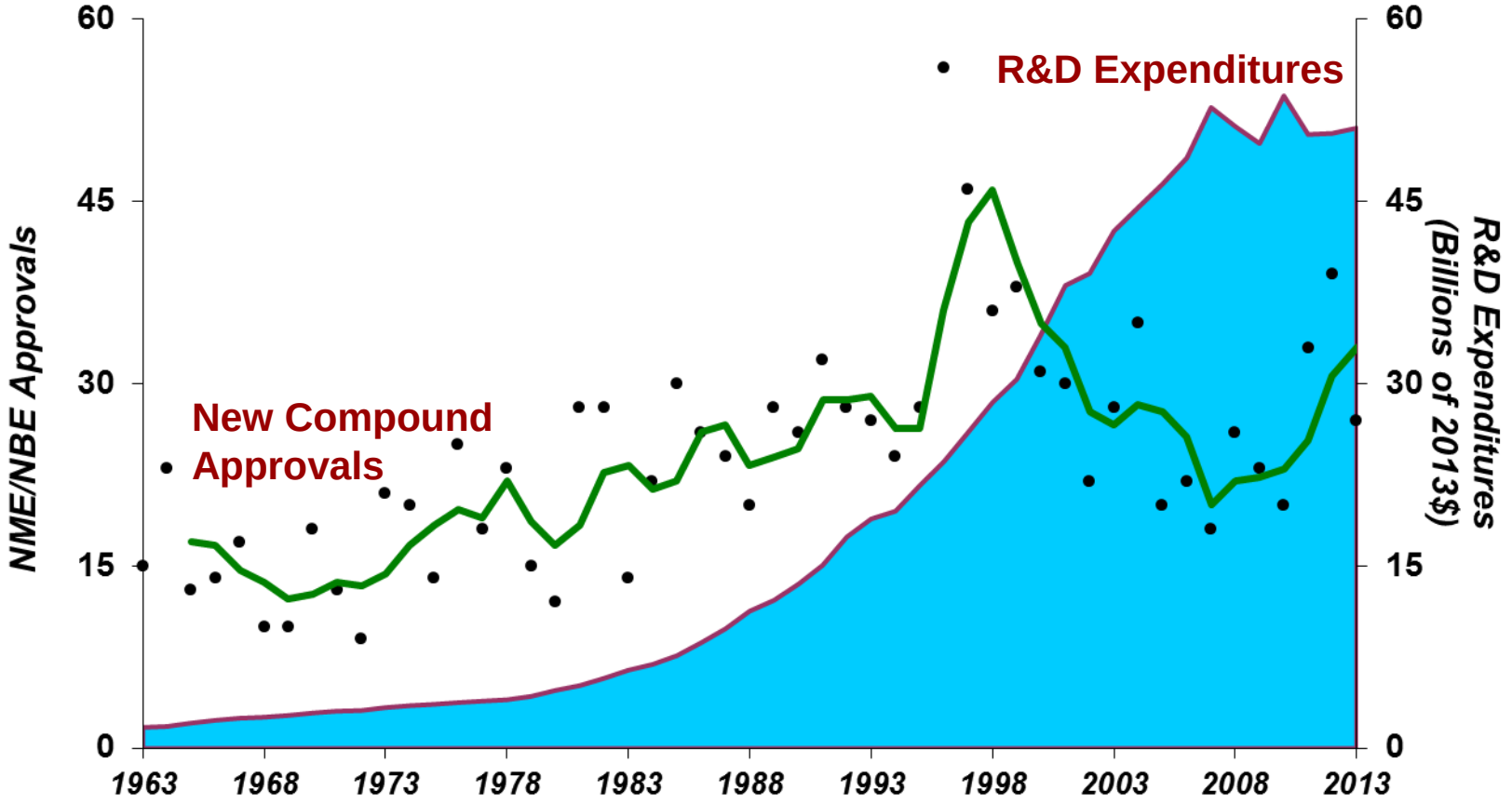
Regulatory Environment for Your Life Science Startup: Plan for the Approved Label

Pravin R. Chaturvedi, Ph.D.
IndUS Pharmaceuticals, Inc.
Woburn, MA

What is a Drug?

