
Silver Linings Playbook: The Positive Side of Negative Trials

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Disclosure/Conflict of Interest Statement

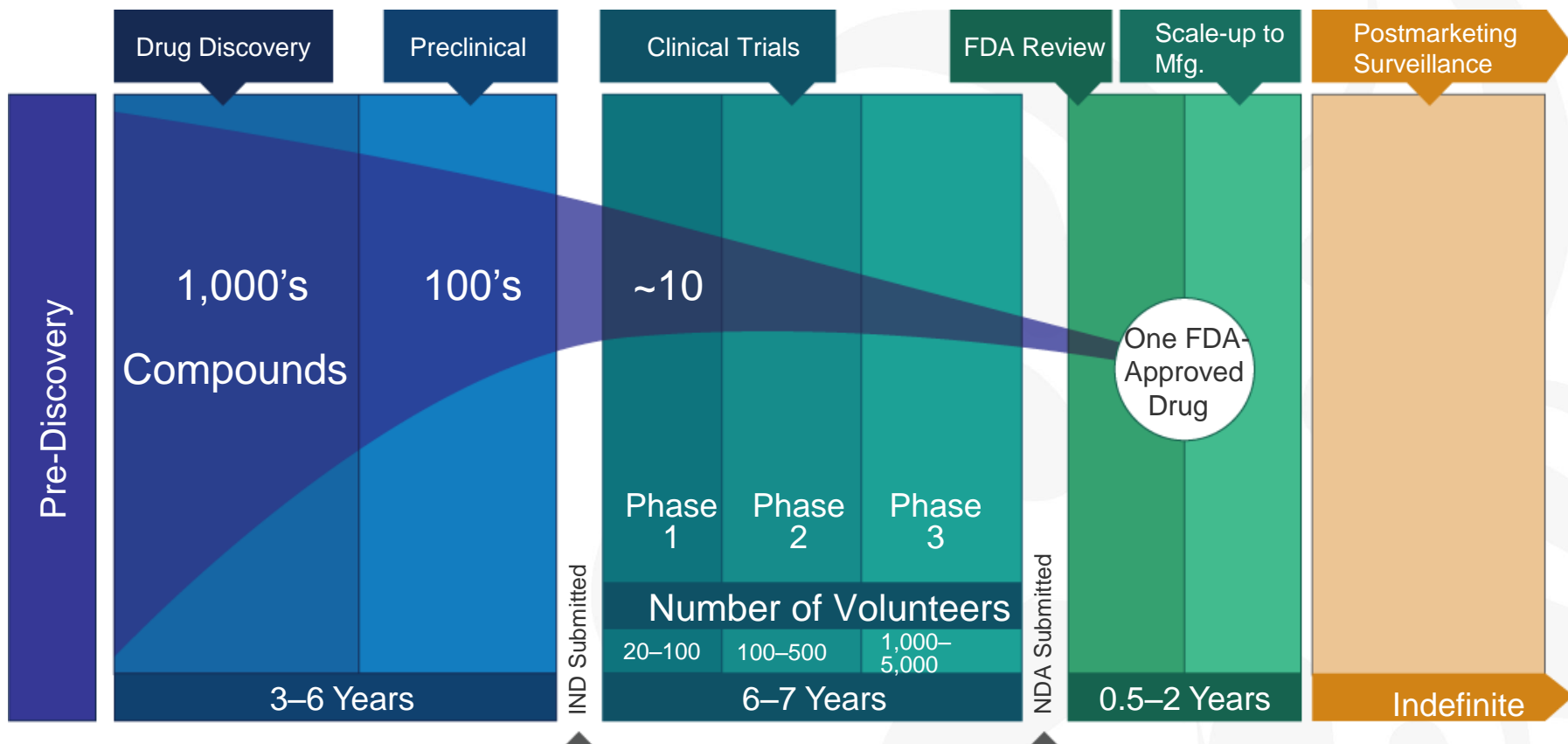
- Full-time employee of Mallinckrodt Pharmaceuticals

