



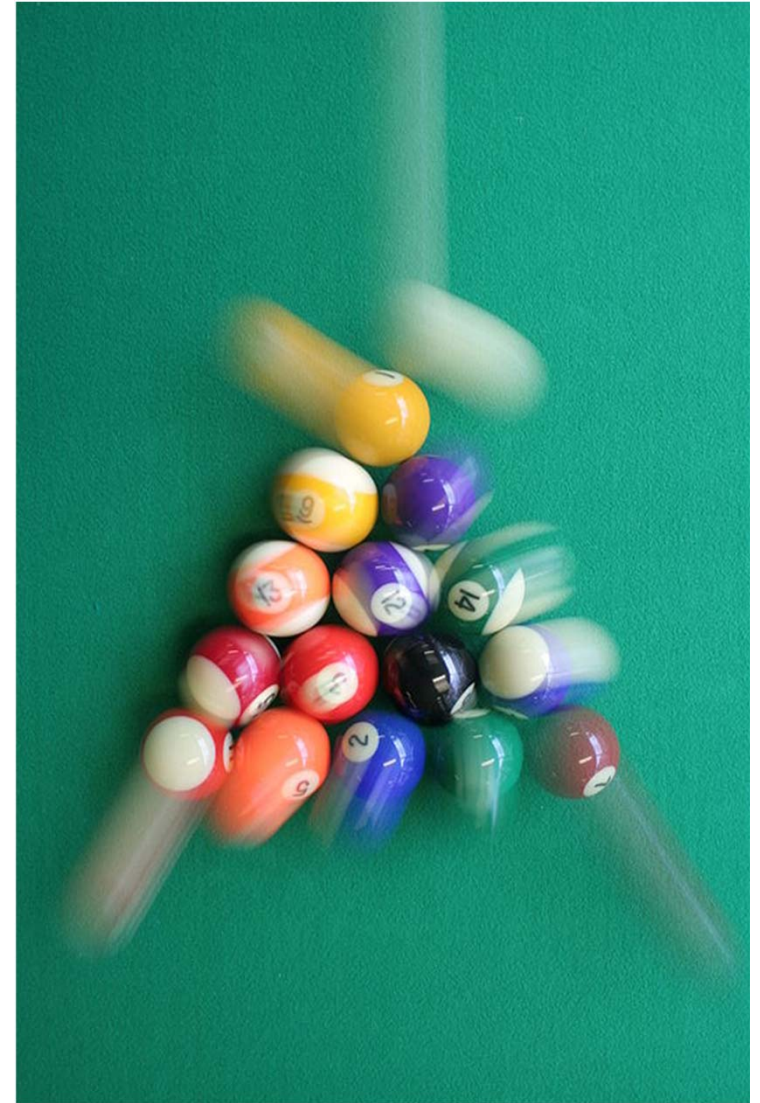
Transition and Translation

Strategic Drug Development Guidelines

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Getting Started

- “An effective break is a lot far more complicated than informal observation reveals. An accurate, solid strike on the target is much more important than the speed of the hit...”





