A Return to Rational CNS Drug Development: De-risking P3 Investments through Rigorous Early Phase Drug Evaluation
ISCTM Autumn Scientific Meeting, October 1, 2013

Steven J. Romano, MD
Senior Vice President
Medicines Development, Pfizer

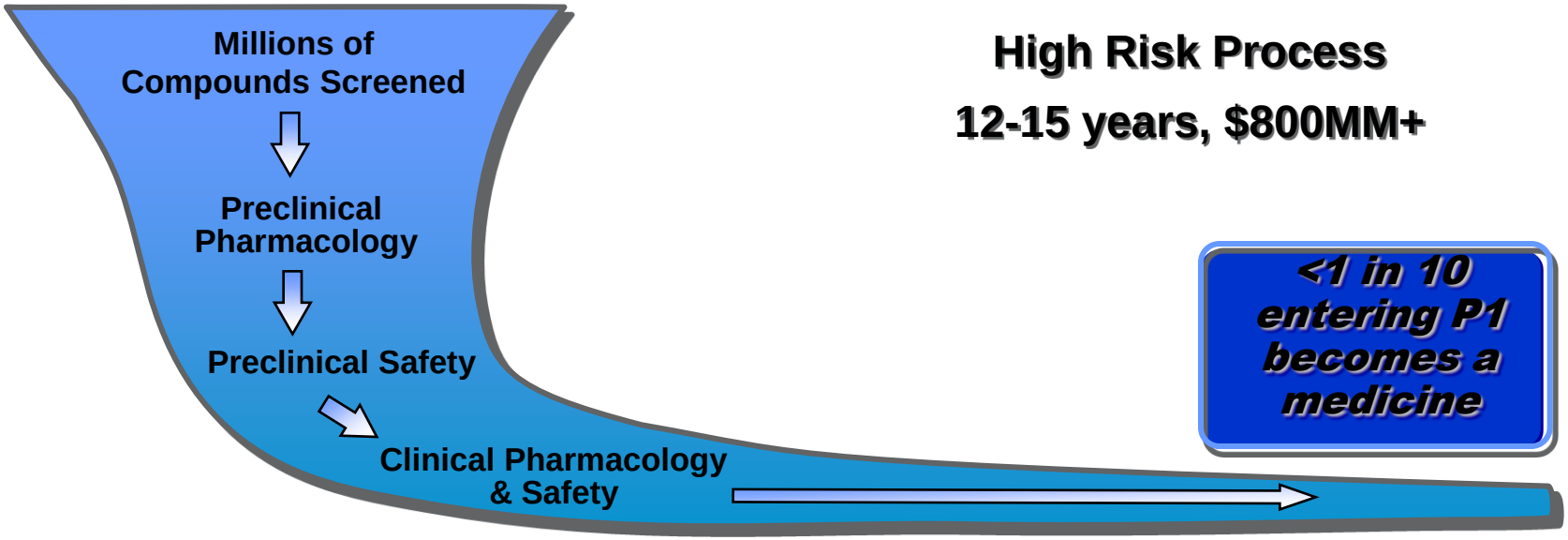
Disclosure/Conflict of Interest Statement

