Towards Faster Adoption of Quantitative Systems Pharmacology (QSP)

Keynote address

QSP Congress Europe 2015

Basel, CH

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The first ever conferences devoted to Quantitative Systems Pharmacology (QSP) have occurred in the last few years.

Congratulations to all of us!

What took so long?

A Focused Early History of the Commercial Field of "QSP"

1992 – 1999 ➤ Demonstration of early impact of "QSP"[1]
- ✓ Aided P&G development of treatment for periodontal disease
- ✓ Averted a very expensive failure in asthma

1996 – 1998+ ➤ Entelos founded, gained numerous early-adopter clients
- ✓ Coincided with founding and growth of Pharsight (PK/PD company)
- ✓ Dramatically different approaches to market development

2002 ➤ Rosa & Co. founded as a 2nd-generation "QSP" company

2013 – 2014 ➤ Rosa & Co. acquires Entelos' service business assets

If "QSP" was impactful 20+ years ago, why has its adoption been much slower than PK/PD?

[1]http://www.forbes.com/forbes/2001/0108/234.html

Agenda

> **What is QSP? Why has mainstream adoption been "slow"?**

> QSP: a peer function to preclinical and clinical development?

> So what? Towards faster adoption of QSP

*Reviewed in Ramanujan, Gadkar, & Kadambi, "Quantitative Systems Pharmacology: Applications and Adoption in Drug Development" in *Systems Pharmacology and Pharmacodynamics*, Eds Mager & Kimko, in preparation.
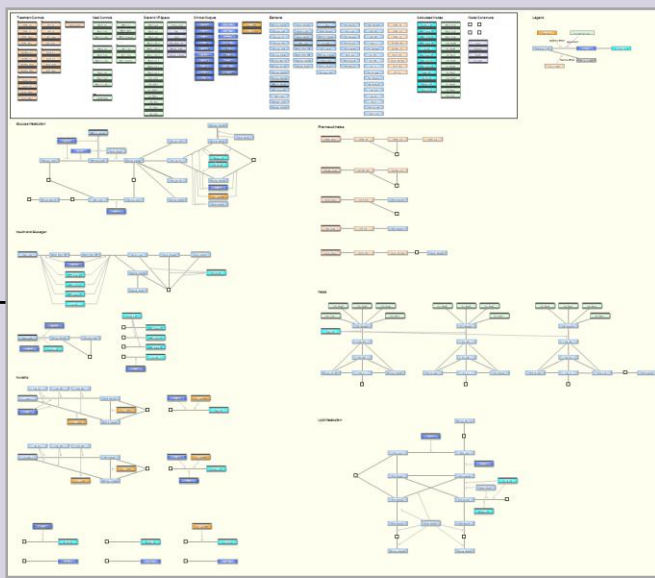
Features of QSP-Style Modeling and Simulation

- ✓ Includes a coherent mathematical representation of drug pharmacology and the key biological mechanisms underlying a disease

- ✓ Integrates diverse data and biological knowledge or hypotheses

- ✓ Includes biological detail that is necessary and sufficient (i.e., "fit") for a purpose

- ✓ Allows quantitative simulation of biologic outcomes given a set of conditions

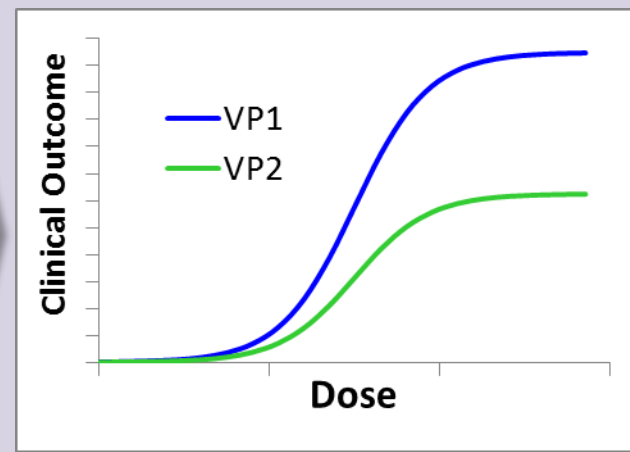These commonalities are reflected in Rosa's PhysioPD™, one version of QSP