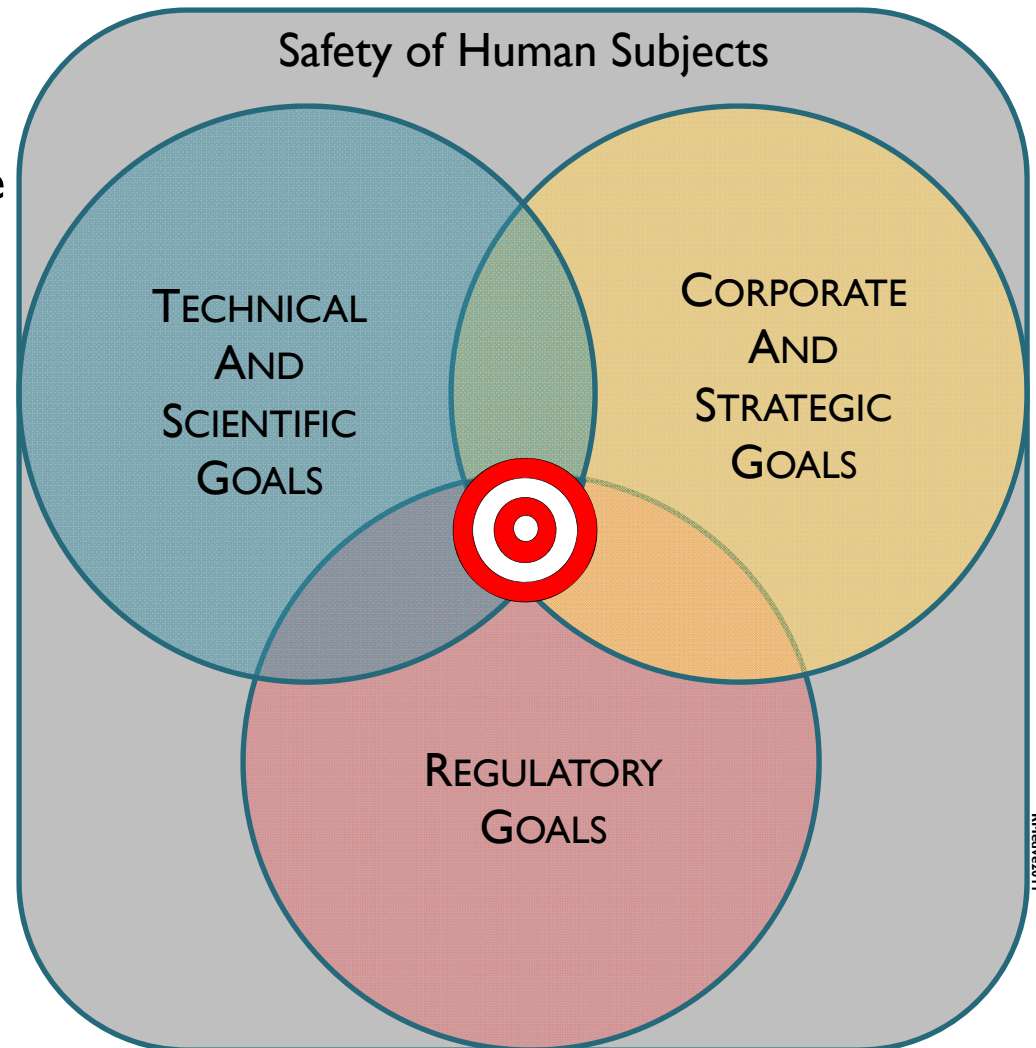
Basic Considerations in Phase I

- **KEY Goals**

- Establish clear goals for phase I program and options to consider as real data is generated
 - Safety, tolerability, dose escalation, human PK
- **Specific Stopping Criteria**
 - Related to general safety and tox observations AND to intended pharmacology
- **Know your targets and shoot for them:**
 - Rushing into and through early phase I can leave critical gaps in a program

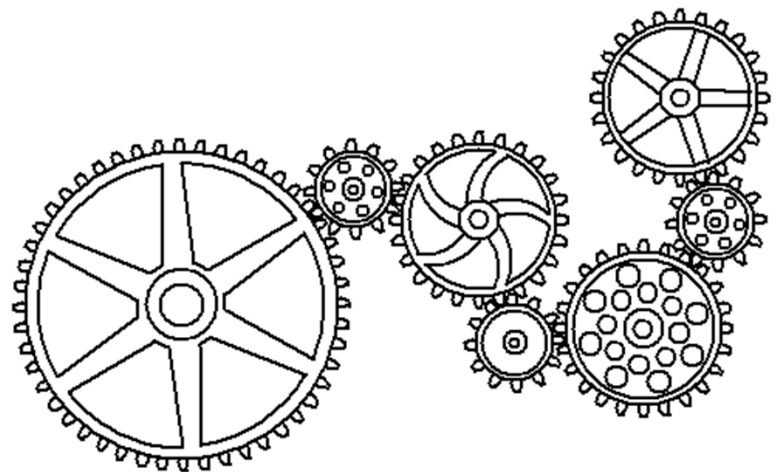
General Principles

- The IDEAL Phase I First-in-Human Study falls in the “sweet spot”
 - Provides an accurate, solid strike on the target
 - Balances scientific, clinical, strategic and regulatory priorities
 - Maintains subjects safety first and foremost



