Primer on Drug Development

Partners in Progress: Cancer Patient Advocates and FDA

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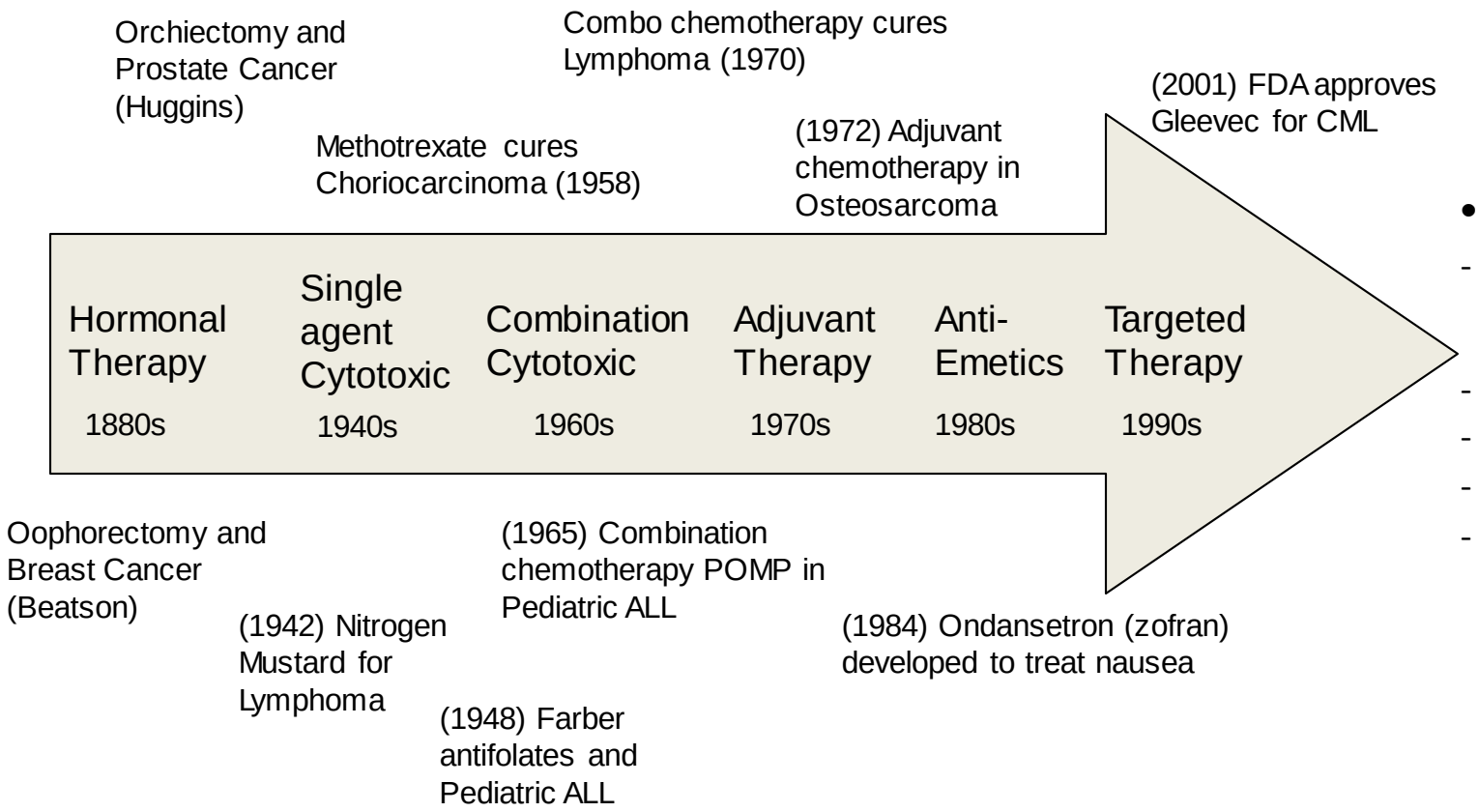
Outline of this talk

- Cancer drug and diagnostic development at 30,000 feet
- Intro to FDA Oncology
- The drug development process
- The drug approval process and expedited programs