- Drug is a substance
  - with pharmacological activity in humans
- Drug is comprised of four parts
  - the drug substance (active ingredient)
  - route of administration
  - frequency of administration
  - disease or condition used to treat
- Regulatory definition of a drug is
  - the actual drug product (formulation) approved by the regulatory authority

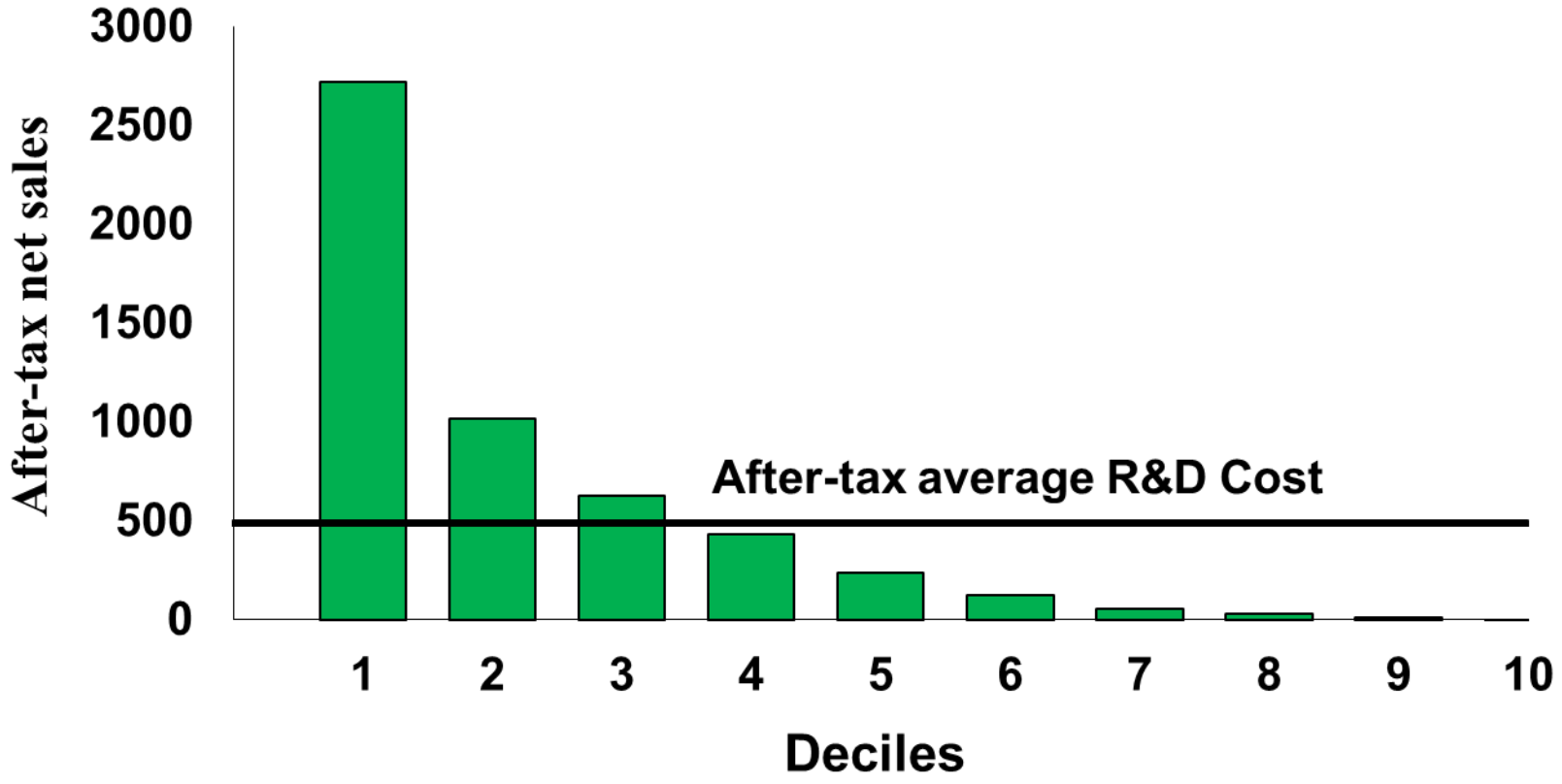
New Drug and Biologics Approvals and R&D Spending



R&D expenditures are adjusted for inflation; curve is 3-year moving average for NMEs

Sources: Tufts CSDD, PhRMA, 2014

Net Returns Relative to R&D Cost for New Compounds by Sales Decile (millions of 2000 $)



