

Discovery and Development of New Medicines – Changing the Clinical Development Paradigm

Robert R. Ruffolo, Jr., Ph.D.
President, Research & Development
Wyeth Pharmaceuticals
Senior Vice President,
Wyeth Corporation

PhRMA Adaptive Designs Workshop
November 13, 2006, Washington, DC

Wyeth
Research

Agenda

- The Evolving Environment in R&D
- Diminishing R&D Productivity
- Managing Change
- Changing the Paradigm for Clinical R&D
- Summary

The Evolving Environment in R&D

The Evolving Healthcare Technology Arena

Description of disease processes



Causal molecular pathology

Empirical intervention



Rational intervention directed to specific molecular pathology

Disease homogeneity



Disease heterogeneity and different progression/prognosis

Uniform patient populations



Patient heterogeneity and individual risk profiles

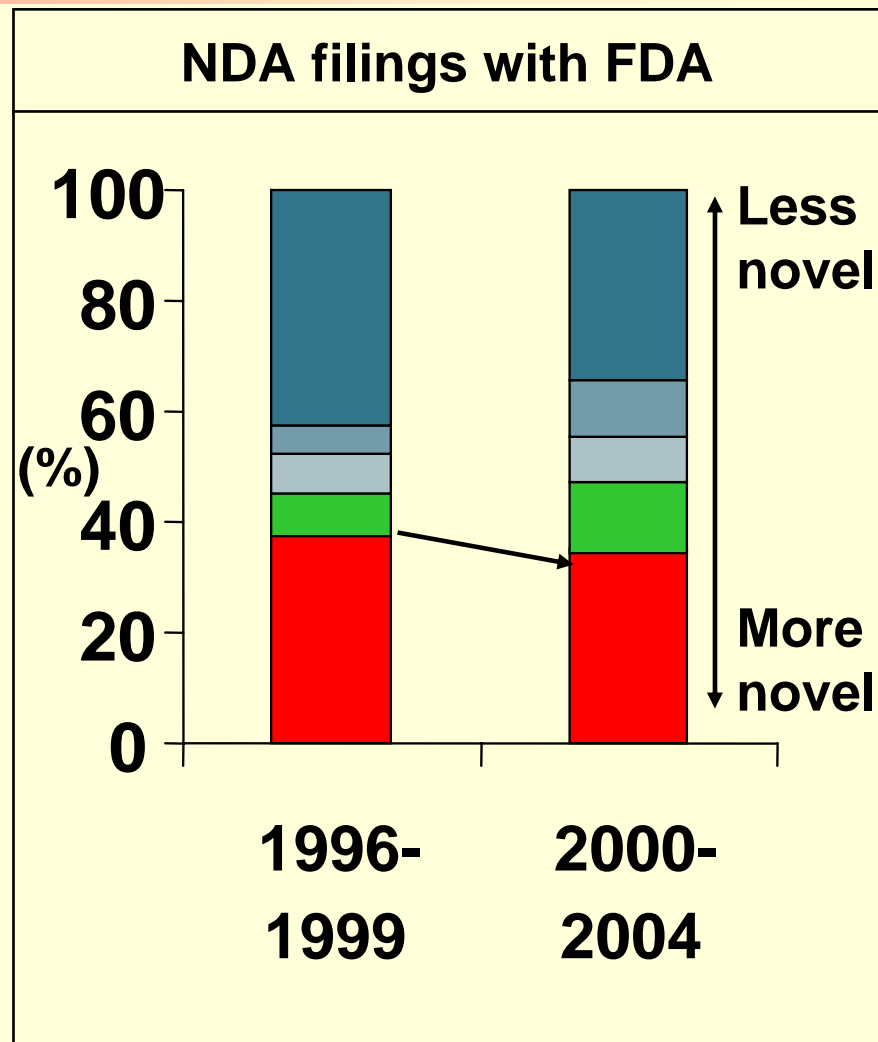
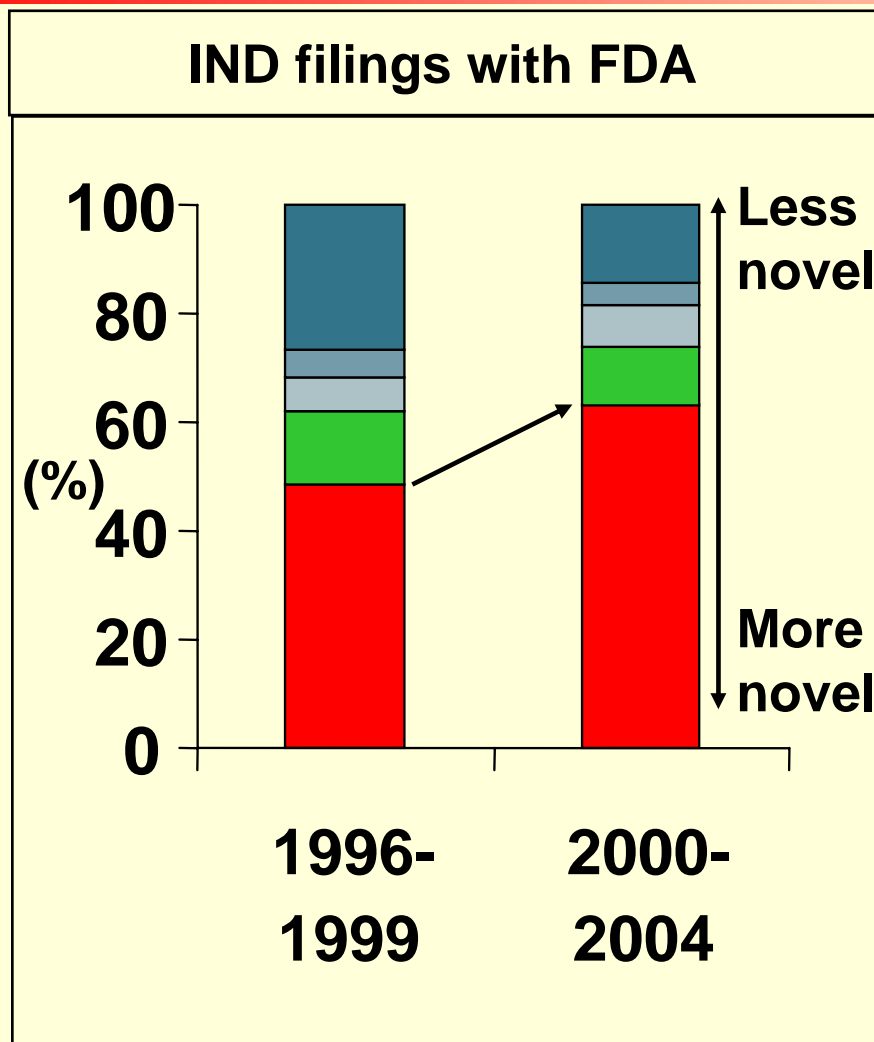
Reactive medicine (post-symptoms)