Drug and device development from 30,000 feet

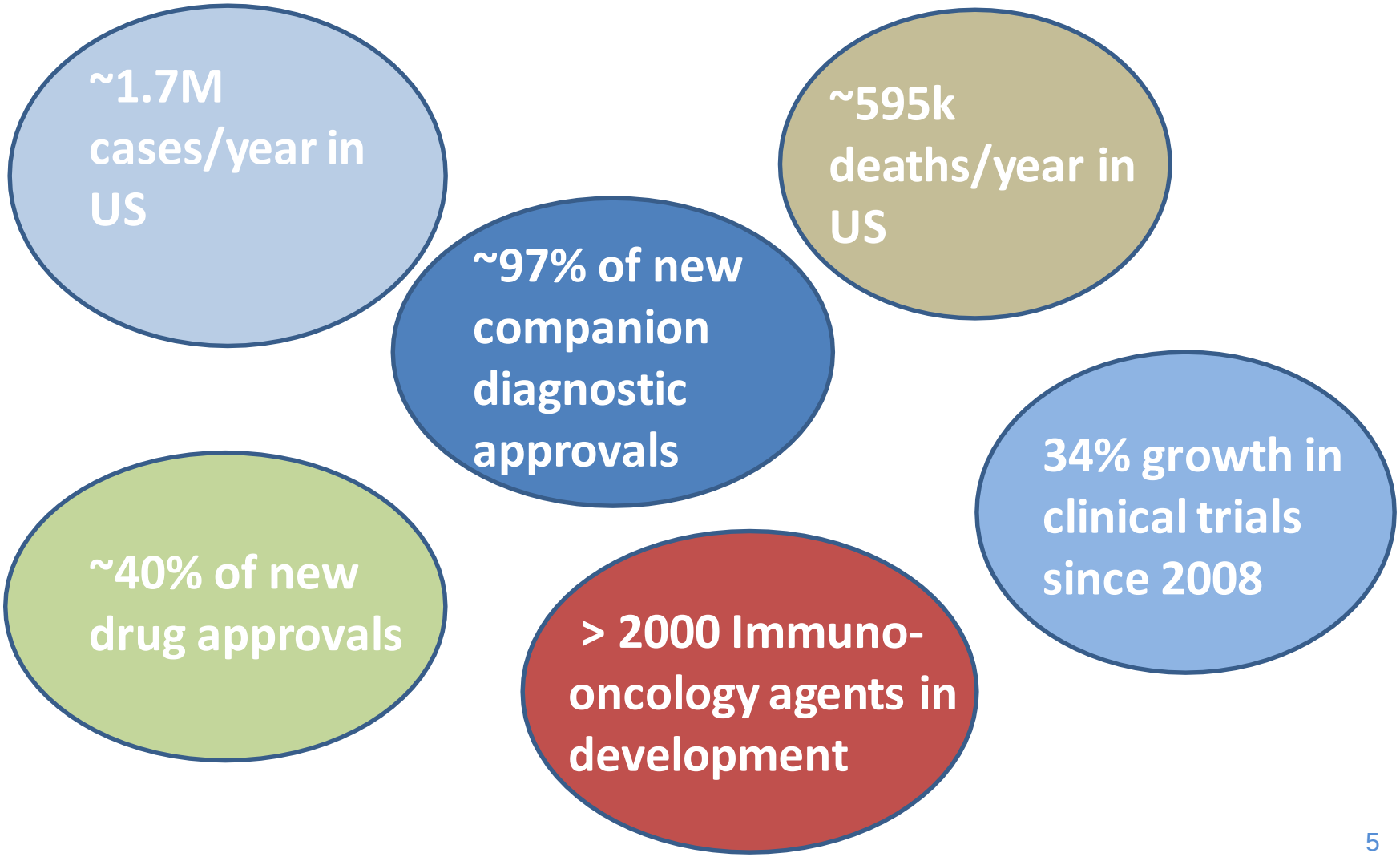
- **Expensive**: estimated $0.6B to $2.7B to develop a drug
- **Takes Time**: estimated average of a decade to go from first in human to FDA approval
- **Risky:** <10% of drugs entering trials are eventually approved
- One of most **complicated human endeavors**! More steps than the lunar landing
- **Increasing complexity**: gene therapy, massively parallel genetic sequencing, immunotherapy

Systemic Cancer Therapy Timeline



- 21st Century
  - Genomics and Personalized Oncology
  - Pathways
  - Immunotherapy
  - Gene Therapy
  - Molecular Imaging