Technical and Scientific Goals

- LEARN:
 - Understand safety, tolerability and PK in single and multiple dose trials in healthy normal subjects
 - Consider surrogate endpoints and indicators of active pharmacology





Corporate and Strategic Goals

- POSITION

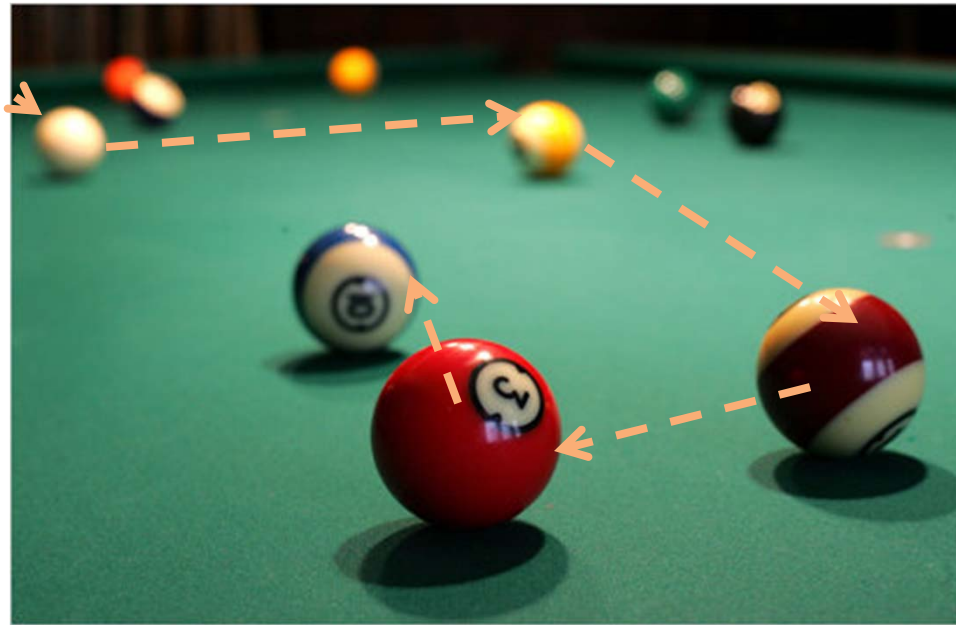
- Apply human data to enable next steps and advance the clinical program
 - Phase I is preparation for Proof of Concept (PoC)
 - What is the core data needed to establish PoC in the target indication
 - Recognize that variability is the enemy of efficiency: minimizing sources of variability will allow a more efficient path to PoC
 - Common sources of variability:
 - food effect, gender, concomitant medications, metabolic differences
 - Target population usually dictates necessary additional steps (drug interaction studies, etc)



Regulatory Goals

- ASSURE
 - Assure adequate safety and exposure to enable PoC
 - Build comfort level around safety endpoints
 - FDA/other regulatory
 - IRB/Sites
 - Stopping Criteria: establish clear criteria for stopping dose escalation, including those related to the pharmacology of the test agent
 - Establish a management plan for events and a fallback position that continues to advance the program
 - Healthy volunteers by definition do not exhibit the target disease: is a dose-limiting effect in volunteers the intended (and therefore perhaps not dose-limiting) effect in the target population?
 - Consider strategies to advance exposure when target pharmacology limits dosing
 - Example: opioids can be dosed with a specific antagonist
 - Make sure PK and other effects of the antagonist are understood in relation to the test article

Strategic Drug Development



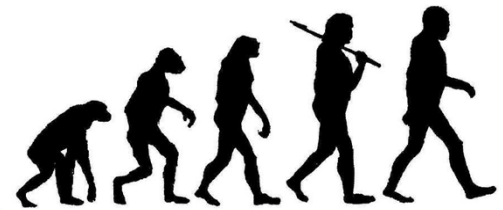
Each study built on what came before and positioning for what must follow.