Proactive disease management based on risk assessment (targeted care)

This is leading to more innovative drugs in all our pipelines

Innovation Comes With a Price: Higher Attrition, Longer Timelines and Higher Costs



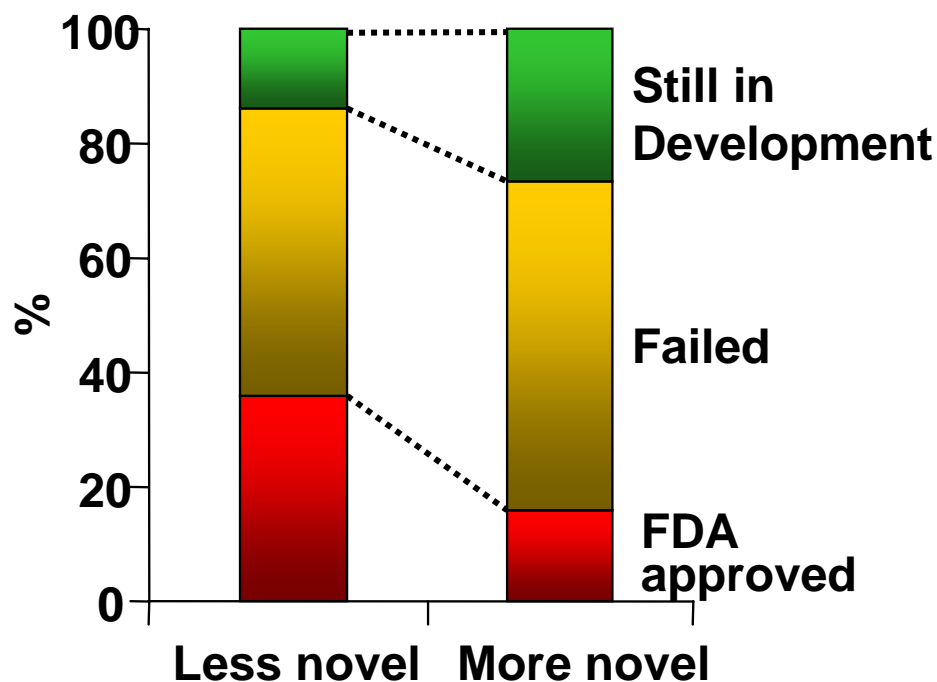
Source: BCG industry compound database; BCG analysis