Agenda

- Problem:
 - Drug development is amongst riskiest, costliest businesses
 - R&D productivity decreased through 2000's
 - Drug development ecosystem evolving, operational complexity increasing
 - CNS development is particularly challenging
- Solution:
 - Explication of human biology of CNS conditions necessary to confidently advance innovative therapies
 - Critical to adhere to rigorous drug development methodology in both early (POM, dose selection, POC) and late phase development
- Reflections on late stage failures

Pharmaceutical R&D is Risky

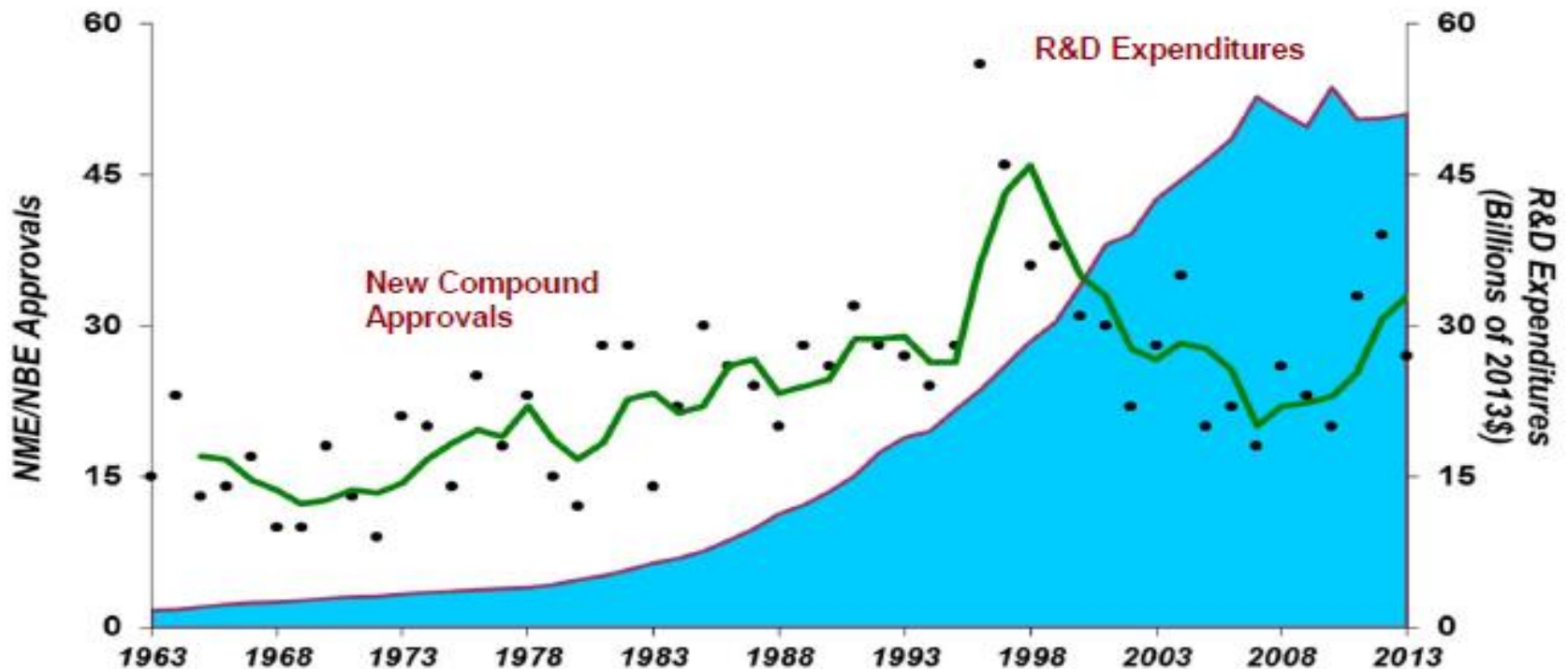
One of the Highest Risk Processes: 10–15 years



Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org; DiMasi and Grabowski, The Cost of Biopharmaceutical R&D: Is Biotech Different?, *Managerial and Decision Economics* 28 (2007): 469-479.