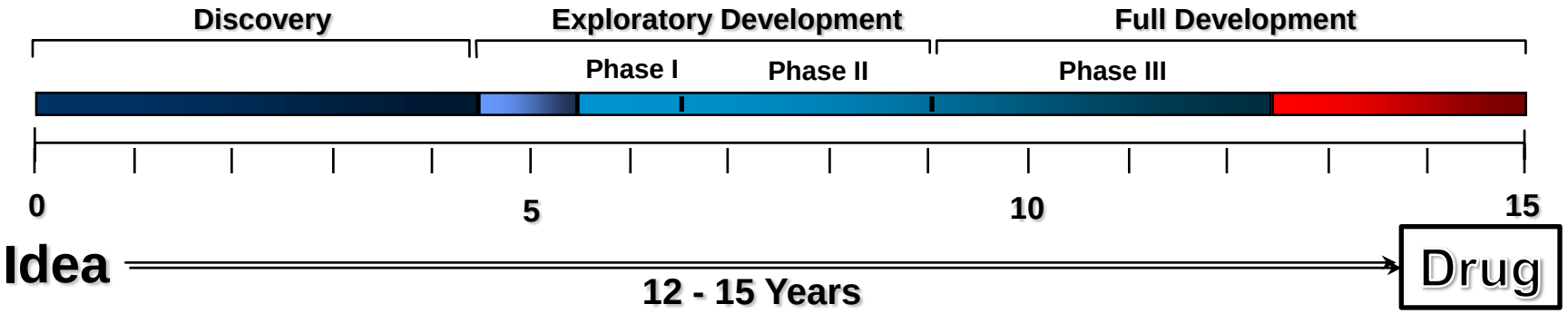
- Full-time employee of Pfizer, Inc

Key Points

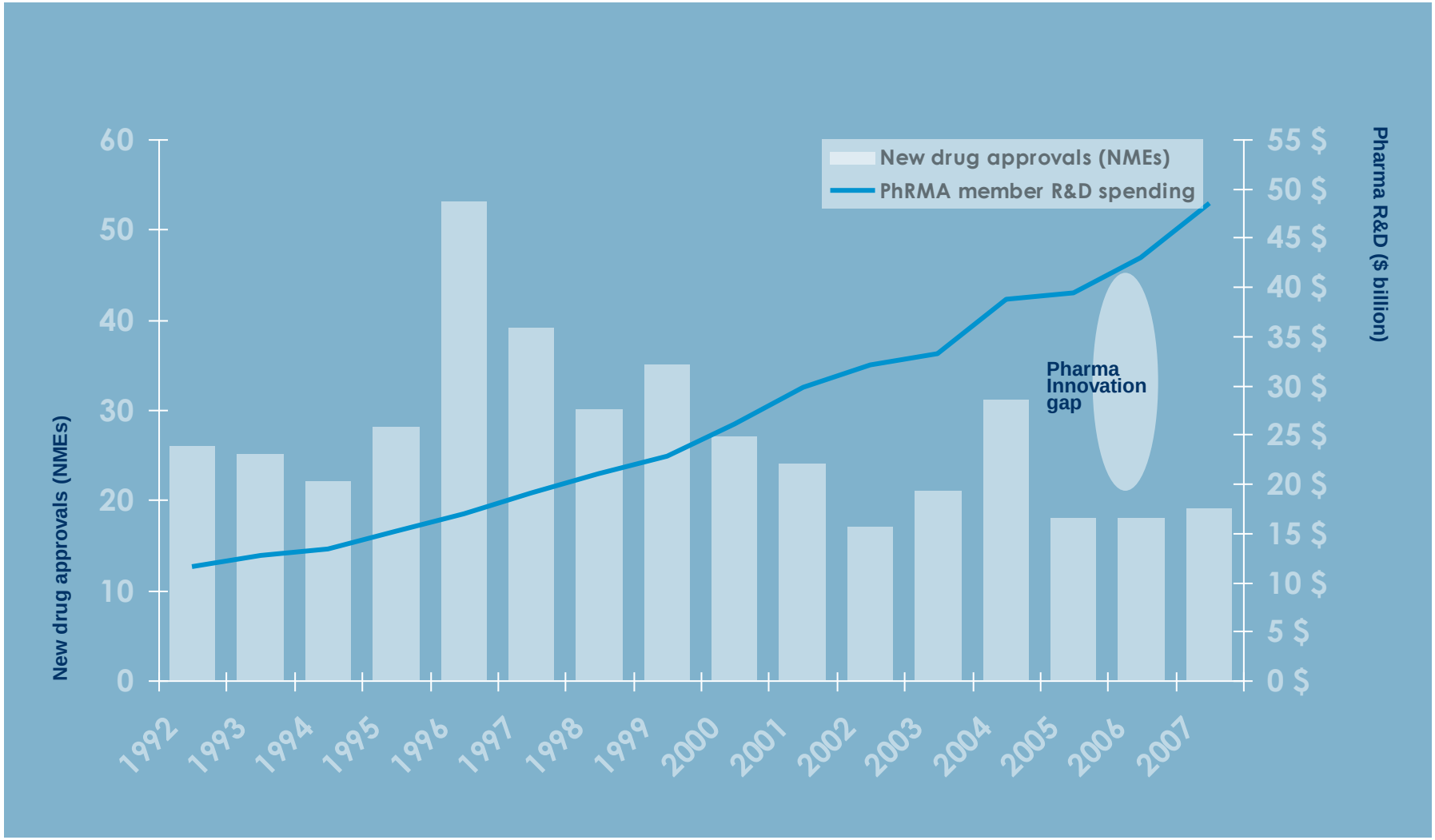
- Drug development is a risky and costly business
- R&D productivity decreased through 2000's
- Investment shifting to areas of greatest need
  - Novel targets/mechanisms carry greater risk
- Need to better understand human biology of CNS conditions to advance innovative therapies
- Critical to adhere to rigorous drug development methodology (POM, dose selection, POC)