More Novel Drugs: Higher Attrition Rates and Longer Development and Approval Times

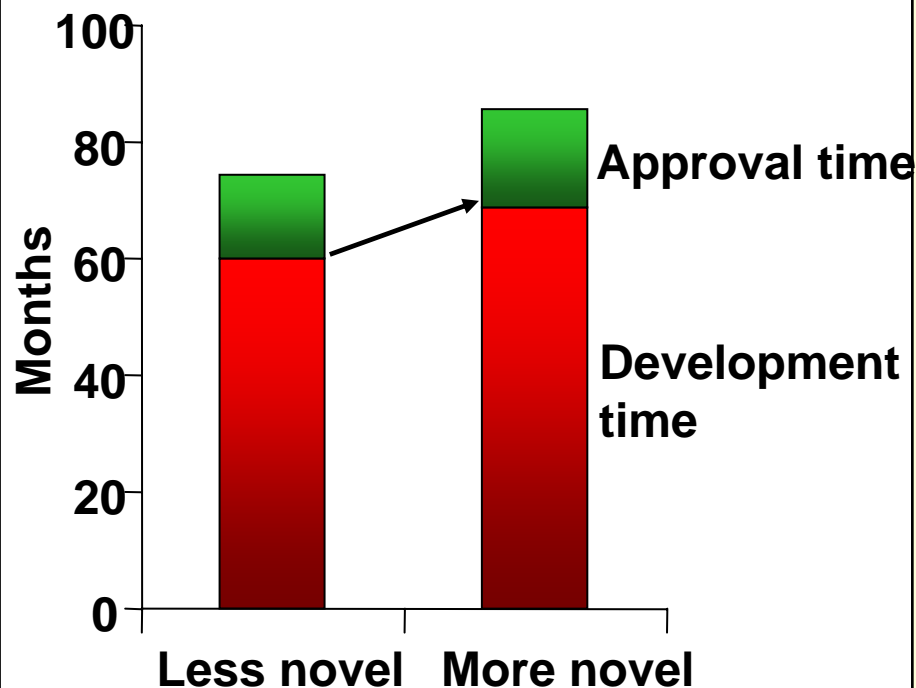
Attrition Rates by Novelty Status

Development Times by Novelty Status

Current status of INDs filed 1996 – 1998



Average cycle time for NDAs submitted 1996 – 2003 and approved

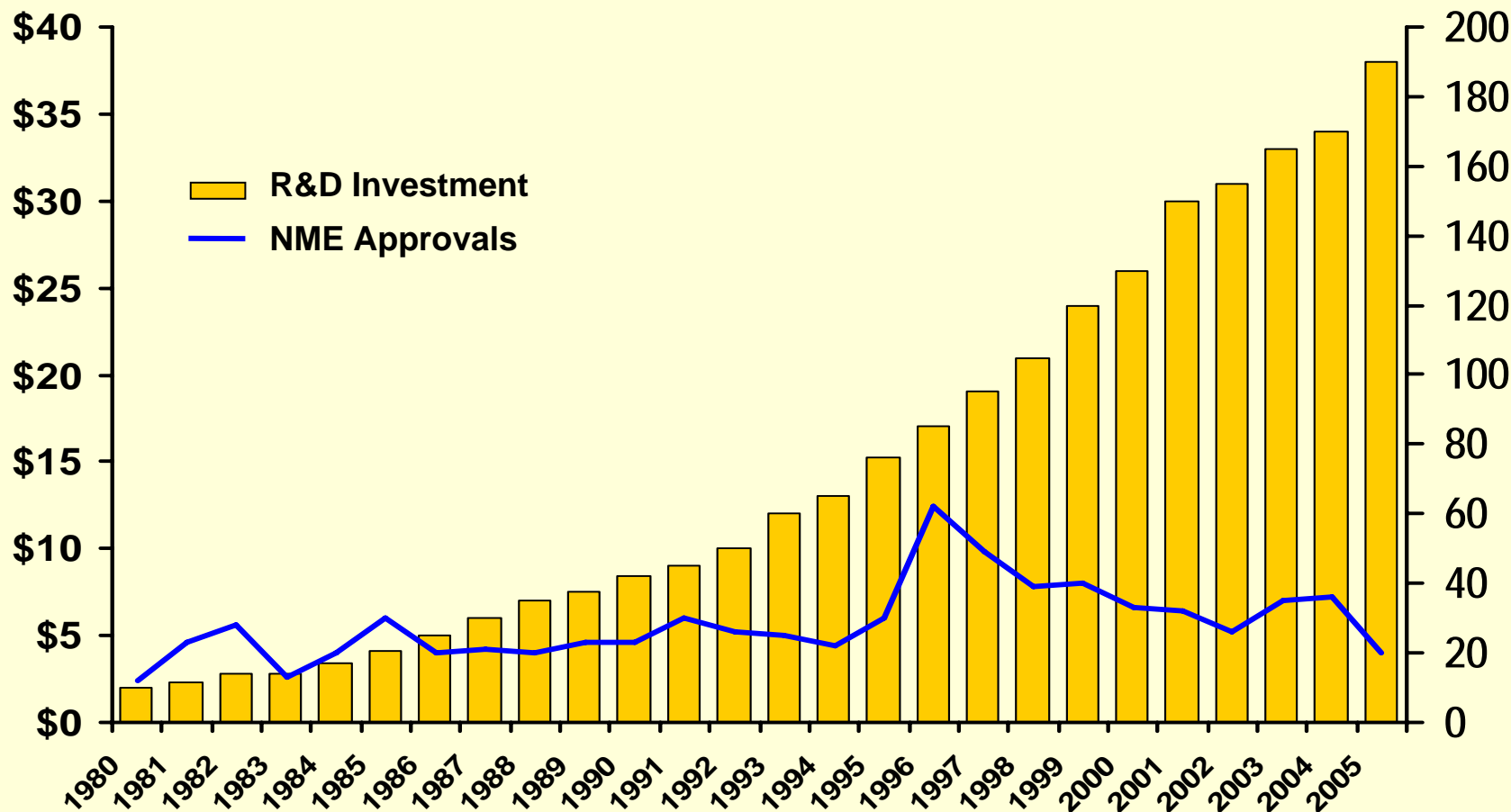


Diminishing R&D Productivity

R&D Productivity is Decreasing

Industry R&D
Expense
(\$ Billions)

Annual NME
Approvals



Source: PhRMA, FDA, Lehman Brothers;

Managing Change

- **Change is important to R&D and to our Company**
- **How We Managed Change in R&D at Wyeth**
 - ▶ Vision
 - ▶ Alignment of R&D staff with the R&D vision
 - ▶ Held R&D staff accountable
 - ▶ Linked compensation to performance against pre-specified objectives
 - ▶ Set aggressive targets
 - ▶ Changed our systems to hit the targets
- **We have developed some level of comfort with change**
- **This can be a competitive advantage**