R&D Spending has Outpaced Productivity

New Drug and Biologics Approvals and R&D Spending

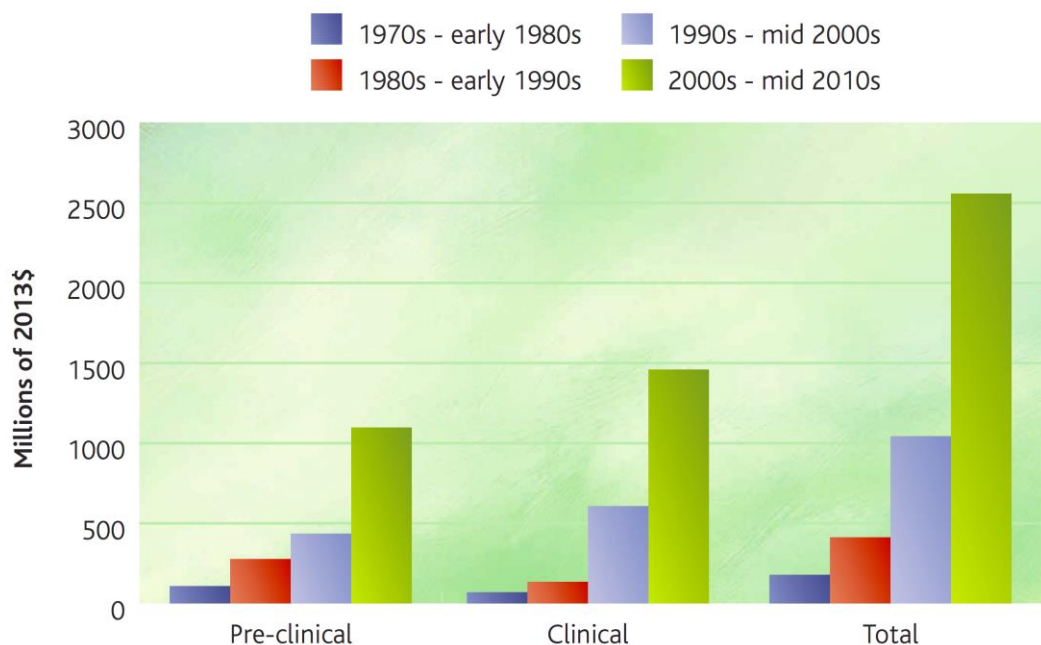


R&D expenditures are adjusted for inflation; curve is a 3-year moving average for NME/NBEs
Sources: Tufts CSDD; PhRMA, 2014 Industry Profile

