Considerations for Clinical Trial Design and Endpoints Supporting U.S. Drug Approval

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Disclosures

I have no financial disclosures.

Outline

- **FDA and OCE Background and Mission**
- Cancer Drug Development
- Clinical Trial Endpoints
- Approval Pathways
- Programs to Accelerate Drug Development
- Conclusions

FDA mission

- Assure the Safety, Efficacy, and Security of:
  - Drug and biological products
  - Medical devices
  - Food supply
  - Radiation products
- FDA does not take into account cost or payment issues.
- FDA does not regulate the “practice of medicine.”

Regulatory Framework

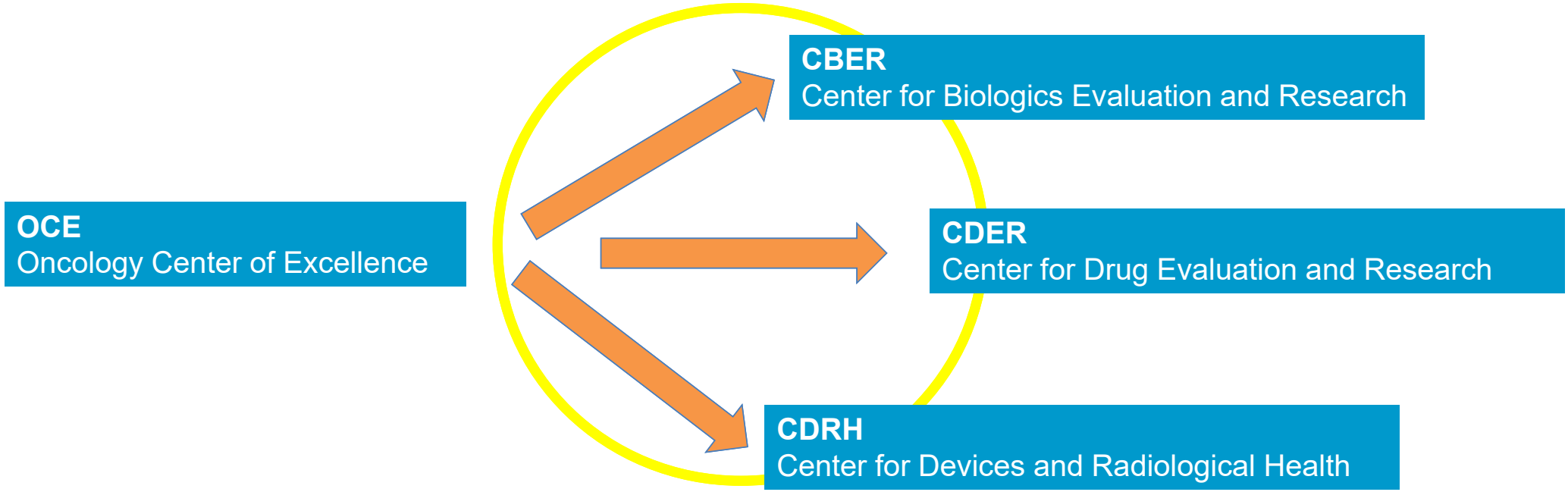
Safety and Efficacy Requirements:

- Drugs – Food Drug and Cosmetics Act
- Biologics – Public Health Services Act

Similar evidentiary framework.

Oncology Center of Excellence

- FDA Inter-center Institute as Part of 21st Century Cures Act
- Fosters unified interaction between 3 FDA Centers



Office of Oncologic Diseases

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Challenges in Oncology Drug Development and Review

Oncology drugs generally treat life-threatening diseases

- Balance between providing widespread patient access and adequately investigating the drug or biologic
- Trials involve small populations with short exposures
- Severe toxicities may be acceptable for modest gains in efficacy
- Indications span the spectrum: from prevention to treatment of incurable cancer
- Risk/benefit changes with different cancers
- Ethical concerns with trial design