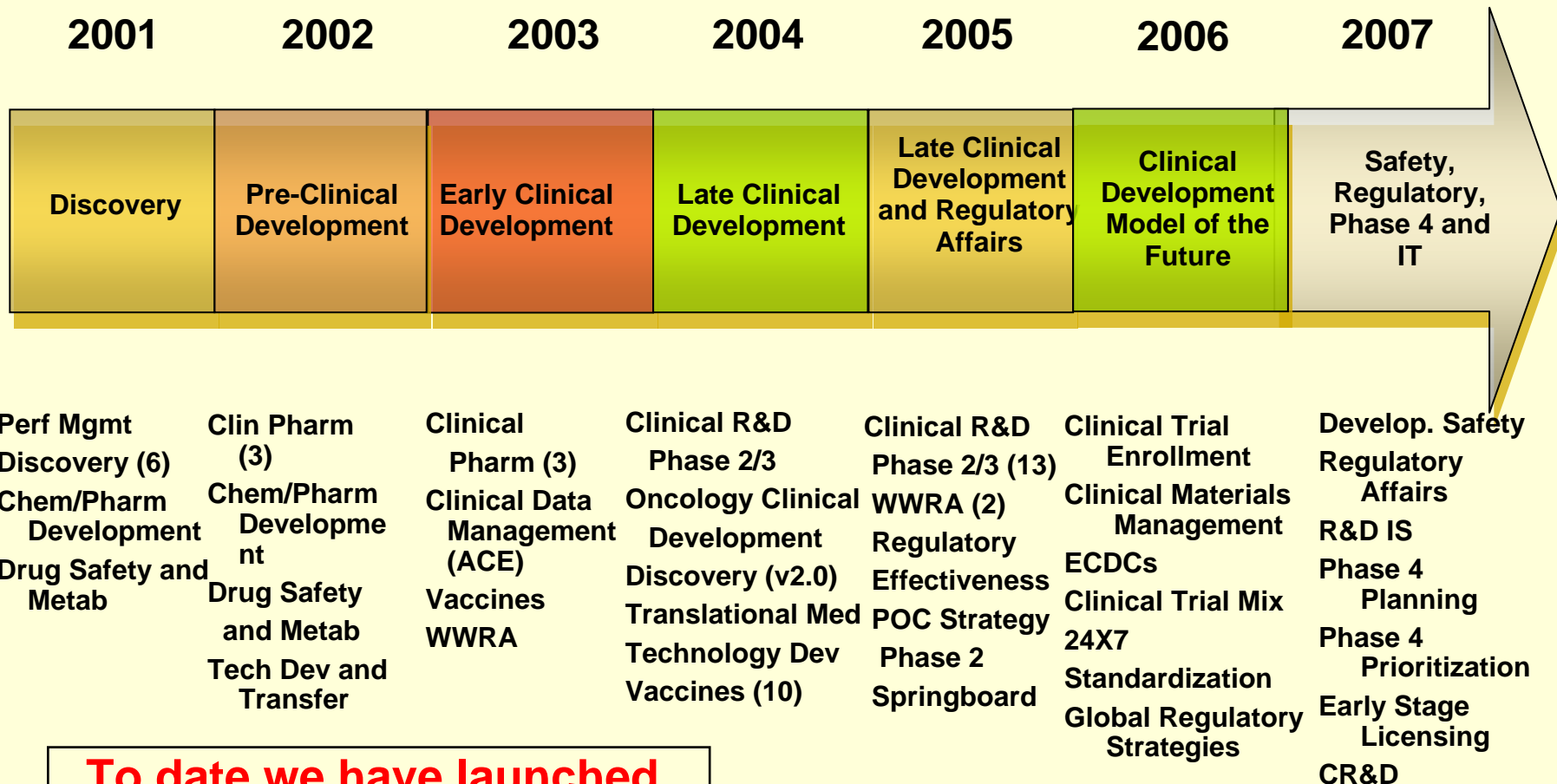
Managing Change Is Difficult With Scientists: ***“Managing the Innovator”* (ISR) - Scientists:**

- **Favor immediate supervisors over upper management**
- **Suspicious of “upper management”**
- **Feel un-empowered**
- **Uncomfortable in taking direction**
- **Criticize their performance appraisals**
- **Are highly dissatisfied with their compensation**
- **Feel less secure in their jobs**
- **Believe that they cannot challenge Company norms**
- **They identify themselves as scientists; not as company employees**
- **Feel limited opportunities for career development**
- **Have a very high degree of stress on the job**
- **Are typically the most dissatisfied employees in a company**

