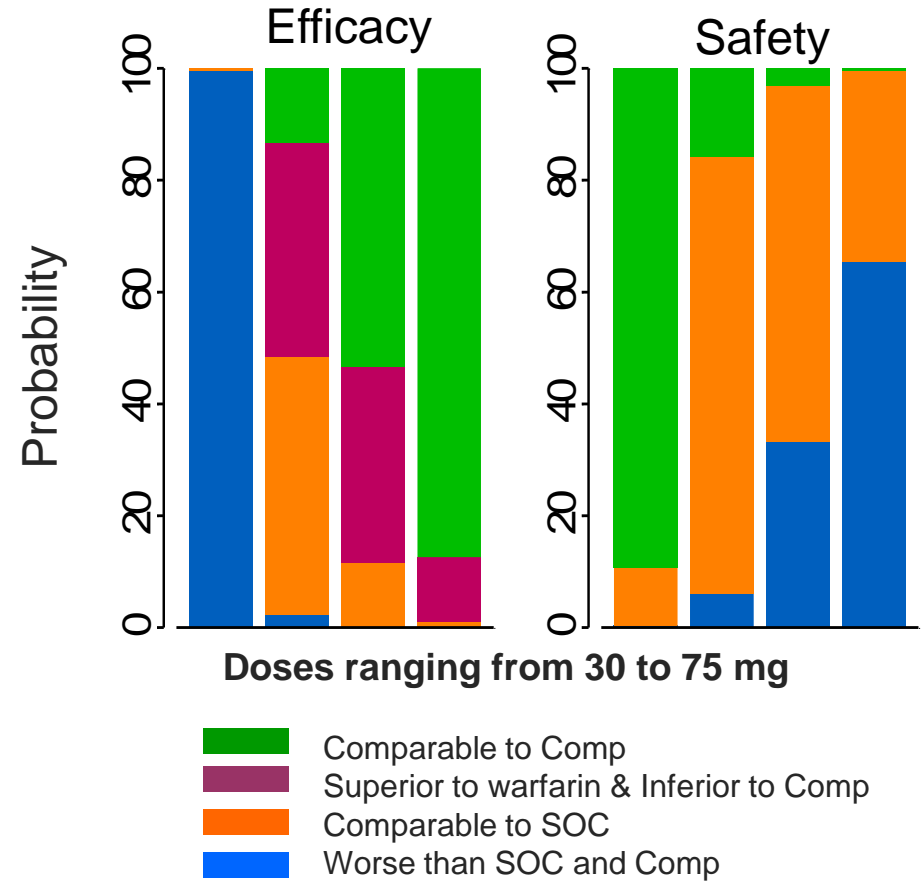
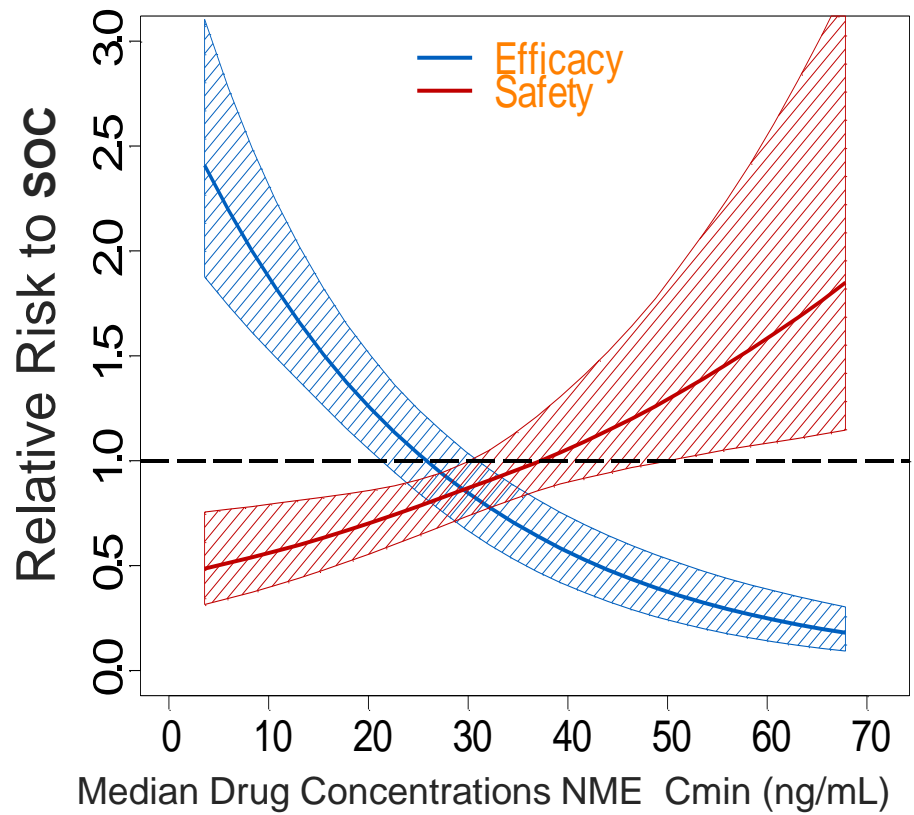