PhysioPD Platforms integrate extensive information and hypotheses to enable investigation of the impact of uncertainty.
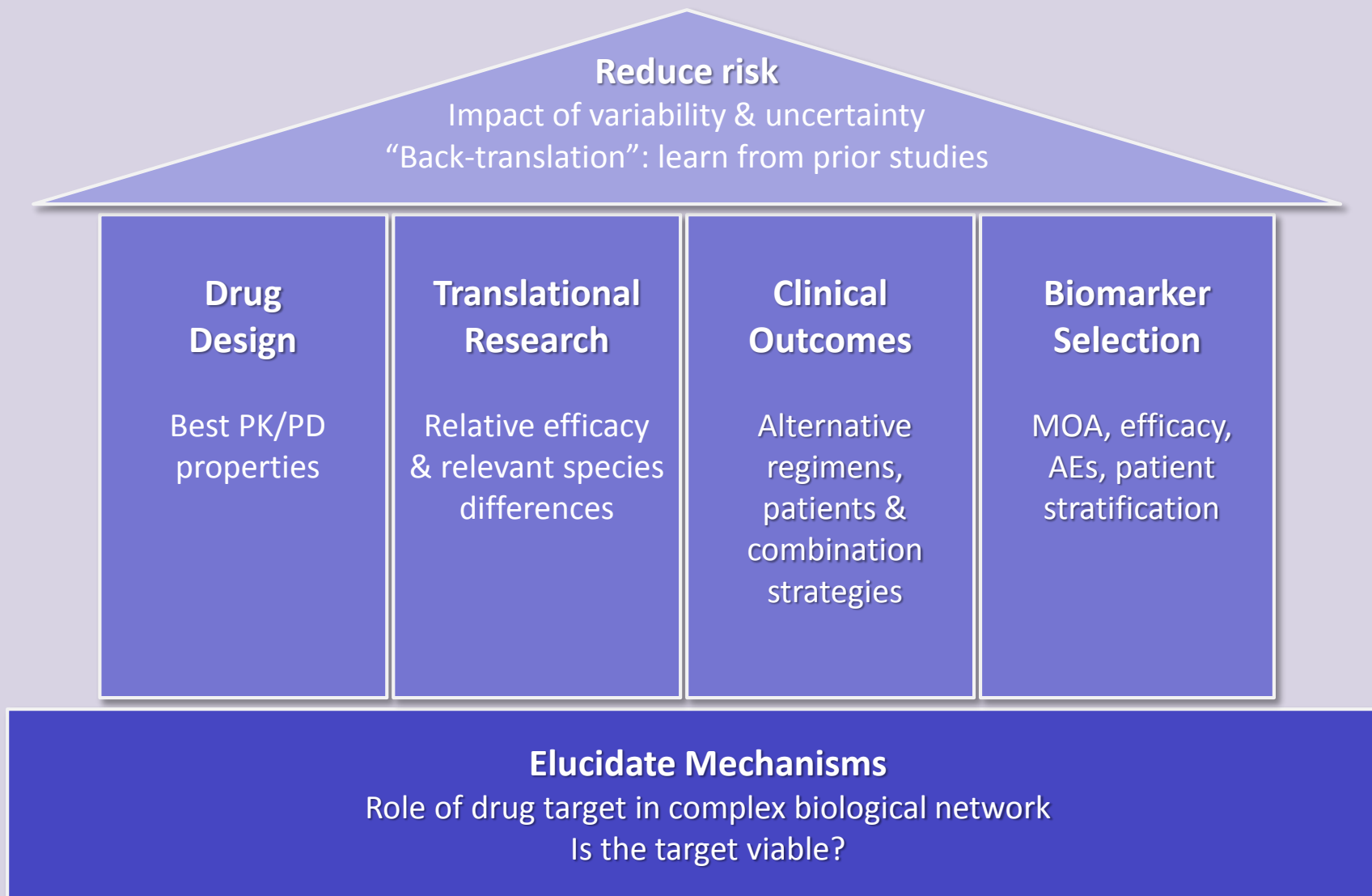
Physical Laws (known)

Healthy & Disease Physiology (partly known)

Target(s) & Drug Mechanism(s) (partly known)

Drug Pharmacology (usually known)

PhysioPD Research Platform (With Hypotheses)

Effect of Alternate Hypotheses on Research Results

Clinical Outcome vs. Dose
— VP1
— VP2

Preclinical and Clinical PhysioPD Research Applications

Reduce risk
Impact of variability & uncertainty
"Back-translation": learn from prior studies

Drug Design

Best PK/PD properties

Translational Research

Relative efficacy & relevant species differences

Clinical Outcomes

Alternative regimens, patients & combination strategies

Biomarker Selection

MOA, efficacy, AEs, patient stratification

Elucidate Mechanisms
Role of drug target in complex biological network
Is the target viable?

