Considerations for Successful Biopharmaceutical Product Development: Discovery to Proof of Concept

-A Panel Discussion

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Session Objectives

- Biopharmaceutical product development is a complex process, requiring extensive time and resources from sponsors and investors.
- Key concepts to consider during the development and approval processes for new drugs;
  - emphasis on how inventors and entrepreneurs can minimize the time to confirm clinical proof of concept (PoC)
- Better understanding of how to simplify this highly interesting, yet complicated process.

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Expertise and credentials

- **Industry- and FDA-trained experts** providing regulatory science and product development consulting services **required for product approval** and product lifecycle management
- **120+** NDA/BLA/ANDA approvals supported
- **500+** INDs supported
- **500+** approved products under maintenance (100+ countries)

40
Years of global experience

800+
Clients served

170+
Regulatory scientists in-house

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Core service areas

Global regulatory development

Nonclinical development

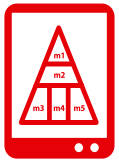
Chemistry, manufacturing and controls

Clinical development and research

Medical writing

Regulatory competencies and offerings

Compliance



Regulatory publishing

Launch and post-approval

Licensing and registrations

Training

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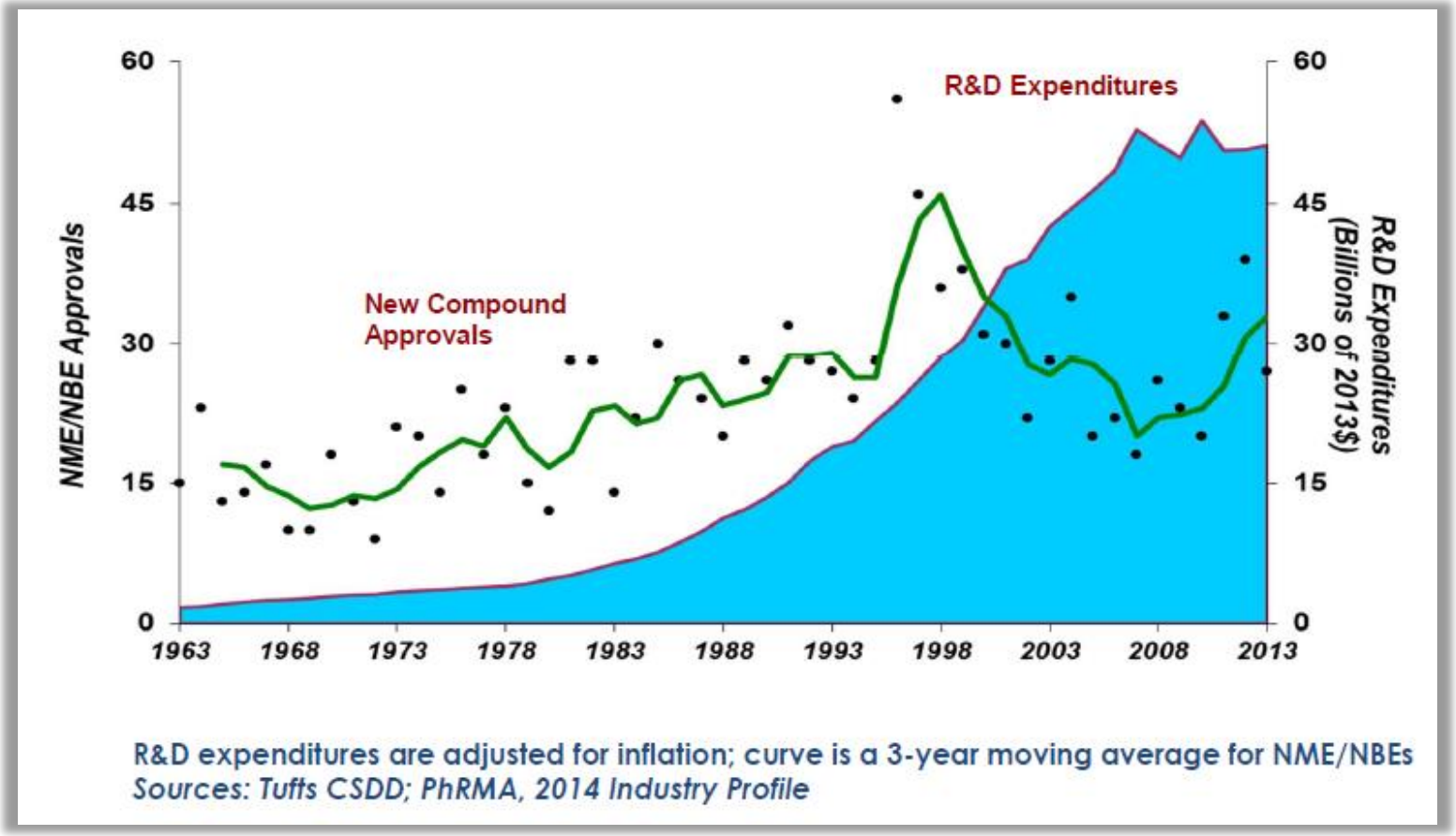
New Drug and Biologics Approvals and Research and Development Spending