Comparative profile of AEDs at their (expected) marketed doses (difference from placebo)



No Dose Which Will Deliver to TPP

Based on 5000 simulations at each concentration



Research and Development Productivity

Enhancing Commercial Value of a Drug Product

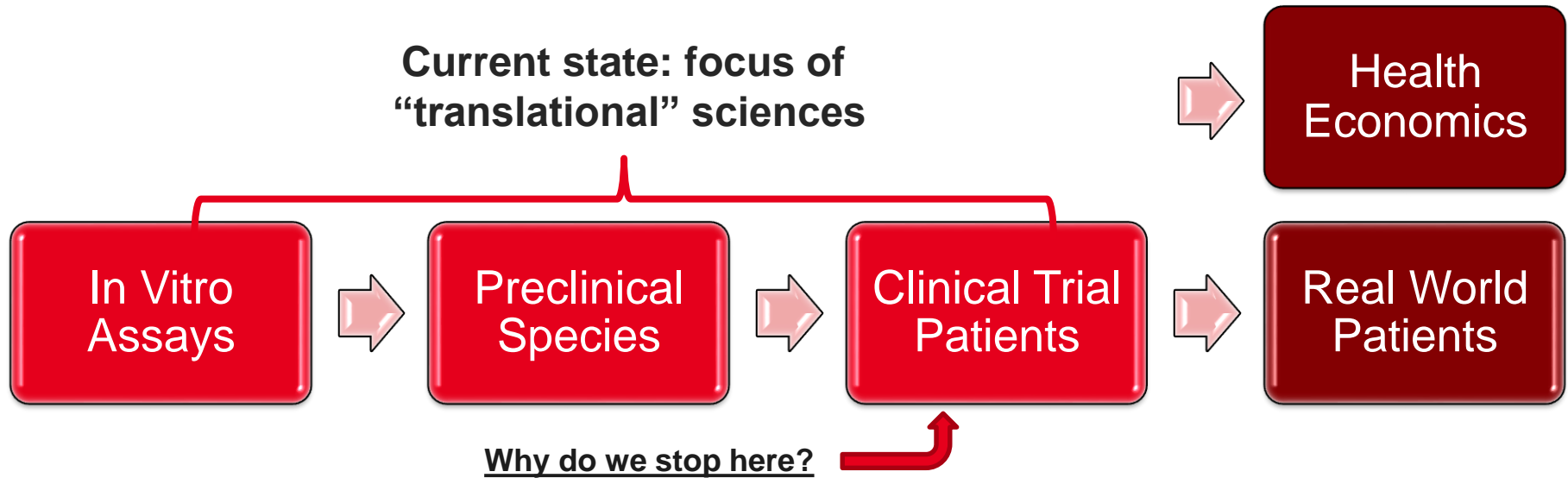


$$\text{Productivity} \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$$

- Expansion of label claims
- Support Differentiation vs. Competitors
- Maximize Clinical Outcomes