Source: Grabowski et al., PharmacoEconomics 2002; 20(Suppl 3):11-29

The Target Product Profile: Intent and Attributes

- Target Product Profile (TPP) is a voluntary submission which represents
  - "*beginning with the goal in mind*"
- Sponsor uses the TPP to specify
  - the label indication and provides the FDA with specific documents that intend to support the drug development program and label indication
- Ideally, a TPP resembles (as closely as possible)
  - the final label approved by the FDA upon its review of the NDA
- Typically, a TPP is a statement
  - of the *overall intent of the drug development program* and
  - provides a *status update* of the drug at any particular time in the drug development process
- TPP is a *dynamic summary* and is
  - updated regularly with new information derived from specific studies
  - to maintain the relevance of the TPP to the target label indication sought by the Sponsor

http://www.fda.gov/cder/guidance/index.htm

Typical preclinical R&D studies on new drugs

- Identification and selection of new drug candidate with
  - supporting data on biological pathway and/or target and *in vitro* mechanism of action
- Synthesis (or purification), manufacturing, testing and release of the new drug candidate
  - ensuring compliance with Good Manufacturing Practices (cGMPs)
- Pharmacology of the new drug candidate:
  - Pharmacokinetics: absorption, distribution, metabolism, excretion, half-life of new drug in relevant animal species
  - Pharmacodynamics: mechanism of action and estimated doses of therapeutic and adverse effects
- Efficacy studies on animal models (if available) for the new drug candidate
  - to provide *in vivo* evidence of pharmacological activity
- Toxicity and safety pharmacology studies on the new drug candidate
  - to support Investigational New Drug (IND) application for “first-in-human” studies
  - additional toxicology studies including carcinogenicity, mutagenicity, and teratogenicity conducted through the drug development process

The Investigational New Drug (IND) Application

- Investigational New Drug (IND) Application
  - requests permission to administer a new drug to humans
- Outlines the proposal to use the new drug
  - for human testing in clinical trials
- Studies in humans can only begin after
  - IND is reviewed and clinical study is allowed by the FDA and
  - by an (independent) institutional review board (IRB)

Outlines of Phase 1, Phase 2 & Phase 3 Clinical Studies

Phase 1 Studies

- Typically involves 20-80 healthy volunteers (no women of childbearing potential allowed)
- Objective is to establish safety and tolerability of escalating dose levels
- Key outcome is establishing maximum tolerated dose (MTD), dose-limiting toxicity (DLT), pharmacokinetics (PK). metabolism and routes of excretion
- Lasts about 1 year
- About 70% of drugs will pass this phase

Phase 2 Studies

- Typically involves 100-300 patients who have the target disease that the drug seeks to treat
- Objective is to show safety and effectiveness (i.e. POC) in target patient population(s)
- Patients receiving the drug are compared to similar patients receiving a placebo or other drug(s) used as standard of care (SoC)
- Lasts about 2-3 years
- About 33% of drugs will pass this phase

Phase 3 Studies

- Typically involves 1000->5000 patients who have the target disease
- Objective is to demonstrate safety and efficacy in target patient population to support label indication
- Confirms through well-controlled studies in “right” patient population the “right” dose level(s) and/or uses new drug in combination with other drugs (for e.g. in cancer)
- Lasts at least 3-4 years
- About 30% of drugs will pass this phase

Finalizing a Target Product Profile (TPP)

- A TPP summarizes specific studies that will provide supporting evidence for target labeling concepts
- TPP is typically organized like an (approved) drug label as follows:
  - *Indications and Usage*
  - *Dosage and administration*
  - *Dosage forms and strengths*
  - *Contraindications, warnings and precautions*
  - *Adverse reactions and drug interactions*
  - *Use in specific populations*
  - *Drug abuse, dependence and overdosage*
  - *Description*
  - *Clinical pharmacology*
  - *Nonclinical toxicology*
  - *Clinical studies*
  - *How supplied & storage and handling instructions*
  - *Patient counseling information*
  - *References*

http://www.fda.gov/cder/guidance/index.htm

Role of the U.S. Food and Drug Administration (FDA)