New Drugs Now Cost Nearly \$2.6B, Shaping Direction of Sponsors' R&D Efforts

Driven mainly by increased out-of-pocket costs & higher failure rates

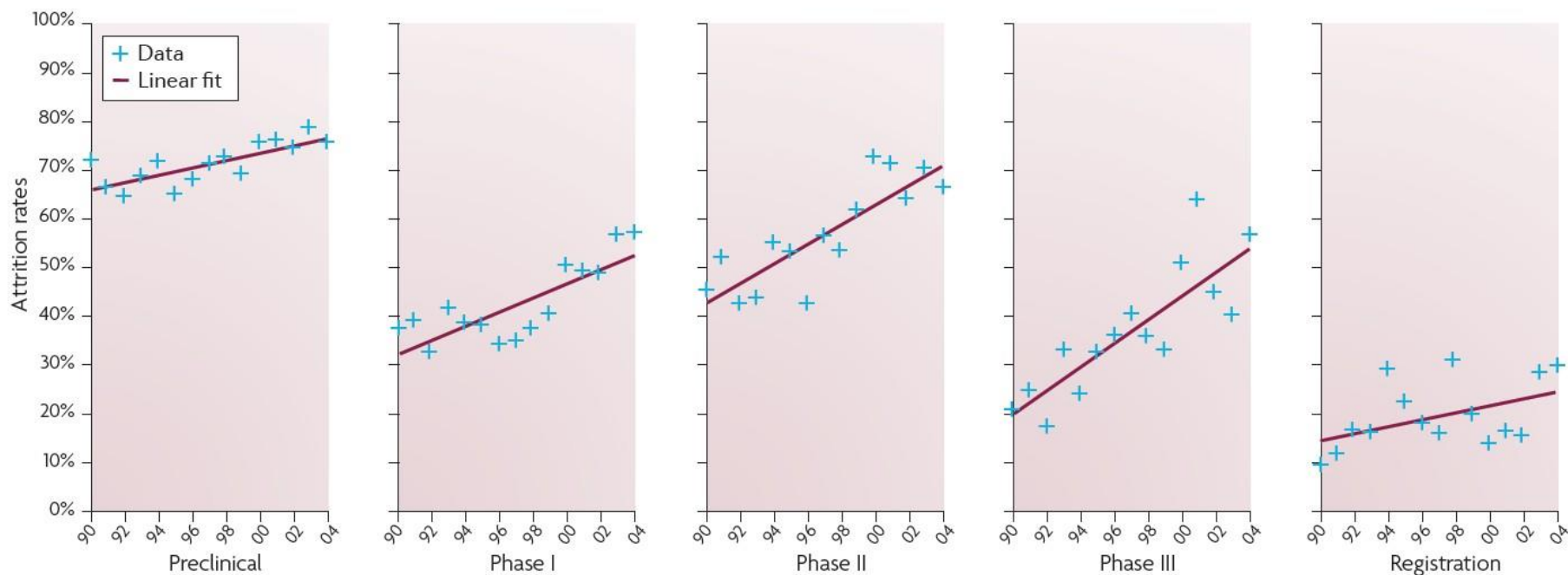
Average Cost to Develop and Win Marketing Approval for a New Drug



- Key drivers of increased clinical costs include clinical trial complexity, larger clinical trial sizes, higher cost from medical sector, testing of comparator drugs to accommodate payer demands for comparative effectiveness data.
- The changes in overall time for development & regulatory approval only has modest effect on increase in R&D costs

Source : Tufts Center for the Study of Drug Development

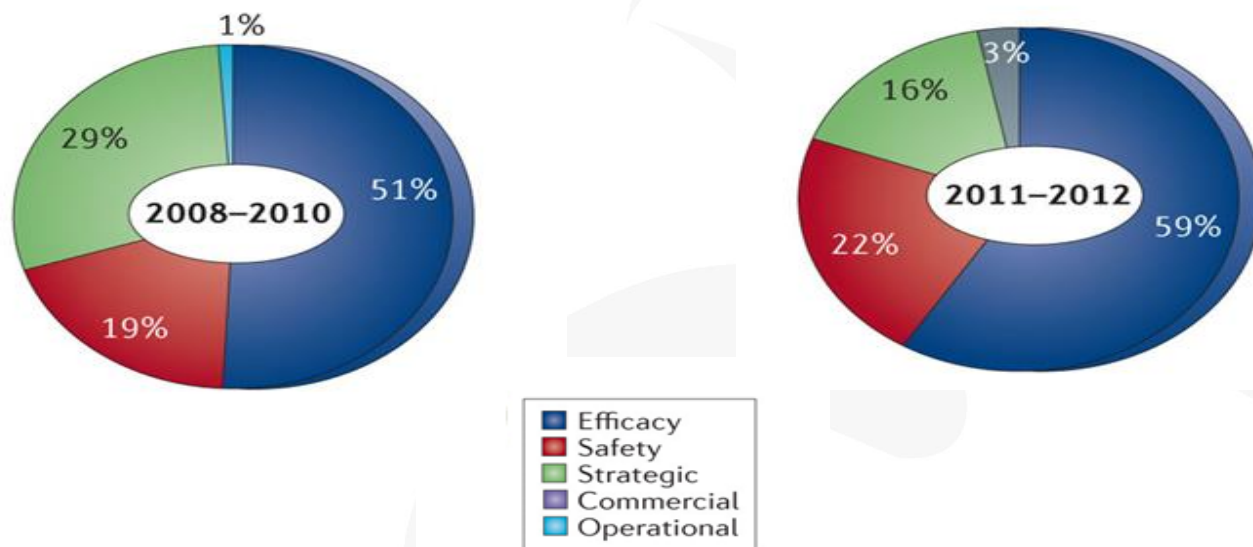
Attrition Rates Have Increased Across Each Phase of Development