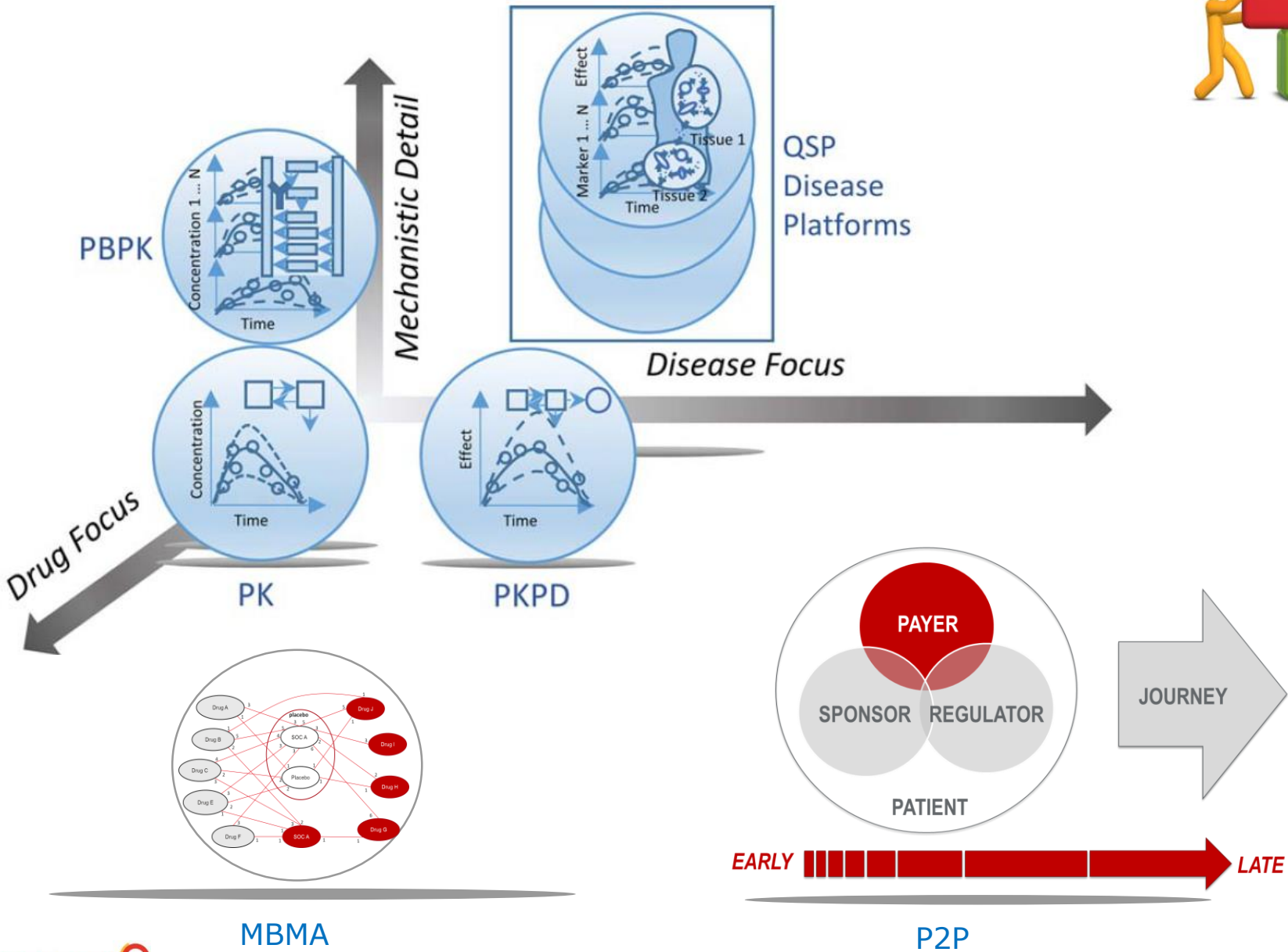
The Future

Translating clinical trial patient (CTP) to real world patient (RWP) and Health Economics



- *Our ultimate goal is to understand the real-world effectiveness of our therapies, which is only partially informed by clinical trial efficacy*
- *Requires robust translation between patient from the randomized clinical trial to the real world patient*