First In Human Studies

- Typically single ascending dose (SAD) in healthy volunteers
- Supported by “IND-enabling” preclinical tox package
- “start low, go slow” approach to human exposure
- Stopping points based on tolerability, not on a specific endpoint determined by pharmacology
 - Role of surrogate endpoints

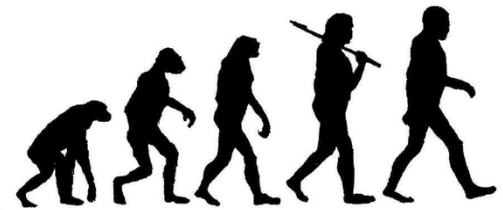


Evolution of Phase I



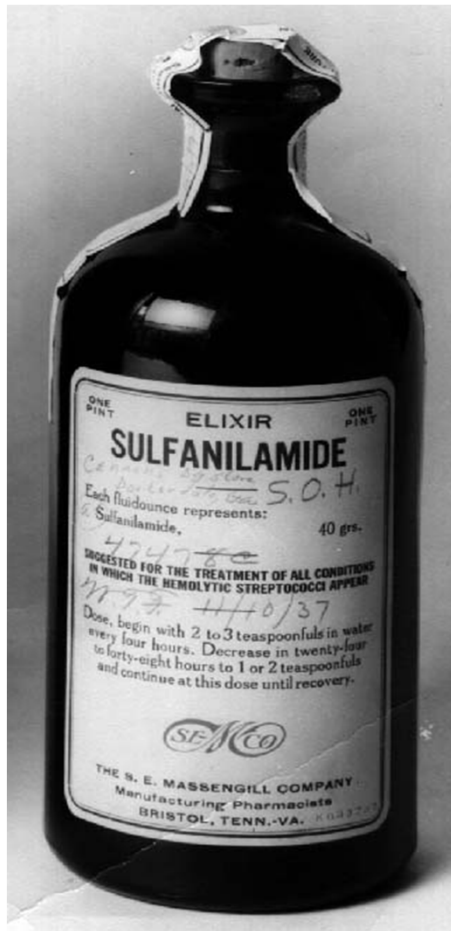
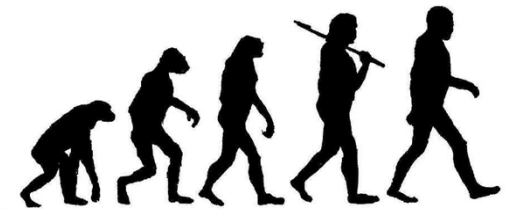
- SAD based upon NOAEL is the traditional model for FIH studies
 - Criteria guiding selection of starting dose are clearly outlined in the FDA Guidance Documents
 - Multiple strategies for dose progression
 - Additive progression
 - Fibonacci progression
 - Subjects monitored for safety with or without pharmacology assessment

Evolution of Phase I



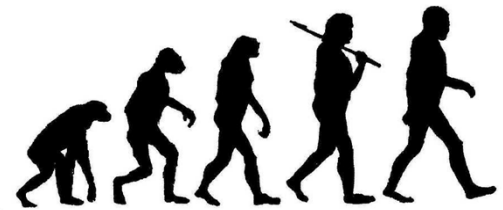
- Phase 0 concepts:
 - “exploratory IND”, “micro-dosing”, etc – using very low doses of development candidate drugs in small numbers of human subjects to assess suitability for continued development
 - Serves as an adjunct to rather than replacement for phase I work
 - Decision-making tool in early development
 - Explore multiple candidates, explore PK, limited PD
 - Approximately 40% of phase I failures are related to PK issues

Evolution of Phase I



- From great tragedy sometimes comes great progress:
 - March 2006: TeGenero
 - TGN1412 produced catastrophic multi-organ failure in human subjects at doses 500 times lower than those found safe in laboratory animals
 - The immune-based reaction was thought to have been mediated through memory T-cells
 - The study drug was administered to 6 subjects in a span of 20 minutes