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QSP works.
Not a Technical Question; Now a Philosophical One

Pipeline Stage	Primary application	Therapeutic Area Focus	Reference
Drug Design	Target identification	Oncology	Schoeberl et al. 2009
	Target identification	Pain	Benson et al. 2013
	Combination Rx	Oncology	Kirouac et al. 2013
	Regimen optimization & combination efficacy	Oncology	Orrell and Fernandez 2010
	Target evaluation	Cardiovascular	Lu et al. 2014
Translational Research	Immunogenicity	Immunology	Chen et al. 2014b
	Combination Rx	CNS	Geerts et al. 2013a
Clinical Outcomes	Combination Rx & subpopulation responses	Cardiovascular	Gadkar et al. 2014
	Efficacy and safety	Cardiovascular	Dziuba et al. 2014; Peskin et al. 2011
	Pre-clinical screening	Cardiac arrhythmia	Davies et al. 2012
	Clinical prediction	Liver toxicity	Howell et al. 2014; Shoda et al. 2014; Leil and Bertz 2014
Patient Stratification and Biomarkers	Exploratory biomarker	Osteoporosis	Visser et al. 2014
	Clinical biomarker identification	RA; Cardiovascular	Rullmann et al. 2005; Kadambi et al. 2011

Why has adoption of QSP been slower than PK/PD?

Select Mainstream Adoption Drivers[2]	PK/PD 1997-2011	"QSP" 1996-2011	"QSP" 2011-2015
Evidence of Impact	✓	✓	✓
Awareness in Mainstream - Technical Buyer - Ultimate Consumer	✓ ✓	✓	✓ ✓
"Killer App"	✓		✓
Ease of Purchase/Use (various)	✓		✓
Regulatory Integration	✓	✓	✓
Internal Change Leadership	✓	✓	✓
Quality Assurance	✓		✓
Philosophical Fit	✓		✓

[2]The definitive analysis of mainstream market adoption is Crossing the Chasm, by Geoffrey Moore.

Agenda

➤ What is QSP? Why has mainstream adoption been "slow"?

➤ QSP: a peer function to preclinical and clinical development?

➤ So what? Towards faster adoption of QSP

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Thought Experiment
Imagine physics without theoretical physicists.

It's hard to imagine because it's absurd: theory is indispensable to the field. But…

Thought Experiment
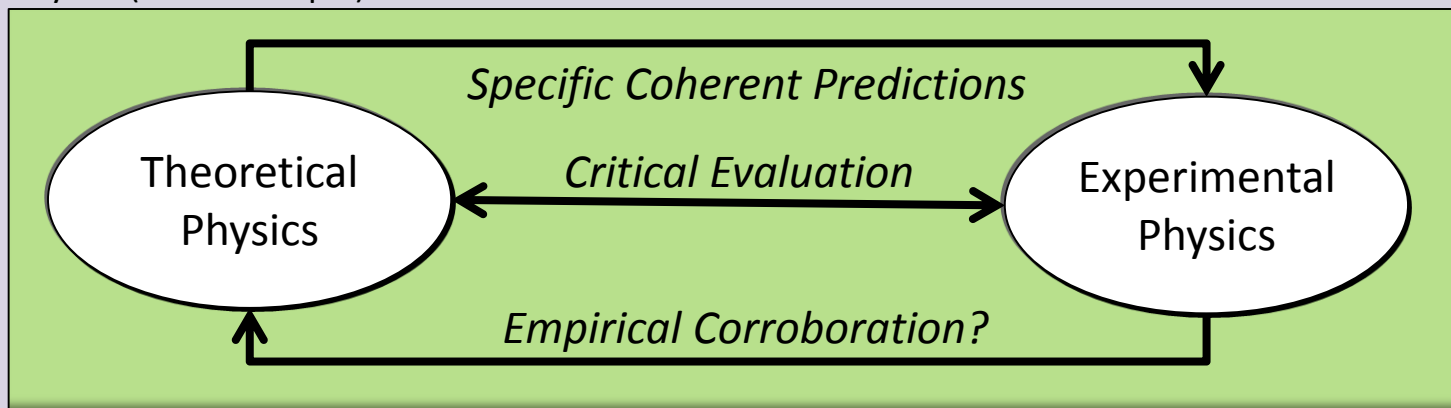## *How would physics function without theoretical physics?*

- Smart people would imagine differing mental models.

- Vague statements of hypotheses; unclear link between hypothesis & outcome

- Experimentalists would design studies to test these vague hypotheses.