Managing Change

- **Managing change is not a democratic process**
- **Complacency can destroy an organization**
- **Hearing the phrase “we do things the XXXX way around here” is a sign of trouble**
- **Successful managers recognize the need to change, and drive change; they need to be rewarded for driving change**
- **Managers who drive change need to have courage; it’s often very lonely during periods of change**
- **Comfort with change can be a major competitive advantage**
- **The need to change never goes away, no matter how good we get; we can always get even better**
- ***“If it’s not broken, break it”***

Changing R&D (Breakthrough Projects): *“If It’s Not Broken, Break It”*



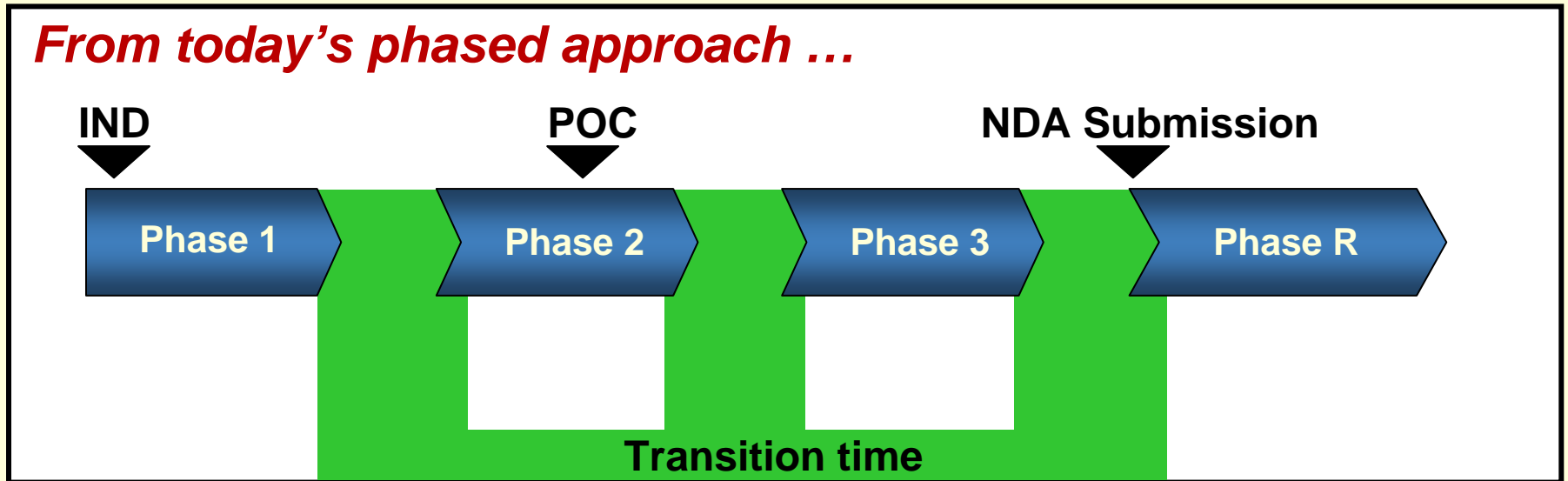
**To date we have launched
 ~70 “Breakthrough Projects”**