Putting it All Together



P2P - Informing Product Value Proposition

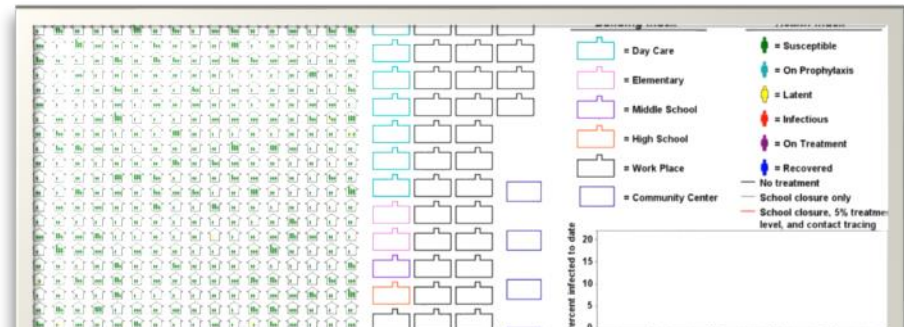
PHARMACOECONOMICS

Interdisciplinary pharmacometrics linking oseltamivir pharmacology, influenza epidemiology and health economics to inform antiviral use in pandemics

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Intervention at 50% drug uptake on cost, life-years (LY) and quality-adjusted LY (QALY) by pandemic scenario. A cost per QALY gained of >0 and <100 000 USD indicates the new intervention is cost effective, and a cost per QALY gained

Emerging Virus Characteristics

- Infectivity
- Virulence
- Resistance

Tshed, β

Comparators (Treatment vs. baseline)	Costs (B)		Costs (B)		Death (A)	Death (B)	Δ Death (A-B)	Δ LYs (A-B)	Δ QALYs (A-B)	Payer perspective		Societal perspective	
	Costs (A) (payer)	(payer - Baseline)	Costs (A) (societal)	(societal - Baseline)						Cost per LY gained	Cost per QALY gained	Cost per LY gained	Cost per QALY gained
Low transmissibility and low severity													
75 mg (A) vs. no treatment (B)	9 225 251	42 578 018	12 998 947	106 995 703	27	439	-412	399	430	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) vs. 75 mg (B)	14 835 713	9 225 251	17 109 649	12 998 947	16	27	-11	10	11	546 753	515 260	400 598	377 524
High transmissibility and high severity													
75 mg (A) vs. no treatment (B)	94 961 869	144 271 547	171 053 550	272 957 742	974	1591	-617	598	629	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) vs. 75 mg (B)	81 019 150	94 961 869	139 379 855	171 053 550	747	974	-227	220	227	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Low transmissibility and high severity													
75 mg (A) vs. no treatment (B)	11 450 971	79 213 439	15 596 974	149 869 617	53	874	-821	795	828	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) vs. 75 mg (B)	16 176 877	11 450 971	18 675 157	15 596 974	32	53	-21	20	21	231 280	223 797	150 642	145 768
High transmissibility and low severity													
75 mg (A) vs. no treatment (B)	54 113 197	77 547 403	123 371 900	194 871 423	489	799	-310	300	330	Cost-saving	Cost-saving	Cost-saving	Cost-saving
150 mg (A) vs. 75 mg (B)	49 689 085	54 113 197	102 809 041	123 371 900	375	489	-114	110	117	Cost-saving	Cost-saving	Cost-saving	Cost-saving

All costs are expressed in 2013 USD.

A, the alternative intervention; B, the baseline intervention.

The Era of Model Informed Drug Development is Here

- Use of modeling approaches to develop drugs is not novel
 - Rather, it is expected
 - At least 15 FDA guidance documents include M&S as best practice
- A pediatric program that does not include M&S is suboptimal
 - Serves as a safeguard to increase likelihood that:
 - Doses utilized are more likely to be safe and effective
 - Optimal doses can be identified as rapidly as possible, exposing fewer patients to suboptimal doses
 - Reducing the number of subjects required for trials
- M&S has proven to be part of the solution to making the enterprise of drug development more financially sustainable
 - Continues to advance and its impact will continue to grow