- Many results generated; hard to interpret in light of mental models alone

- Ambiguity in results leads to many "successes", but limited learning[3]

[3]Thomas Kuhn, <u>The Structure of Scientific Revolutions, 50th Anniversary Edition</u> (2012). See in particular p 65. and p. 165.
Karl Popper, <u>Conjectures & Refutations</u> among many other works.

Why can physics provide dramatic improvements in our understanding of the universe, but ~50% of Phase III trials fail?

Physics (as an example)

Specific Coherent Predictions

Theoretical Physics — *Critical Evaluation* — **Experimental Physics**

Empirical Corroboration?

Mathematics is a critical tool for hypothesis, prediction, and integration.

Pharmaceutical Science

Specific Coherent Predictions?

Mental Model(s) — *Critical Evaluation?* — **Studies & Trials**

Lots of Data
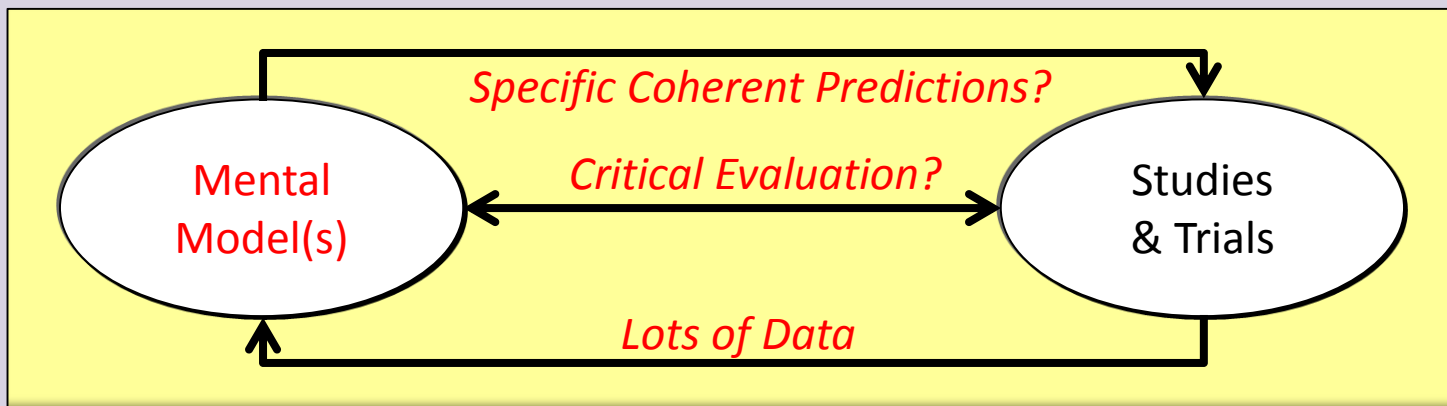
Disease physiology and pharmacology requires a more quantitative approach.

QSP is the foundation for a modern scientific method in pharmaceutical science.
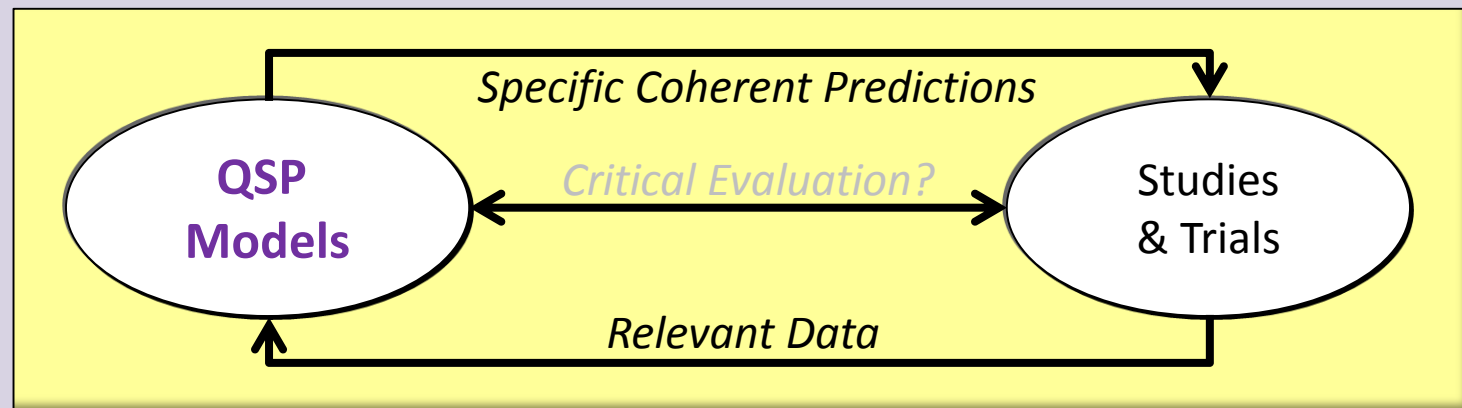
In a healthy scientific field, theory and experiment are <u>peer</u> functions.