Evolution of Phase I



- Current Concepts
 - Staggered dosing using “sentinels” or early dosers to assess for unexpected reactions prior to larger scale exposure
 - Increased drive to include PD evaluation through surrogate markers, experimental models, and other methods to assess pharmacological in volunteers without target disease

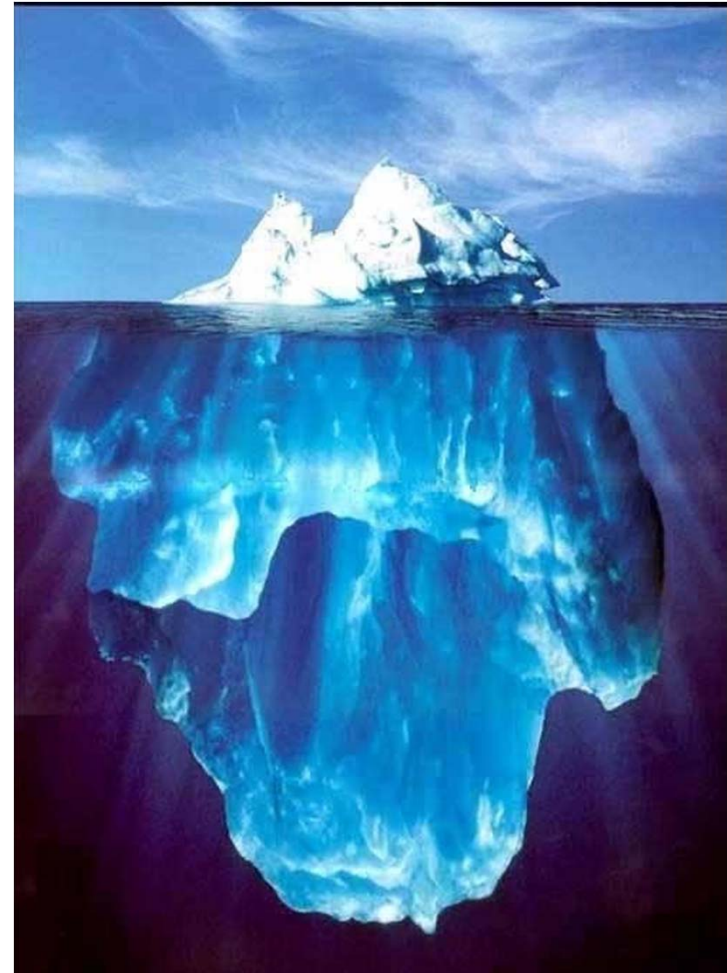


Multiple Dose Constructs

- Model PK based upon single ascending dose data
 - Predict dosing interval and accumulation potential: model steady state
 - Predict changes in clearance or distribution with ascending dose
- Are safety and tolerability issues related to peak level (C_{max}) or exposure (AUC)
- Dosing to steady state