Oncology by the numbers



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Key FDA Centers in Oncology Drug Development

Center for Drug Evaluation and Research (CDER)

- Drugs and Antibodies

Center for Biologics Evaluation and Research (CBER)

- Cellular and Gene Therapies, Vaccines

Center for Devices and Radiologic Health (CDRH)

- Devices, In Vitro Diagnostics, Diagnostic and Therapeutic Radiologics

Oncology Center of Excellence / Office of Hematology and Oncology Products

Oncology Products 1

- Breast cancer
- Gynecologic cancers
- Genitourinary cancers
- Supportive care

Oncology Products 2

- Lung, head and neck cancers
- Gastrointestinal cancers
- Melanoma and sarcoma
- Pediatric cancer, neuro-oncology and rare cancers

Hematology Products

- Benign hematology
- Hematologic cancers
- Hematologic support

Hematology and Oncology Toxicology

Pharmacologists / toxicologists supporting each clinical division

Multi-disciplinary Teams

Chemists
Pharmacologists
Toxicologists

Statisticians

Project
Managers

Clinical

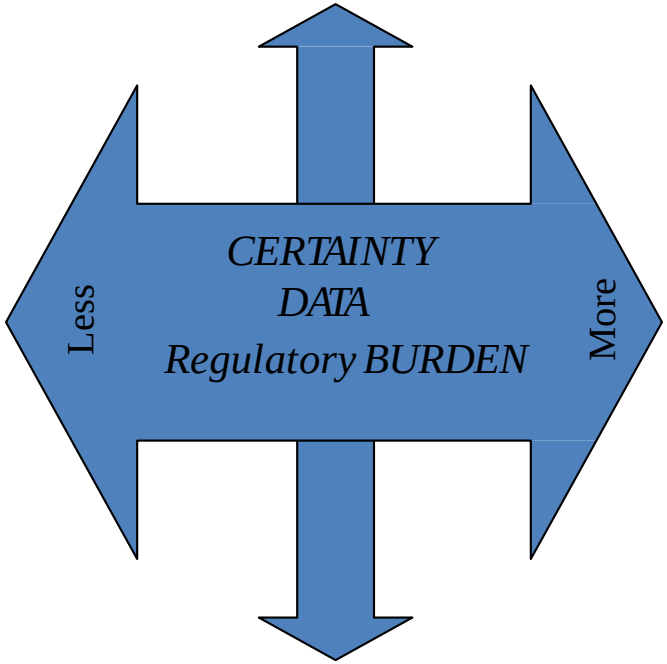
Striking the Balance

Flexible, Efficient, Interactive

"Toxic deaths!

Delayed safety findings!

FDA asleep at the Wheel"