QSP's Role in a Modern Scientific Method for Pharmaceutical Drug Development

1) <u>ENHANCE UNDERSTANDING</u>

   – Integrate diverse relevant information

   – Highlight (apparent) inconsistencies in extant results

   – Enable efficient communication via a common framework

2) <u>FOCUS EXPERIMENTATION</u>

   – Identify and guide most informative experiments

   – Provide specific predictions of outcomes to test empirically

   – Aid interpretation of data and evaluation of hypotheses

3) <u>ENABLE ARTICULATION</u>

   – Derive non-obvious "truths" that can be taken as given

   – Provide clear boundaries within which these "truths" are valid

   – Replace expensive studies or trials

➢ What is QSP? Why has mainstream adoption been "slow"?

➢ QSP: a peer function to preclinical and clinical development?
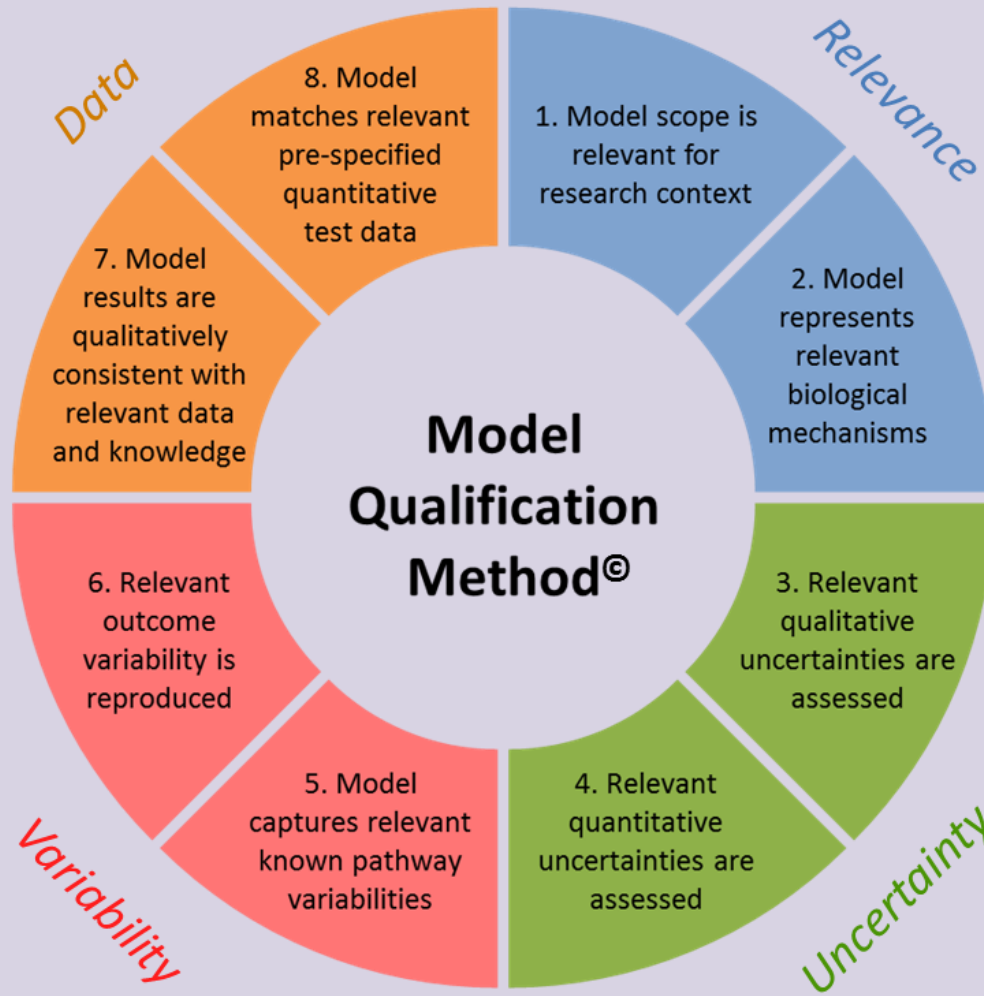
➢ So what? Towards faster adoption of QSP