Challenges in Oncology Drug Development and Review

Observations in clinical trials may not predict the "real-world" experience

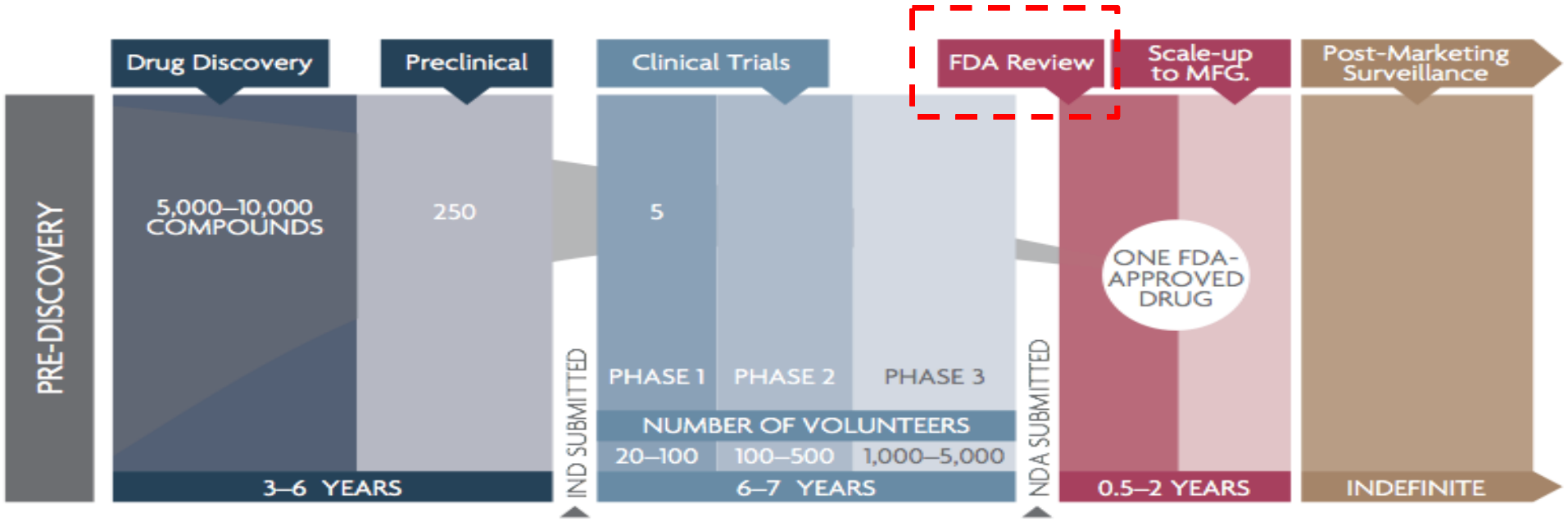
- Adverse event causality: drug, disease, or both?
- Exclusion of patients who might receive the drugs post-approval
  - Marginal performance status
  - Brain metastases
  - End-organ dysfunction
- Inadequate demographic representation
- Health care quality and attention greater for clinical trial patients
- Frequent off-label use

Striking the Balance

Flexible, Efficient, Interactive

Consistent, Thorough, Independent

Phase Success and Likelihood of Approval for Oncology Drugs



Source: PhRMA[6]

Investigational New Drug

Investigational

Any experiment in which a drug is administered or dispensed to or used involving one or more human subjects.

Drug

Recognized in US Pharmacopoeia, Homoeopathic Pharmacopoeia.

Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

Two IND categories:

Pharmaceutical company → Commercial

Investigator IND → Research (non-commercial)

Role of the FDA with INDs

- An IND is needed whenever trials in humans are conducted in the U.S.
- Multidisciplinary FDA review teams
- FDA teams may send Information Requests for revisions or clarifications
- FDA has 30 days to review an IND and to make a decision
  - May proceed
  - May proceed contingent upon revisions to protocol and/or informed consent document
  - Clinical hold
- Report a safety event to the FDA if it meets all three criteria:
  1. suspected adverse reaction
  2. serious
  3. unexpected

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Safety and Efficacy

- How do we measure safety?
  - **Safety** is characterized by **adverse events** reported by Investigators
    - Single arm safety data is of limited value (was the event due to the drug or due to the disease?)
    - We have traditionally accepted higher drug toxicity in oncology due to the high mortality rates associated with cancer

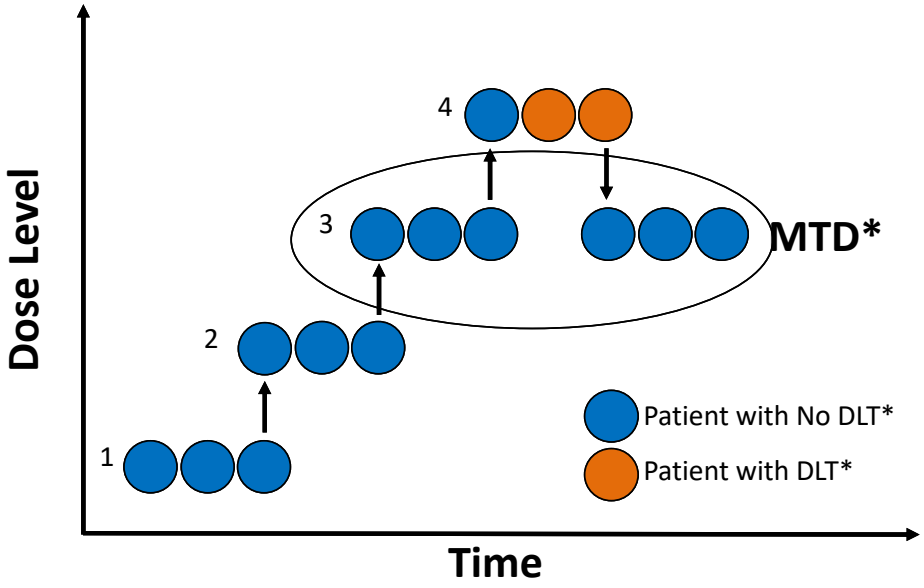
- How do we measure efficacy?
  - Clinical trial **efficacy endpoints**