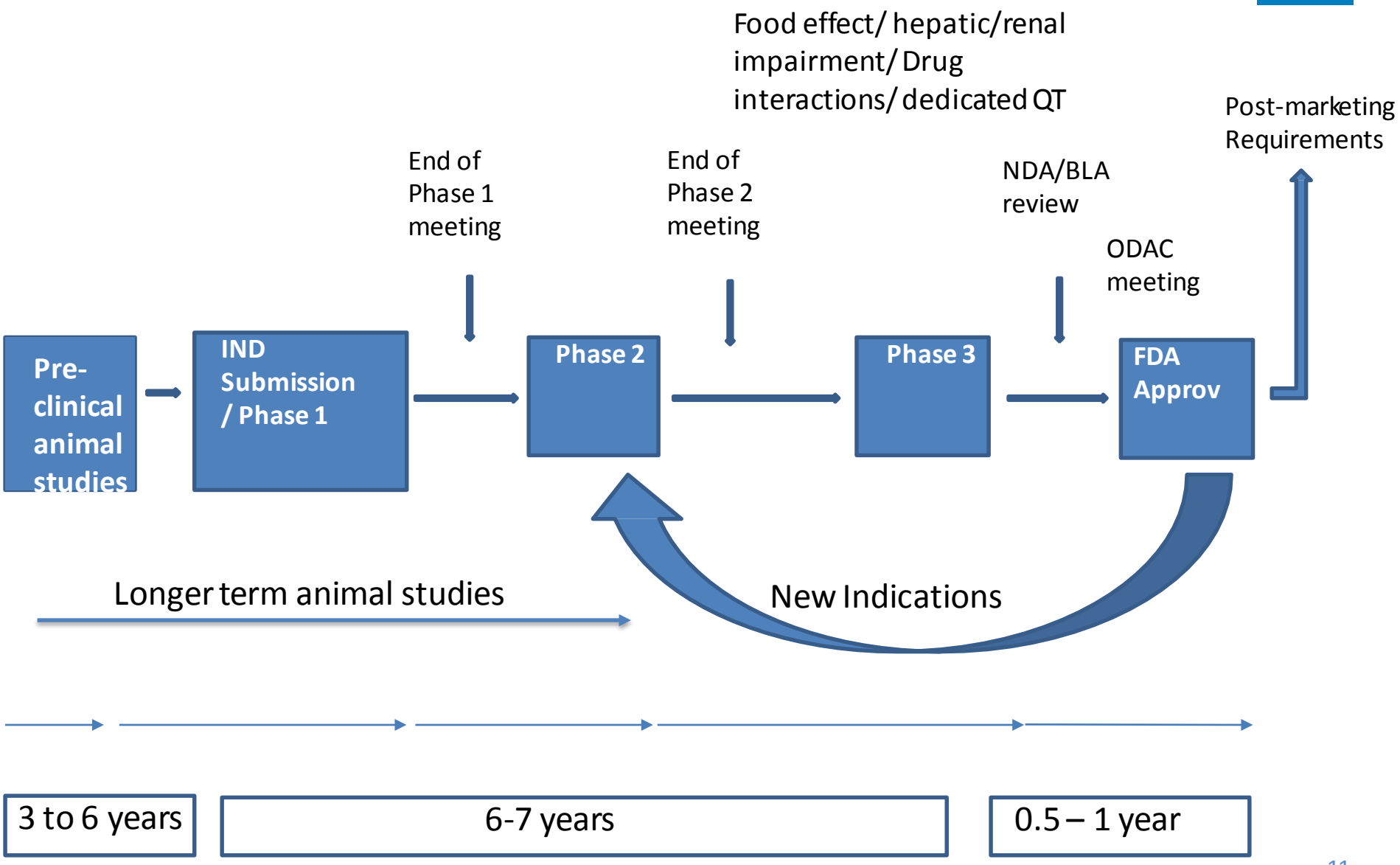
"Too Cautious!

Stifling Innovation!

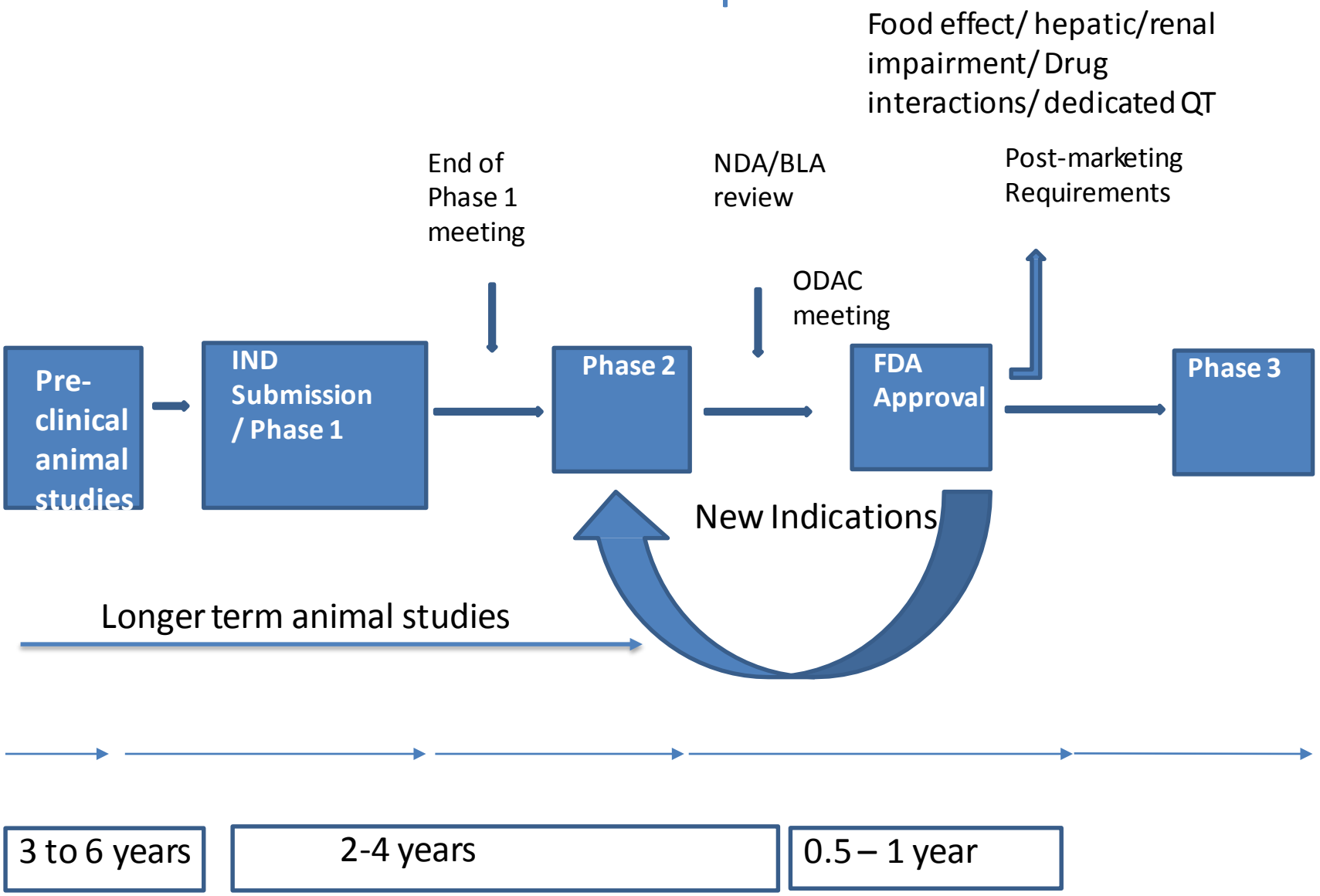
Reduce regulatory burden!"