Action Agenda for Accelerating
Mainstream Market Adoption of QSP

Select Mainstream Adoption Drivers	QSP 2015 - 2020	Action Item
Evidence of Impact	☑	
Awareness in Mainstream		
- Technical Buyer	☑	
- Ultimate Consumer	☐	
"Killer App"	☐	
Ease of Purchase/Use (various)	☑	*E.g., transparent, fit-for-purpose models, non-proprietary software*
Regulatory Integration	☐	
Internal Change Leadership	☐	
Quality Assurance	☑	*Emerging standards for QSP model qualification*
Philosophical Fit	☐	

Rosa's Model Qualification Method is an exemplar method for ensuring model "quality" (fitness for purpose).
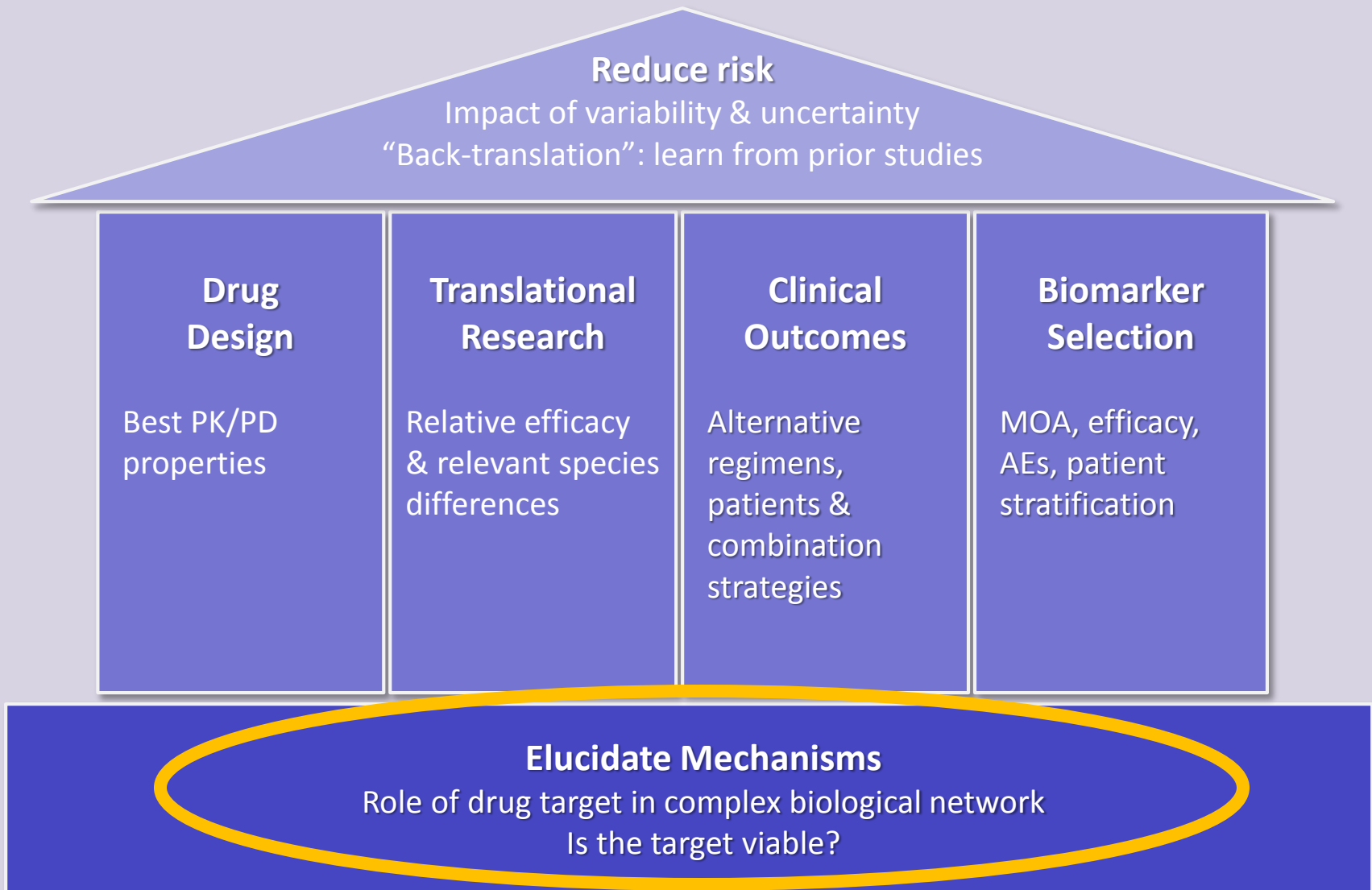