Joseph A. DiMasi. Cost of Developing a New Drug [Briefing]. Tufts University Center for Drug Development. Nov 18, 2014. http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf, http://csdd.tufts.edu/news/complete_story/cost_study_press_event_webcast

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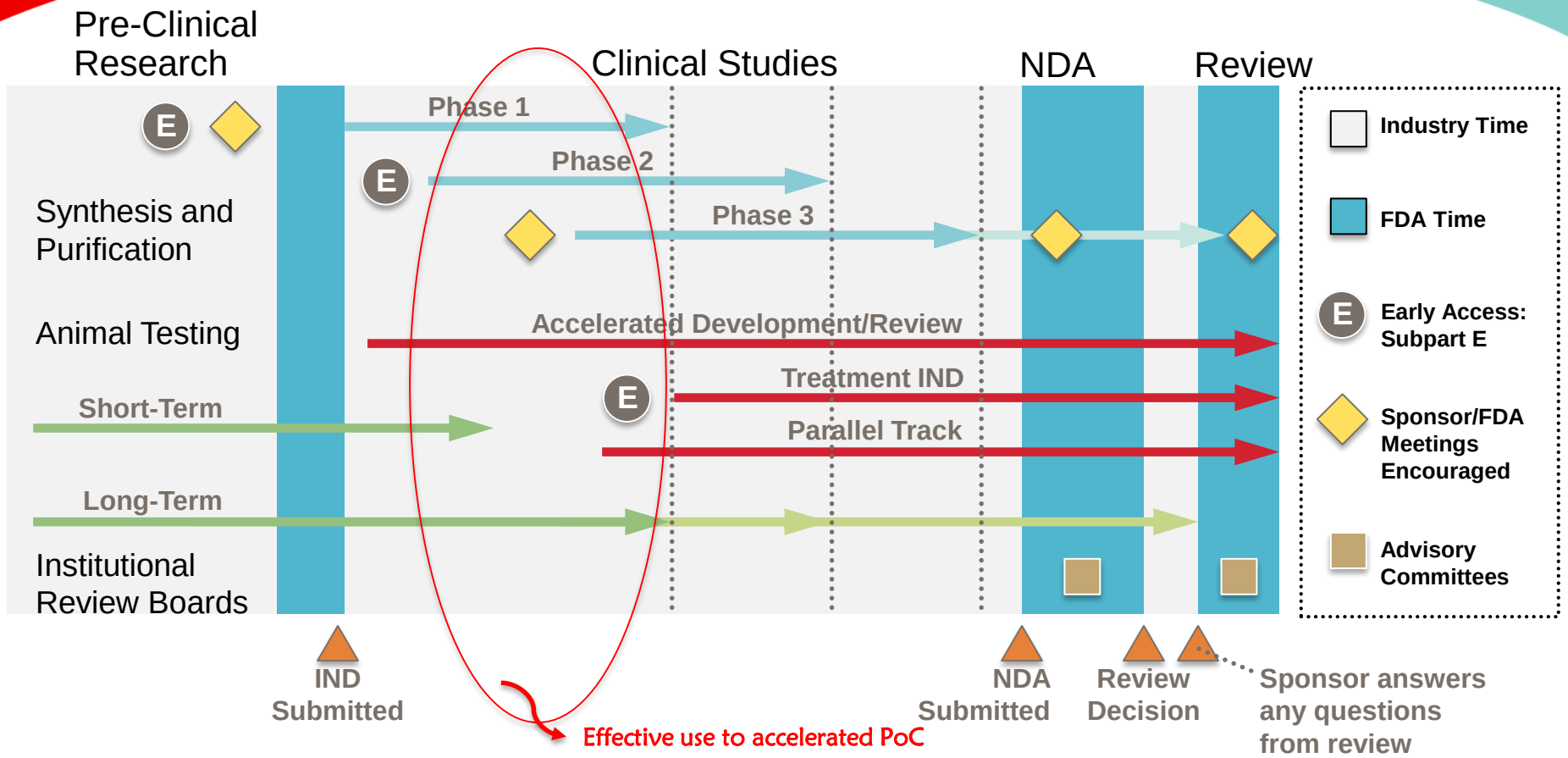
The New Drug Development Process