Consistent, Thorough, Independent

Traditional Drug Development



Drug Development paradigm in era of breakthrough therapies



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“Phase I” studies

- Goal: Is the drug safe in humans?
  - Identify dose-limiting toxicities (DLTs)
  - Identify the recommended phase 2 dose (RP2D)

- Dose
  - Single-arm, small numbers of patients
  - Traditionally 3+3 design, or Bayesian adaptive design

“Phase II” studies

- Goal:
  - Initial assessment of clinical activity alone or in combination
  - Further define safety
  - Test/validate biomarkers to identify patients more/less likely to respond
- Design:
  - Frequently: single-arm trial measuring response rate

"Phase III" Studies

- Goal: confirm that the drug is effective
- Design:
  - Usually randomized
  - Ideally "double blind" and compared to placebo
  - In oncology: often not blinded and compared to standard available therapy or added to standard therapy

Recent trends in oncology clinical trials

- Increased reliance on single arm trials, expansion cohorts in phase 1 for breakthrough, transformative therapies
- Increased use of biomarker tests to better predict who will benefit
- Reevaluation of eligibility criteria to improve access and generalizability
  - Organ dysfunction
  - Minimum age
  - Brain metastases
  - Co-infection with HIV
- Increased patient engagement in design, conduct and interpretation of clinical trials
- Utilization of "Real World Evidence" to generate evidence on a drug's safety and effectiveness

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New Drug Application (NDA) or Biologics License Application (BLA)

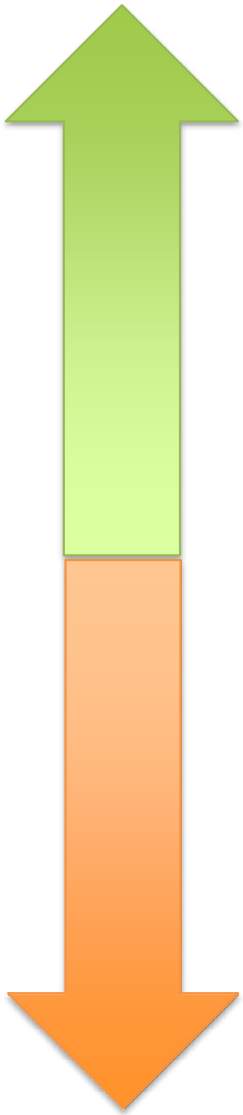
"Sponsor" wants FDA to approve a drug for marketing in the U.S. for use in a specific patient population.