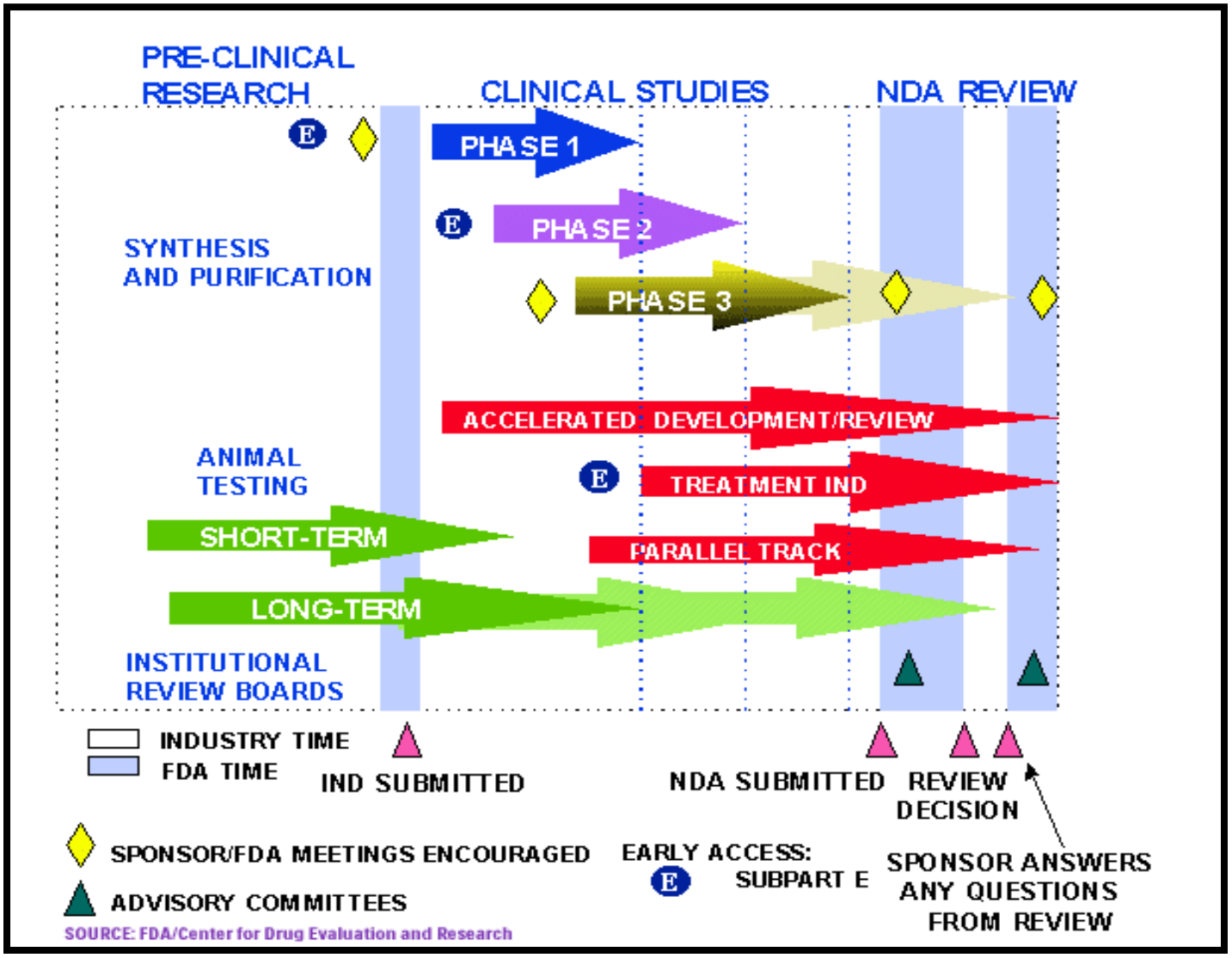
- The Food and Drug Administration (FDA) is required to
  - review and approve all new drugs in the United States
- The FDA reviews and evaluates new drugs based on
  - the evidence presented from the clinical research studies
  - performed by the drug sponsor
  - typically a pharmaceutical company

Resource: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm

Classification of Expedited Review Processes for New Drug Approvals

- Fast-track
  - Have the potential to address unmet medical needs
- Breakthrough Therapy
  - Have preliminary clinical evidence that indicates that the drug may result in substantial improvement in at least one clinically significant endpoint over available therapies for serious or life-threatening conditions
- Priority Review
  - CDER determines that the drug could potentially provide a significant advance in medical care
- Accelerated Approval
  - Allows FDA in more flexibility in endpoints to approve a drug that offers significant benefit over current treatments for serious or life-threatening illnesses