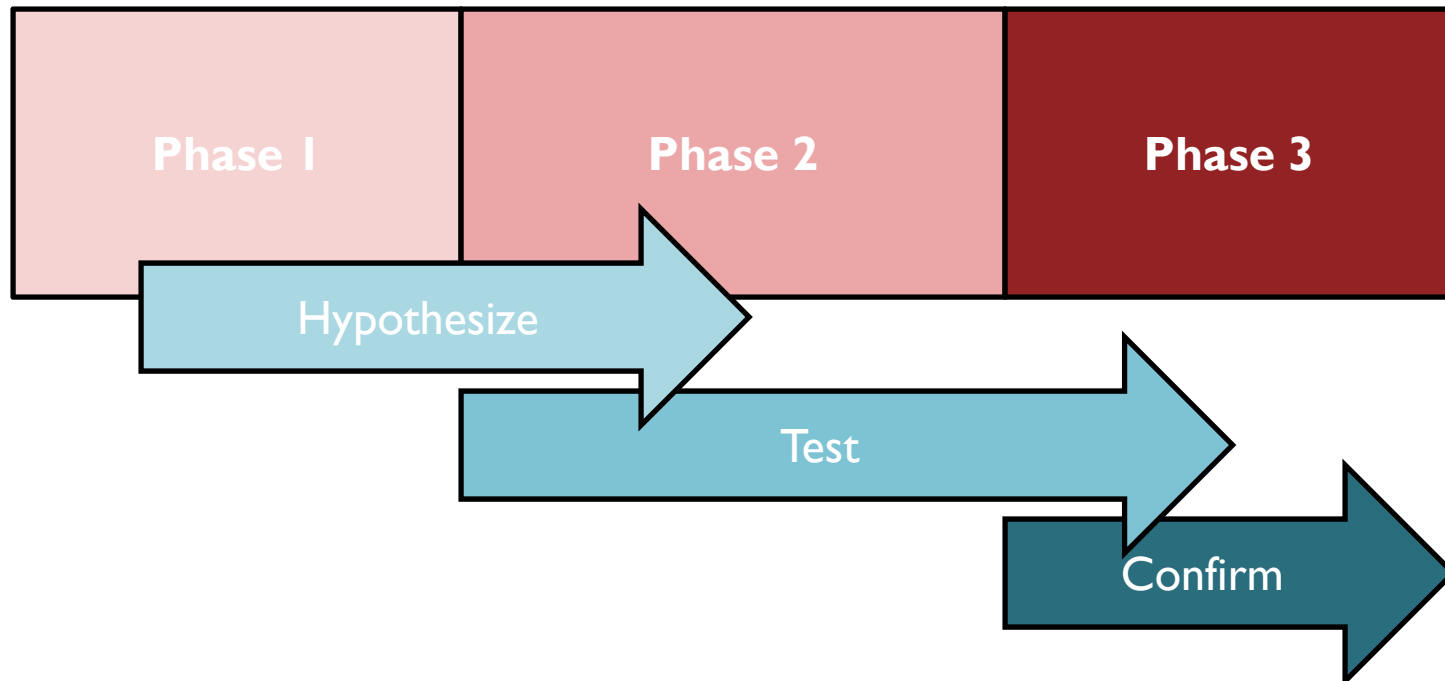
Looking beyond Phase I

- Phase I is an ongoing process
 - Sponsors move on to proof of concept (PoC) as soon as possible, using initial phase I studies to define the drug candidate and the performance of the dosage form intended for use in PoC studies
 - The bulk of the Phase I work remains to be completed once a determination has been made regarding the viability of the drug candidate and the development program