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

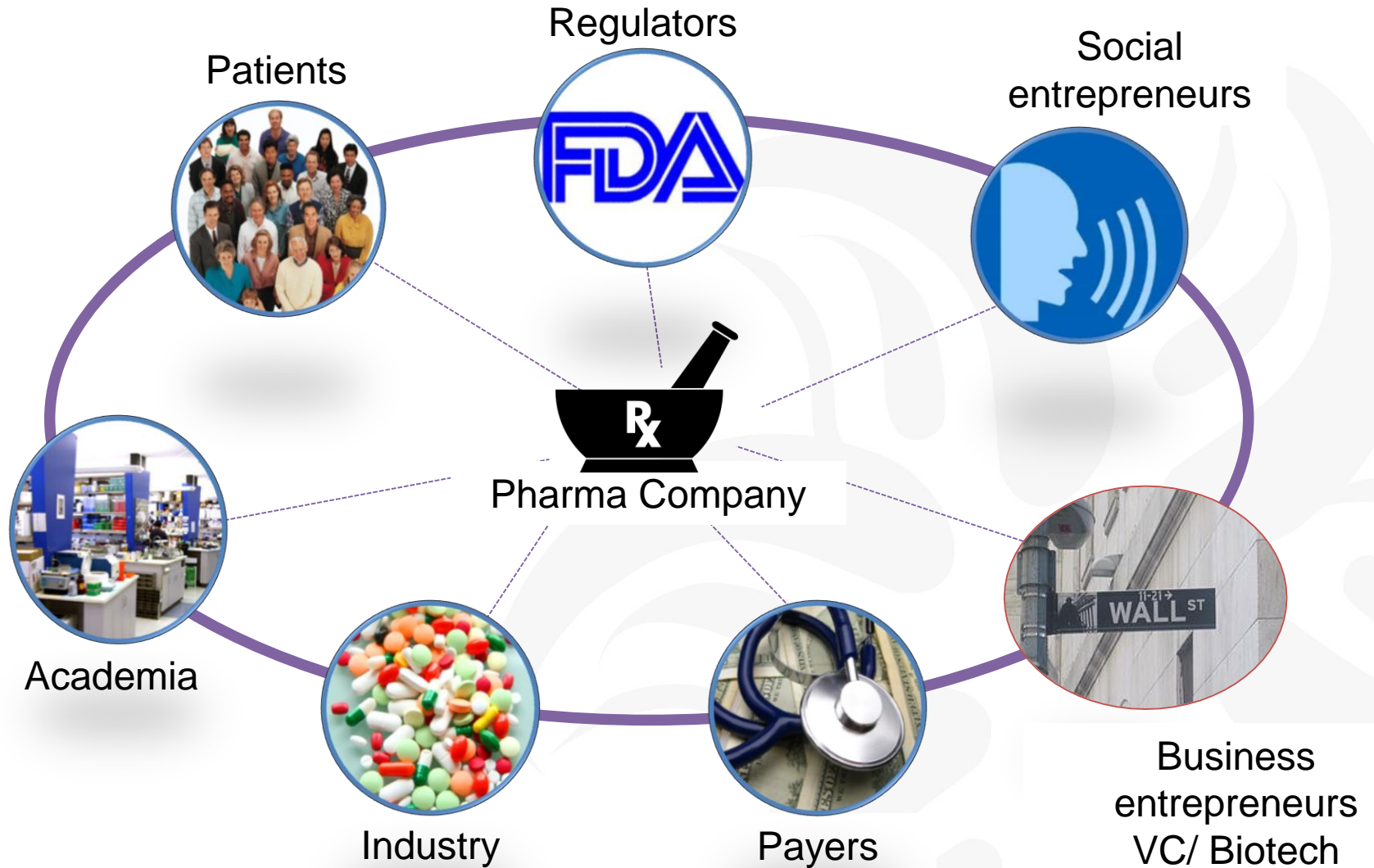
Phase II Failure Rates, in Particular, Impact Productivity

Phase II success rates remain low (~20%) with insufficient efficacy as most frequently cited reason for failure