Summary of Drug Development & Evaluation



The New Drug Application (NDA) for Marketing Approval

- Pre-NDA period:
  - FDA and drug sponsors meet (several times if needed) and discuss (pending) submission
- Submission of NDA:
  - Formal request from the Sponsor to the FDA to consider approving a drug for marketing
- FDA has 60 days to decide whether
  - it will file it for approval consideration (or refuse to file (RTF))
- If filed, a review team is assigned by the FDA
  - to evaluate the new drug

FDA Review Decisions and Phase 4 Studies

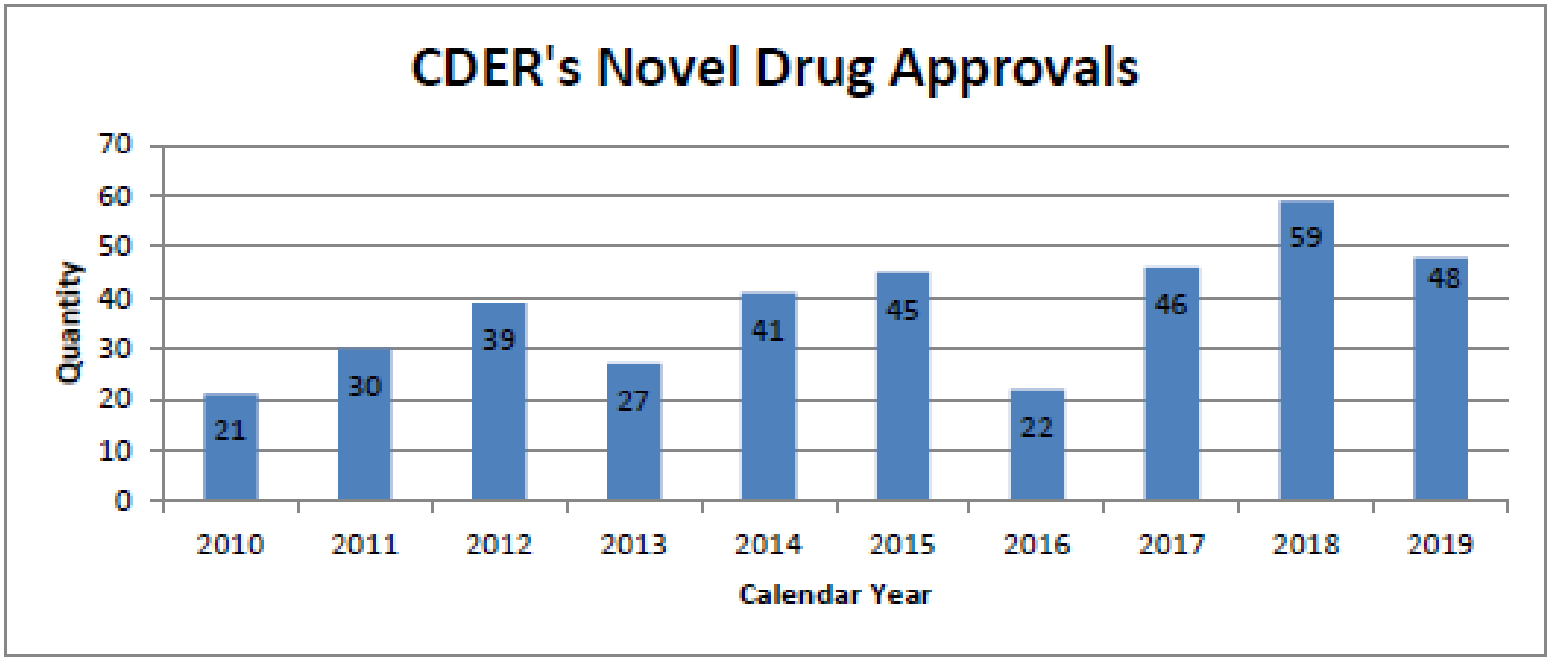
FDA Review Outcomes

- If not approvable, FDA sends Sponsor a Complete Response Letter
- If approvable, the FDA requests additional information from the sponsor to ensure appropriate labeling
- The NDA is again reviewed to specify label indication and dose levels
- Following drug approval, sponsors of the drug will be required to continually assess the safety of the drug

Phase 4 Studies

- Post-market surveillance of the drug to continually assess the safety of the drug
- FDA may request following the risk-mitigation (REMS) strategies
- May include evaluation of incidence and severity of rare adverse reactions, cost-effectiveness analyses, comparative trials, and quality of life studies

Drug Approvals by CDER from 2010-2019



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