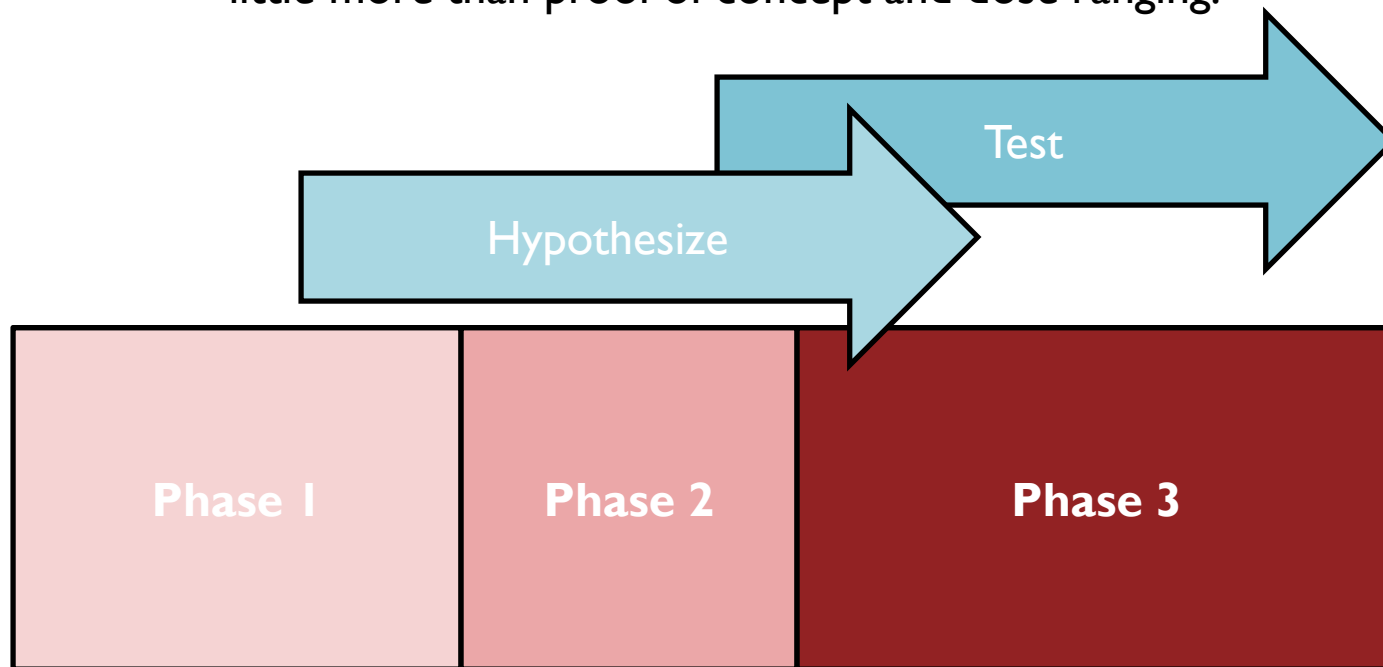
Drug Development

Traditional model emphasizes hypothesis testing in Phase 2.
Results are determined and CONFIRMED in Phase 3 prior to filing.



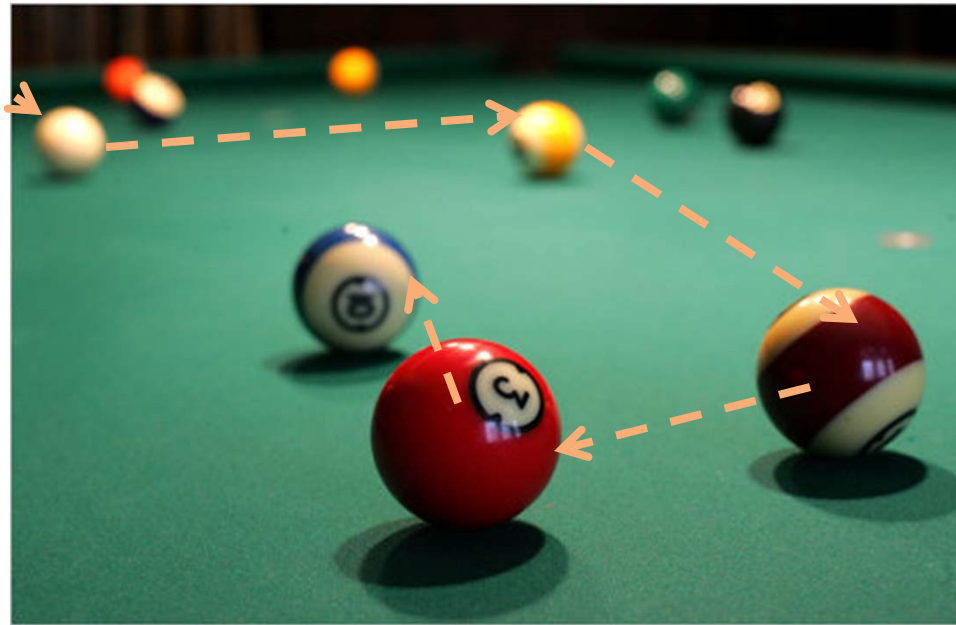
Drug Development

There is increasing emphasis placed on being in Phase 3, which has come at the expense of a thorough Phase 2 program. The current model relegates Phase 2 to little more than proof of concept and dose ranging.



This shift away from Phase 2 may play a role in the increased Phase 3 failure rates observed in the past decade.

Strategic Drug Development



Each study built on what came before and positioning for what must follow.

This target applies to every study