Process:

- Sponsor submits patient-level data to FDA
- Analysis/ Discussion of benefits vs. risks by FDA
- If needed: outside opinion through ODAC (Oncologic Drugs Advisory Committee)
- Negotiate Labeling, post-marketing studies
- Regulatory decision

certainty

Benefit vs. Risk



Overall Survival: will I liver longer?

Progression Free Survival: will it take longer for my cancer to get worse?

Response Rate: will my cancer shrink?

Mild symptoms

Moderate symptoms

Severe symptoms

Life-threatening symptoms

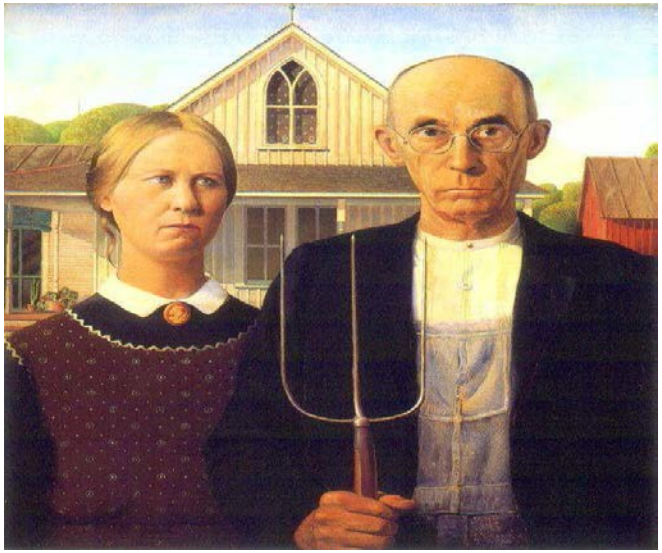
Death

uncertainty

Interpretation:

How Much Interpretation is Required?
How much residual uncertainty exists?

Unformed Figure, Jackson Pollock



American Gothic, Grant Wood

Expedited Programs

Why do we have expedited programs?

- To ensure therapies for **serious** conditions are developed efficiently and approved expeditiously

Expedited Programs

Expedited Programs

Fast Track Designation

Fast Track designation may be granted on the basis of **preclinical or clinical data**

<u>Requirements:</u>

1. Intended to treat a serious condition
2. Nonclinical or clinical data demonstrate the **potential** to address unmet medical need

Expedited Programs

Fast Track designation	**Breakthrough designation**
Priority Review designation	Accelerated Approval

Breakthrough Designation

Breakthrough designation may be granted on the basis of **clinical data**

Requirements:

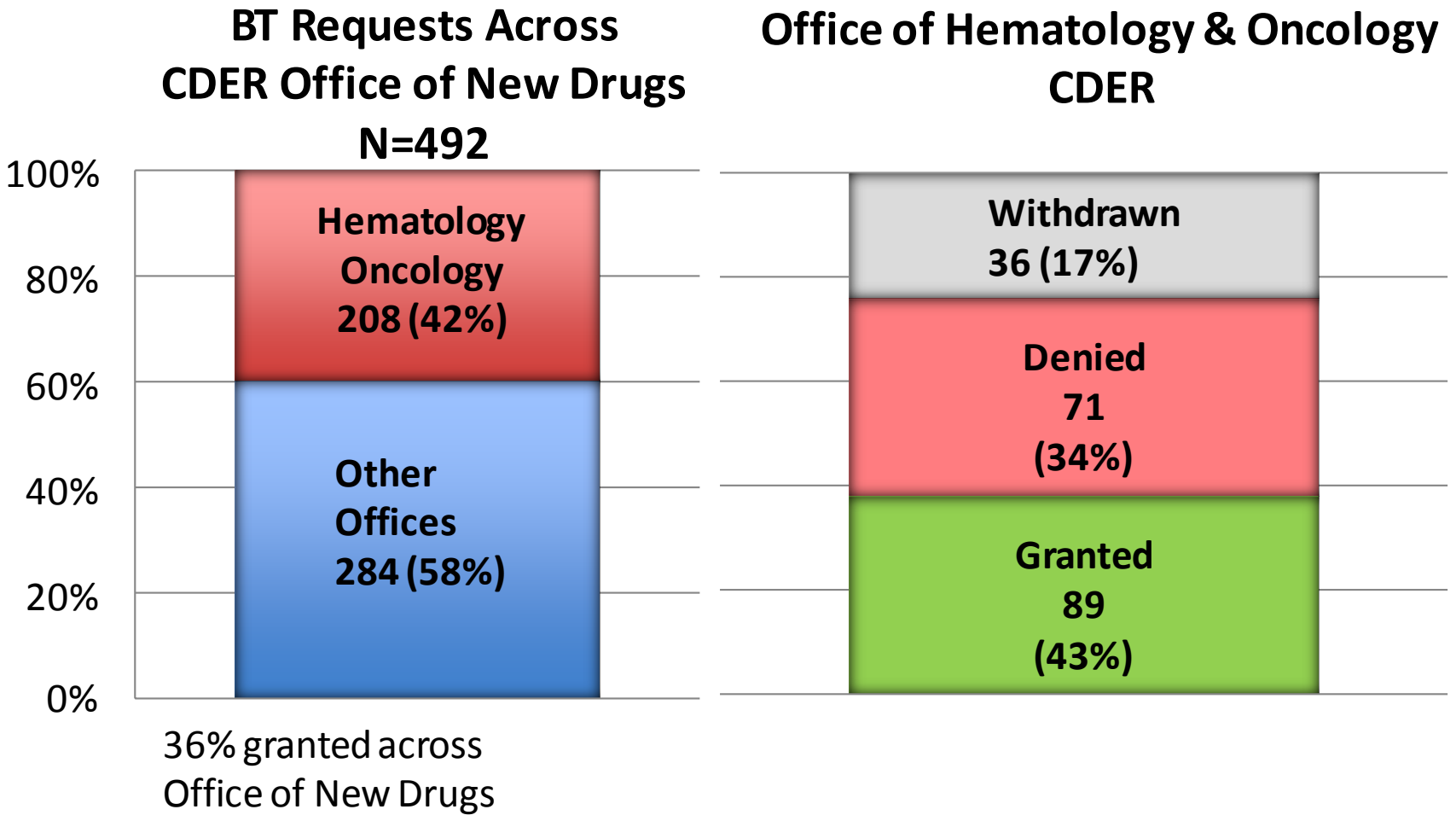
1. Intended to treat a serious condition
2. Fill an unmet medical need
3. Preliminary clinical data to indicate that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints

Breakthrough Designation

What does a breakthrough designation get you?

- Intensive guidance from FDA
- Organizational commitment
- Rolling review

Breakthrough (BT) Designations to Date*



36% granted across
Office of New Drugs

* as of September 6, 2017

Drug or Biologics applications- review and approval pathways

Expedited Programs

Fast Track designation	Breakthrough designation
Priority Review designation	Accelerated Approval

Review Pathways

- Standard review
- Rolling review
- Priority review
  - NDA or BLA for a drug that treats a **serious condition**
  - If approved would provide a **significant improvement in safety or effectiveness**
  - **6** month vs **10** month review clock
- Expedited review

Expedited Programs

Fast Track designation

Breakthrough designation

Priority Review designation

Accelerated Approval

Approval Pathways

- Regular Approval: based on clinical benefit

- Accelerated Approval: based on effect on endpoint that is **reasonably likely to predict clinical benefit** (e.g., response rate in a single arm trial)

Accelerated Approval

- Benefits: smaller, quicker trials with earlier outcome data
- Risks: meaningful clinical benefit has not been confirmed yet
- 10% of accelerated approvals in oncology have been withdrawn for failure to confirm a benefit

A drug has received FDA Breakthrough Therapy Designation. Which statement is true?

a) The drug has shown promise based on results from animal studies
b) The drug has shown promise based on results from early clinical studies in humans
c) The drug has been approved for use on the U.S. market based on “breakthrough” results

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A drug has been approved by FDA under the accelerated approval program.

Which statement is true?

a) The drug has shown an effect on overall survival in several large randomized trials
b) The drug has shown to have response rate similar to available therapy in a single-arm trial
c) The drug has shown to have a better response rate than available therapy in a single-arm trial

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FDA Drug Review vs. Label

Drug review

- Full review by each discipline
- Drugs@FDA

Drug label

- Agreed upon language between FDA and Sponsor
- Essential scientific information needed for the safe and effective use of the product
- Drugs@FDA, google, sponsor's website, etc.

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FDA
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