The 148 failures are divided according to reason for failure when reported (105 drugs)

Drug Development Ecosystem has become more Complex and Demands Collaboration



Operational Challenges Conspire against Success



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Tufts Center for the Study of Drug Development

TUFTS UNIVERSITY

Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

High turnover, protocol noncompliance plague the global site landscape

Half of all unique investigators in 2013 were first-time 1572 filers

- The number of active unique principal investigators (PIs) conducting FDA regulated clinical trials worldwide has reached a record of nearly 40,000, but growth is slowing.
- North America continues to lose its share of active global FDA-regulated PIs.
- The numbers of active PIs in India and China, countries once expected to see the most dramatic relative growth, have declined by 16% and 5%, respectively.
- Investigator turnover has increased dramatically: half of all unique PIs who filed a form 1572 in 2009 have yet to file again, up from 40% four years ago.
- The number of annual CDER inspections of sites outside the United States has tripled since 2001, while declining by 36% inside the U.S.
- Protocol noncompliance, the area of performance deficiency that has grown the most during the past decade, accounted for 46% of all investigative site deficiencies.

Specific 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

Nosology is 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...”

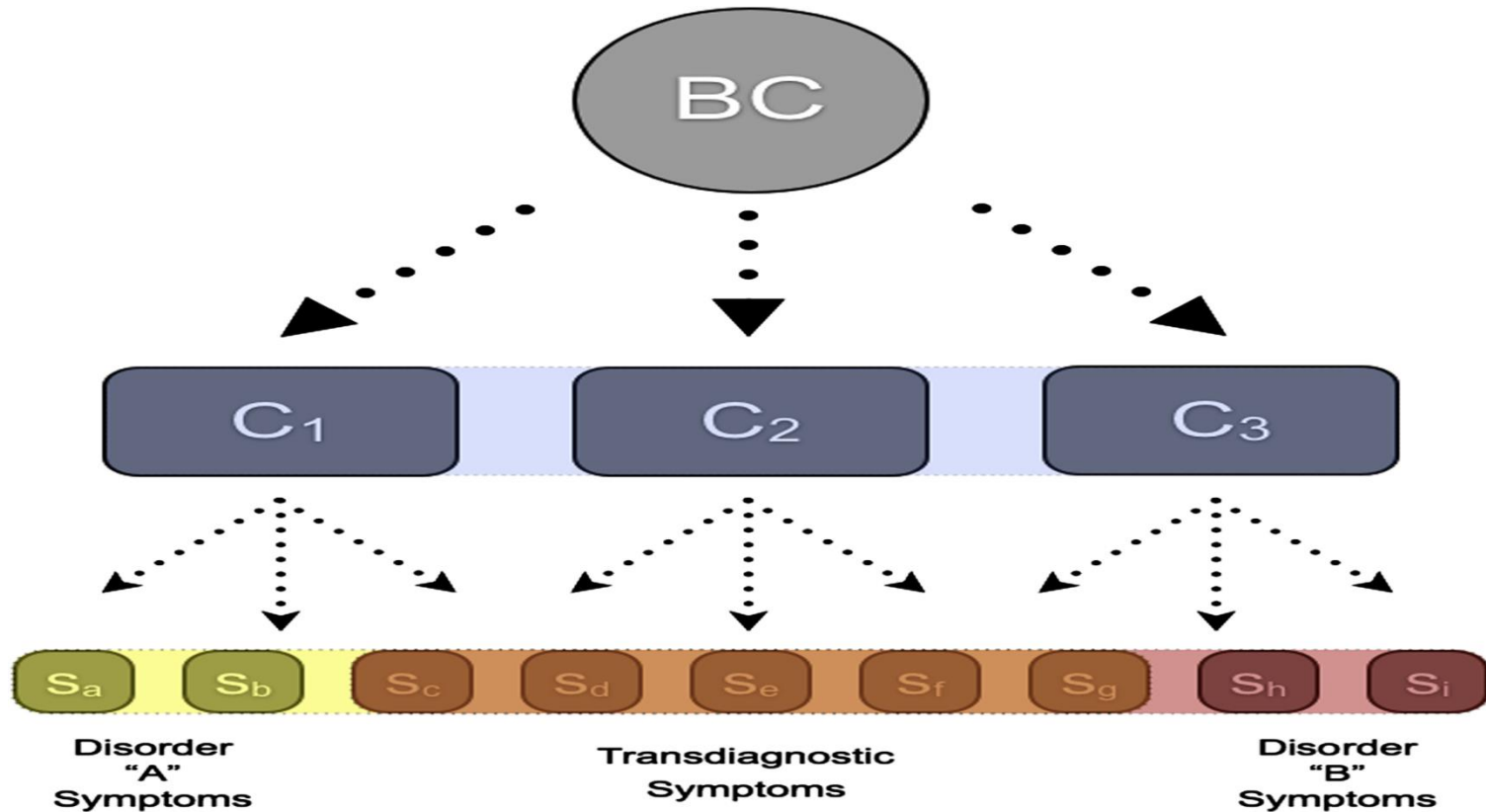
Insel/Lieberman News Release, APA, May 14, 2013