Ref: Friedrich et al. (2011)

Action Agenda for Accelerating Mainstream Market Adoption of QSP

Select Mainstream Adoption Drivers	QSP 2015 - 2020	Action Item
Evidence of Impact	☑	
Awareness in Mainstream		*Market to ultimate consumers "horizontally" and "vertically"*
- Technical Buyer	☑	
- Ultimate Consumer	☑	
"Killer App"	☑	*Emphasize "killer app" & benefits, message relentlessly*
Ease of Purchase/Use (various)	☑	
Regulatory Integration	☐	
Internal Change Leadership	☐	
Quality Assurance	☑	
Philosophical Fit	☐	

The elucidation of mechanisms is QSP's "Killer App".

Reduce risk
Impact of variability & uncertainty
"Back-translation": learn from prior studies

Drug Design	**Translational Research**	**Clinical Outcomes**	**Biomarker Selection**
Best PK/PD properties	Relative efficacy & relevant species differences	Alternative regimens, patients & combination strategies	MOA, efficacy, AEs, patient stratification

Elucidate Mechanisms
Role of drug target in complex biological network
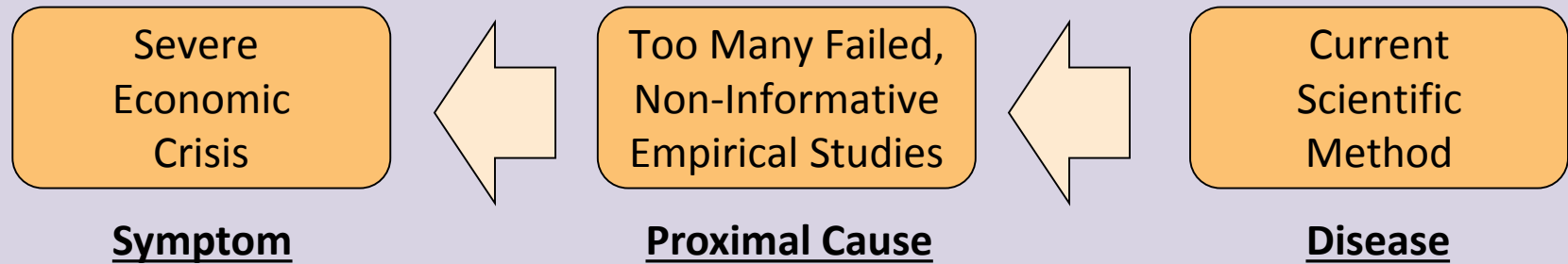Is the target viable?

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Action Agenda for Accelerating Mainstream Market Adoption of QSP

Select Mainstream Adoption Drivers	QSP 2015 - 2020	Action Item
Evidence of Impact	☑	*Market to ultimate customers: Horizontally and vertically*
Awareness in Mainstream - Technical Buyer - Ultimate Consumer	☑ ☑	
"Killer App"	☑	*Emphasize "killer app" & benefits, message relentlessly*
Ease of Purchase/Use (various)	☑	*Push for routine use of QSP in sponsor-agency discussions*
Regulatory Integration	☑	
Internal Change Leadership	☑	*Deliberate, broad, multi-step, multi-year process[3]*
Quality Assurance	☑	
Philosophical Fit	☑	*Inculcate belief: QSP is integral to pharmaceutical science*

[3]See, for example, John P. Kotter, Leading Change.

QSP may be a large part of a potential "cure" for the challenges being faced by the pharmaceutical industry.

Severe Economic Crisis	←	Too Many Failed, Non-Informative Empirical Studies	←	Current Scientific Method
Symptom		**Proximal Cause**		**Disease**

Organization
QSP is a peer to
to pre-/clinical functions

"CURE"
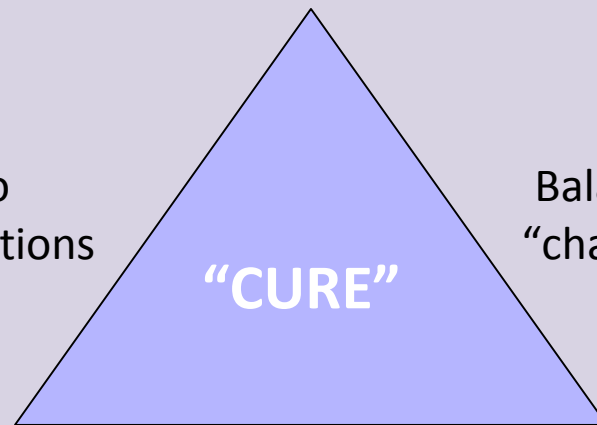
Incentives
Balance over-riding
"championship" bias

Modern Scientific Method
QSP is integral to pharmaceutical science

Taken together, these three changes represent a profound <u>cultural</u> change in the approach to (early) drug development.