Developing New Medicines is a Risky, and Costly, Business



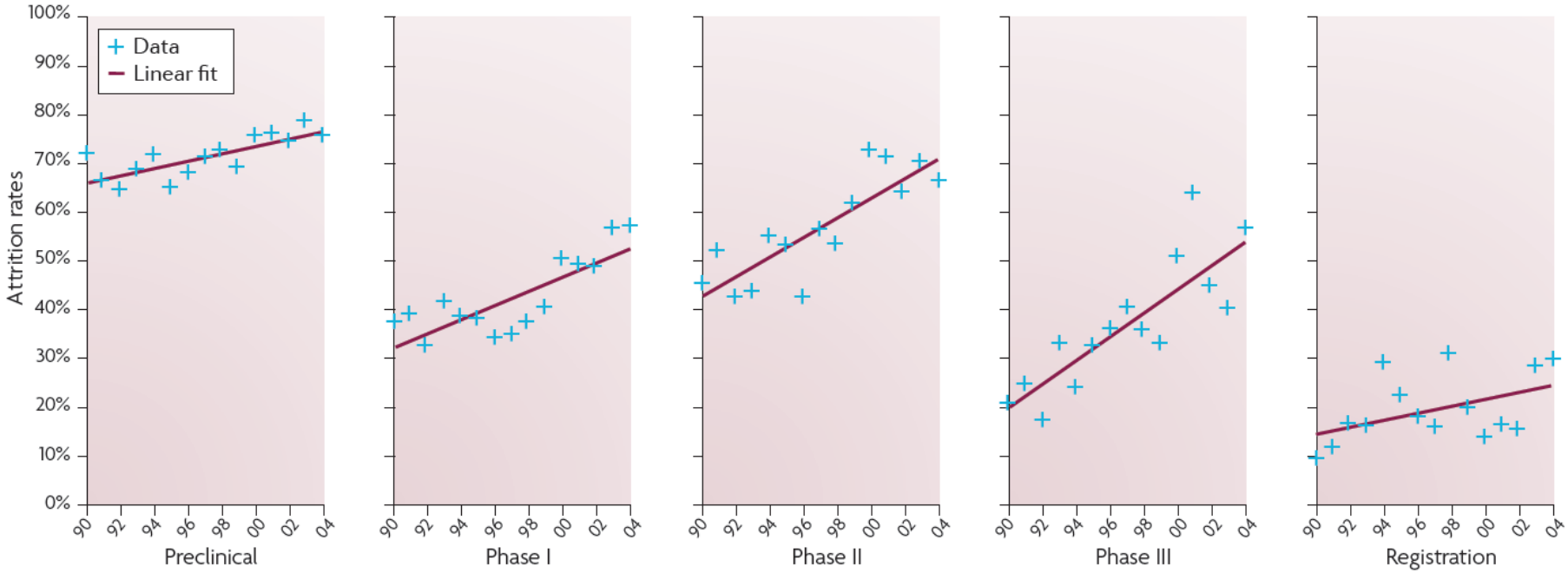


Despite Significantly Increased Spending, R&D Productivity has Declined



Source: Burril & Company, US Food and Drug Administration

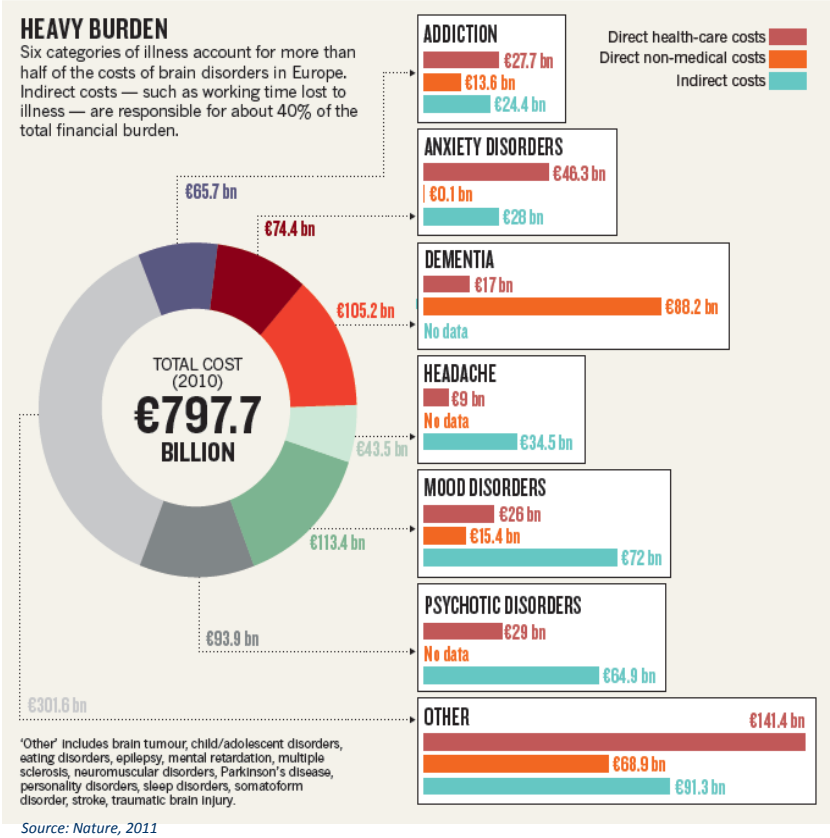
Attrition Rates Have Increased at Each Stage of Development



Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov. 2011 Jun;10(6):428-38.