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm

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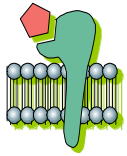
Target selection & validation

Discovery

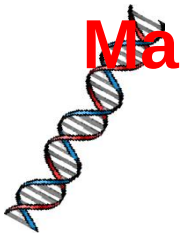
Development

Studies of
Disease Mechanisms

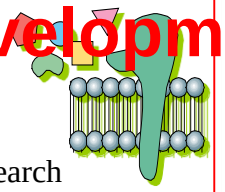


Target
receptor; ion channel;
transporter;
enzyme; signalling molecule

Drug Candidate
safety testing



Molecular Studies

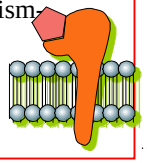


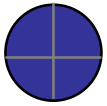
Lead Search
-Develop assays (use of automation)
-Chemical diversity
-Highly iterative process

Human Studies
Phases I,II, III

Animal Studies
- relevant species
- transgenic KO/KI mice
- conditional KOs
- agonists/antago
- antibodies
- antisense
- RNAi

Lead optimization
-selectivity
-efficacy in animal models
-tolerability: AEs mechanism
based or structure-based?
-pharmacokinetics
-highly iterative process





Drug Approval
and Registration

Mapping Product Development Stages

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Target Selection & Validation

- Define the unmet medical need (disease)
- Understand the molecular mechanism of the disease
- Identify a therapeutic target in that pathway (e.g. gene, key enzyme, receptor, ion-channel, nuclear receptor)
- Demonstrate that target is relevant to disease mechanism using genetics, animal models, lead compounds, antibodies, RNAi, etc.

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Discovery through Nonclinical Development

- Develop an assay to evaluate activity of compounds on the target
  - *in vitro* (e.g. enzyme assay)
  - *in vivo* (animal model or pharmacodynamic assay)
- Identify a lead compound
  - screen collection of compounds (“compound library”)
  - compound from published literature
  - screen Natural Products
  - structure-based design (“rational drug design”)
- Optimize to give a “proof-of-concept” molecule—one that shows efficacy in an animal disease model
- Optimize to give drug-like properties—pharmacokinetics, metabolism, off-target activities
- Safety assessment, Preclinical Candidate!!!

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Drug Product Design

- Selection Criteria for Dosage Forms
  - Clinical Needs
  - Dose/Onset/Duration of Action
  - Product Performance
  - Patient Compliance/Acceptance
  - Marketing Considerations