Modern Pharmaceutical R&D Culture

Organization

CULTURAL CHANGE

Incentives

Modern Scientific Method
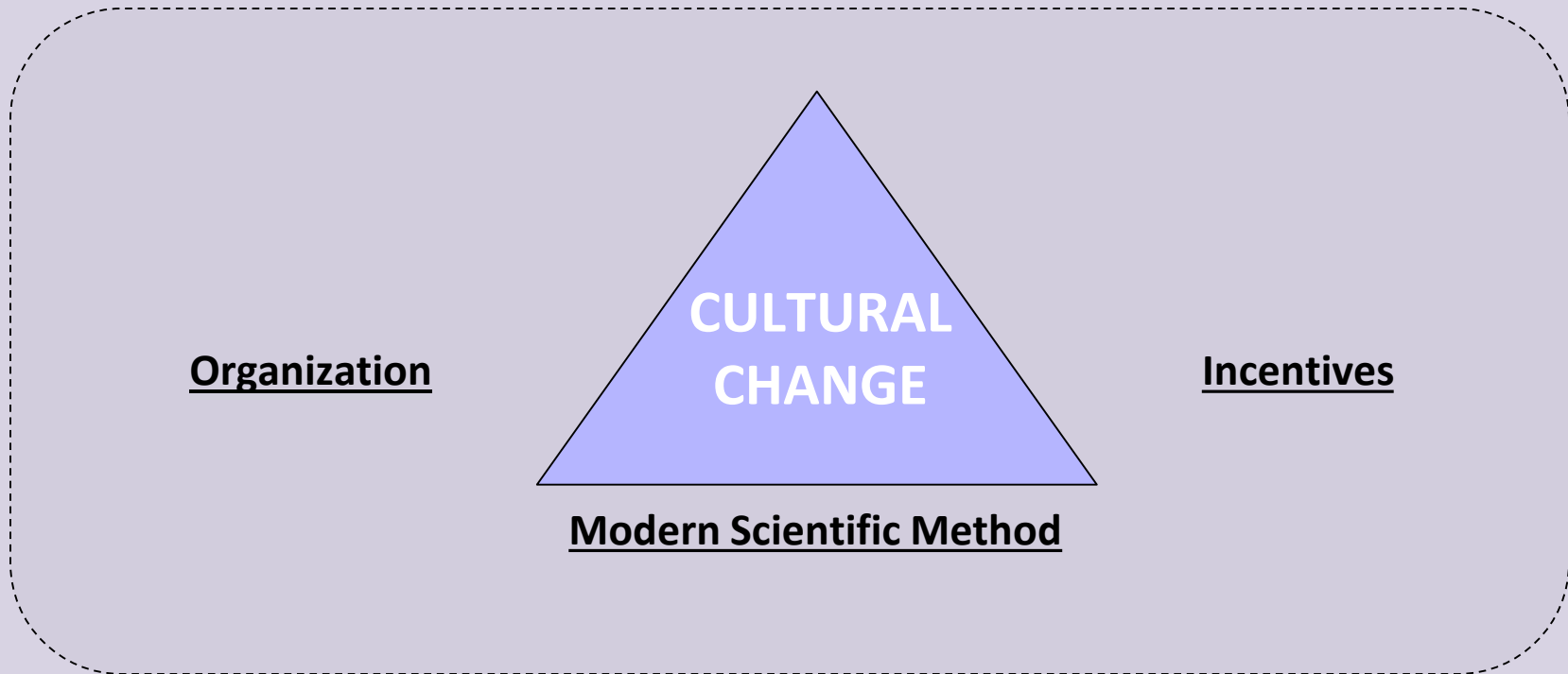
Those that can first achieve this will have significant competitive advantage in R&D – and the implications for long-run value creation that follow.

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The leadership of those here today will determine the future success of QSP approaches.

- QSP works. That should not be in question.

- The task ahead is to expand adoption by the mainstream market.

- We have proposed an action agenda to continue to move this process forward.

- A key element is a cultural change towards greater emphasis on QSP.

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