Changes In Clinical Development

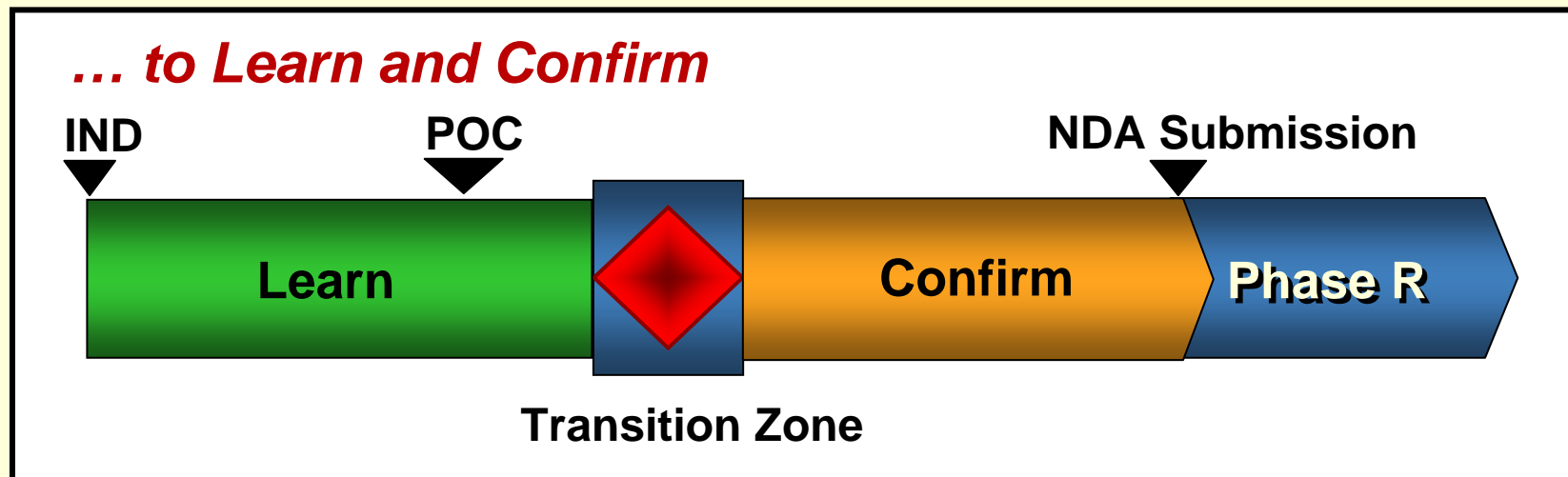
Changing the Clinical Development Paradigm: Objectives

- **Increase efficiency**
- **Increase quality**
- **Reduce costs**
- **Reduce cycle times**
- **Improve consistency**
- **Increase success rates**
- **Improve decision-making**

Shift From a Phased Development to a “Learn and Confirm” Paradigm



Shift From a Phased Development to “Learn and Confirm” Paradigm



Learn

- Learn Teams based on disease area
- Many compounds/Learn Team
- Optimize understanding
- Ability to prioritize
- Maximize medical value
- Enhance rate of information acquisition
- Enable early “kill” decisions
- Deliver compounds ready for Confirm

Confirm

- Excellence in Execution
- One Confirm Team/Compound
- No/minimal change in plans
- Objective to deliver target product profile
- Focus on efficiency and safety
- Escort Teams

Components of Learn and Confirm

- Learn and Confirm Teams
- Clinical Data Management
- Early Clinical Development Centers (ECDCs)
- Site identification
- Site standardization
- Contracting
- Global patient mix
- Patient identification
- Patient recruitment
- Adaptive clinical trial designs
- Clinical trials materials management
- Remote data capture
- Standardization of data collection
- Standardization of data lifecycle packages
- Submission ready components
- Research learning services
- 24 X 7
- Cost optimization tool
- Simultaneous development in Japan

Relevance of Adaptive Trials to Learn and Confirm

- **Regulators stress the need to improve quality of the “Learn” phase**
- **Our initial focus with Adaptive Designs will be around “Learn” to increase our knowledge of dose-response**
- **This will allow us to:**
 - ▶ Fail efficiently
 - ▶ Succeed efficiently
 - ▶ Make better use of biomarkers and Translational Medicine
 - ▶ Transition seamlessly from Phase 2 to Phase 3
 - ▶ Potentially with time to use Adaptive Designs in Phase 3
- **To accomplish this, we need to work with regulators, which is the purpose of this conference**

Expected Outcomes From Re-Engineering Clinical Research & Development

- Lower clinical development costs per launched compound
- Shorter clinical development cycle times
- Increase throughput in Phase 2 and Phase 3
- Increase return on R&D investment per launched compound
- Greater consistency across therapeutic areas
- Higher quality dossiers for submission

Summary

- The environment in R&D is changing, and innovation is increasing; there are costs associated with this
- R&D Productivity has decreased despite increased investment
- We have made many changes to create a new paradigm for Discovery and Clinical development; Our new paradigm is mostly in place
- Regulator's reactions have been positive to date
- All parts of the clinical development process have been changed
- These changes will speed development, lower costs and further increase the quality of our clinical trials