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
 - Neuroimaging (structural/neuroanatomical, functional/neurocircuitry)
 - Biochemical/Neuroendocrine
 - Cognitive/Neuropsych
- Development of more relevant animal models to facilitate translational efforts

Neurocircuitry of Pathological Domains May Better Inform Drug Development

“Common Symptoms arise from common circuit dysfunction” *



*From Buckholtz and Meyer-Lindenberg, Neuron 74, June 21, 2012 Elsevier Inc.
BC=Brain Circuit; C=Cognitive process 1-3

Functional Imaging Provides Insights into Dysconnectivity, Informs Future Research

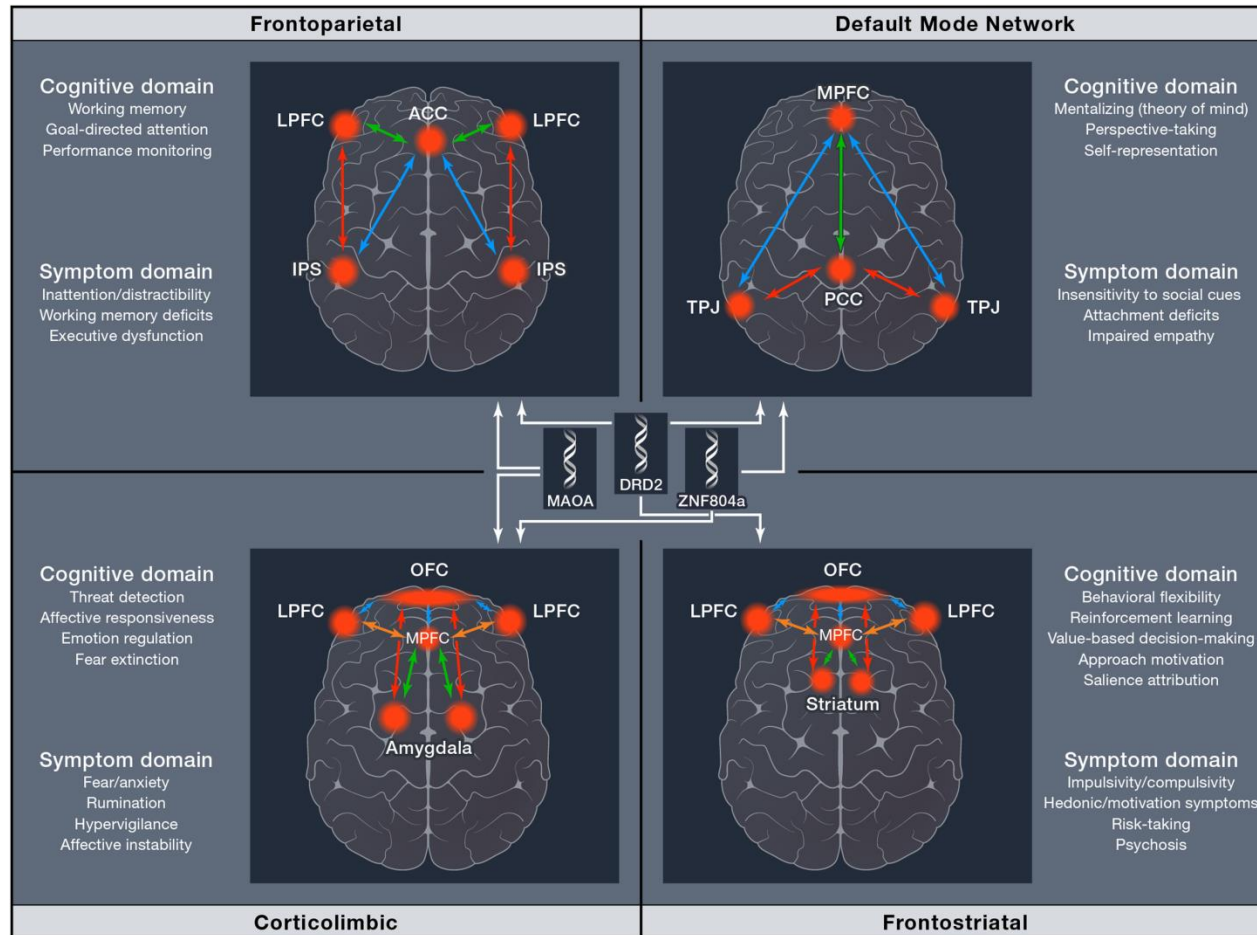


Figure 3. Genetic Variation Affects Risk for Psychopathology by Disrupting Cognition-Specific Brain Circuits
 *From Buckholtz and Meyer-Lindenberg, *Neuron* 74, June 21, 2012 Elsevier Inc

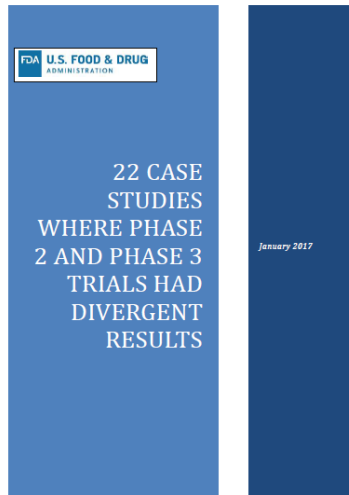
Adherence to Rational Drug Development is Critical

- Proof of Mechanism (POM): “3 Pillars”
 - Exposure at target site
 - Interaction with pharmacological target
 - Evidence of relevant, expected pharmacological activity
- Proof of Concept (POC)
 - Optimize signal detection
- Dose finding studies (P2b)
 - Rigorous evaluation of exposure/response for key variables to optimize P3 dose selection
 - Incorporation of adaptive dose range design
- Pivotal trials (P3)
 - Continuity with P2 population characteristics and outcome measures
 - Minimize placebo response and variability