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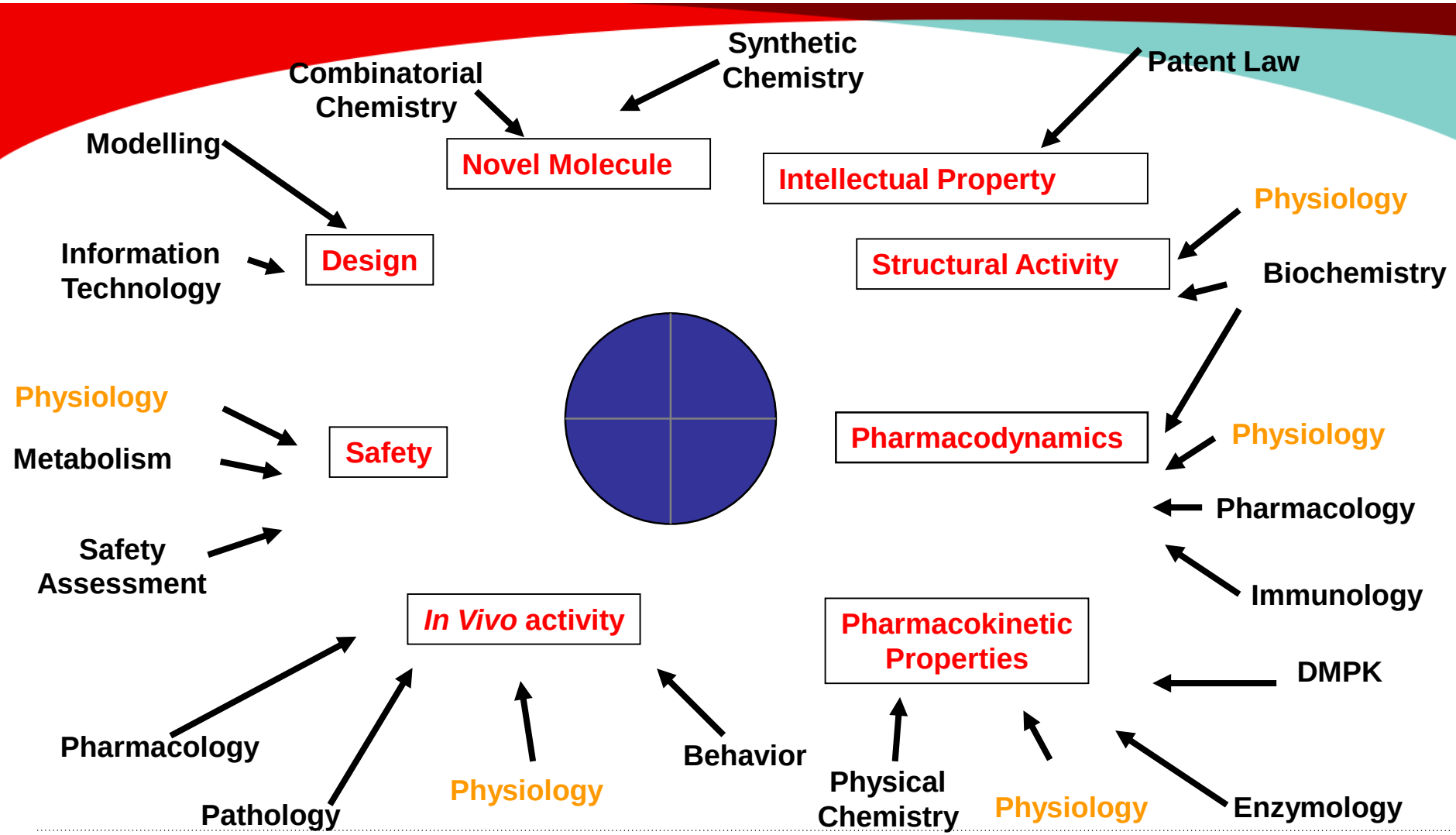
Discovery to Nonclinical - Convergence of Disciplines



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Clinical Development

- Submit Investigational New Drug (IND) Application
  - Provides exemption from a federal statute
  - Effective in 30 days if FDA does not object or request additional information
- Phase 1 Clinical Trials
  - Approximately 1 year in duration
  - Requires 20 to 80 subjects
  - Assess the safety profile, pharmacokinetic (PK) characteristics, and safe dosage range (SAD, MAD, MTD studies)*
  - Evaluate absorption, distribution, metabolism and excretion (ADME studies), and the duration of presence/action

***Single ascending dose (SAD), Multiple ascending dose (MAD), Maximum tolerated dose (MTD)**

Modified based on information obtained from: www.fda.gov

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Clinical Development

- Phase 2 Clinical Trials
  - Approximately 2 years in duration
  - Controlled studies composed of 100 to 300 patients
  - Dose ranging in the target patient population
  - Assess safety and efficacy of dosing and formulation variances
- Phase 3 Clinical Trials
  - Approximately 3 years in duration
  - Requires 300 to 3,000 or more patients (intended use population)
  - Compare new therapies with existing standard of care and assess safety and efficacy of final (commercial) formulation product

Modified based on information obtained from: www.fda.gov

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Developmental Clinical Pharmacology: Emphasis on PoC

- Typically short, involving relatively few HVs/patients
  - FIH (SAD/MAD; with one patient cohort)
  - Phase 1 Biomarker
  - PK/PD
- Intelligent Go/No-Go endpoints
  - Proof of Mechanism
  - Proof of Efficacy
- Generally lack statistical significance
- High quality read-outs (PD, biomarker, etc..)
  - Clinical physiology
  - Adaptive designs

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Discussion