CNS Disease Burden: A Compelling Reason to Invest

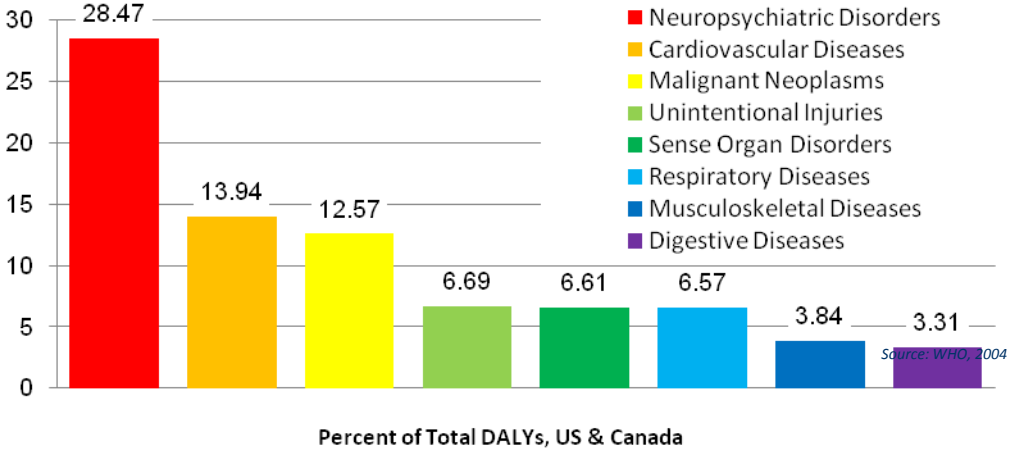
Central Nervous System (CNS) Diseases Cost Europe $1 Trillion per Year



Source: Nature, 2011

Burden of Disease: Disability-Adjusted Life Years (DALY)

(# of years lost due to ill-health, disability or early death)



Challenges in CNS Drug Development

- Brain inviolate, biology unclear, genetics complex
- Few validated molecular targets
  - Molecular targets for major pharmacological classes (antidepressants, anxiolytics, antipsychotics), decades old
  - Until recently, we've been looking under the same stones!
- Few compelling biomarkers
- Most animal models not true "disease models"
  - Used to screen for known pharmacology
  - Evaluate effects on behavioral dimensions (anxiety, apathy, anhedonia) that may not readily translate to relevant condition in humans

Is Nosology Constraining Innovation?

- Diagnostic system is phenomenological, based on observed or reported symptoms/complaints
- Classification is not biologically determined (though clinically useful)
- Co-morbidity more the rule than the exception
- Heterogeneity of patient populations confounds signal detection
- Since DSM informs regulatory pathway, development has been focused on currently defined syndromes

Signs of Change

- “The National institute of Mental Health (NIMH) has not changed its position on DSM-5…It is increasingly evident that mental illness will be best understood as disorders of brain structure and function that implicate specific domains of cognition, emotion, and behavior. This is the focus of the NIMH’s Research Domain Criteria (RDoC) project…” *Insel/Lieberman News Release, APA, May 14, 2013*

Breakthroughs in CNS Drug Development Require Rational Approaches

- Explication of human biology
- Deconstruction of complex behavioral syndromes
  - Syndromes are complex phenotypes
  - Syndromes are polygenic and multi-factorial
- Identification of endophenotypes to inform gene analysis, clarify genetic determinants, and identify relevant targets
- Development of more relevant animal models to facilitate translational efforts

In Conclusion: Have We Reached an Inflection Point?

- Neuroscience basic research knowledge exploding
  - Preclinical biology, genetics
- Human experimental biology platforms being refined/incorporated into development paradigms
  - Neuroimaging, biomarker development, quantitative neuropsych
- Clarification of functional domains/relevant neurocircuitry should allow for more effective de-risking in earlier phases of development
- Above trends should positively influence Industry's investment posture

A Return to Rational CNS Drug Development

- Part 1: Translational and early Development Strategies and Tools
  - Doug Feltner and Bill Potter
- Part 2: Designing the Right Series of Experiments
  - Atul Mahableshwarkar and Gary Sachs
- Part 3: Operational Challenges
  - Carla Canuso and Amir Kalali