 - Thorough oversight of operational execution

Certain Trends are Encouraging

- Neuroscience basic research knowledge expanding
 - 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 future productivity

Recent FDA Review: 22 Case Studies Where Phase 2 and Phase 3 Trials had Divergent Results



CNS Related Examples:

- **Bitopertin**, Roche, schizophrenia
- **Dexmecamylamine**, Targacept/Astra Zeneca, depression
- **Lithium**, bipolar disorder

- **NicVAX Vaccine**, Nabi Biopharmaceuticals, smoking cessation
- **Olanzapine Pamoate** (Zyprexa Relprevv), Eli Lilly, schizophrenia
- **Semagacestat**, Eli Lilly, Alzheimer's Disease

Methodological Issues Highlighted:

- Large RCTs can produce unexpected results across all types of products, patients, and conditions
- An experimental product's presumed mechanism of action does not automatically predict clinical effects
- Many biomarkers do not reliably predict clinical outcomes

Reflections: Other Issues Impacting Outcomes?

- Are we over-estimating the likelihood of reproducing an effect size seen in P2?
 - Are we taking into account fully the complexities attendant transition and expansion into large, multinational P3 trials?
 - Are we pushing forward programs with less than required confidence?
 - Are we pressured into completing programs that should have been terminated earlier in development?
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