- Taking the safety and efficacy data together with the disease, available therapy, and the current state of the science, the FDA review goal is to answer the following:

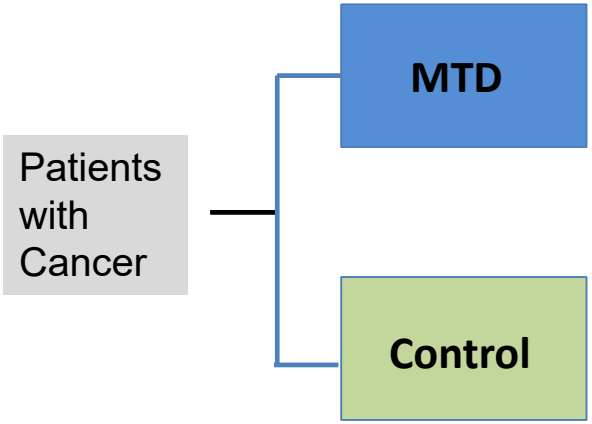
Does the product provide meaningful clinical benefit to patients?

Traditional Dose Selection Strategy

Dose Escalation



Registration



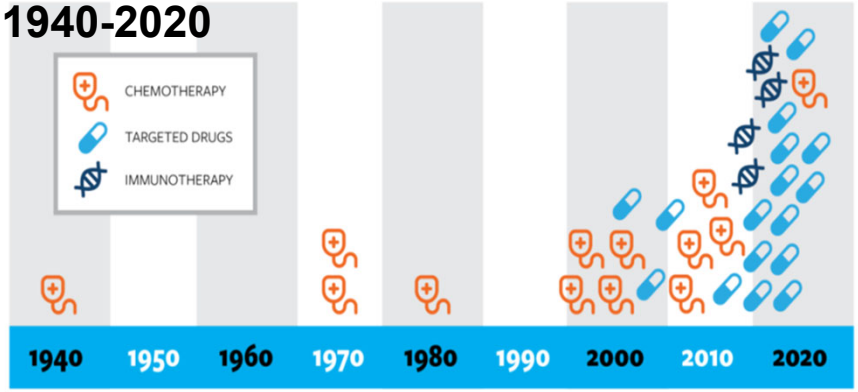
*DLT= Dose-limiting toxicity,
*MTD= Maximum tolerated dose

Hallmarks:

- Few patients at each dose
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

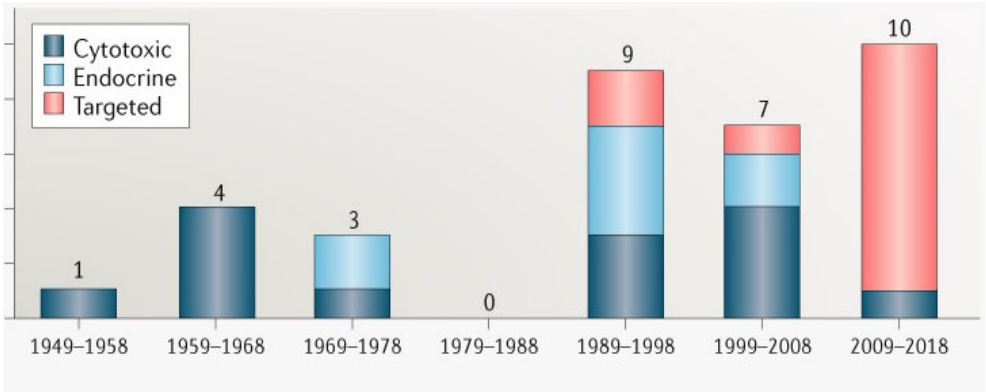
Cancer Drugs are Changing

Types of Drugs Approved for Lung Cancer, 1940-2020



Lung Cancer Research Foundation, 2020

Types of Drugs Approved for Breast Cancer, 1949-2018



Nature Reviews Drug Discovery, 2019

Key Differences

Cytotoxic Chemotherapies

- Steep dose-response, narrow therapeutic index
- MTD reached
- Fixed number of cycles or short duration of treatment
- Serious toxicities predictable, occur early
- Patients recover with time off of treatment

Molecularly Targeted Agents

- Different dose-response, potentially wide therapeutic index
- MTD may not be reached (or needed)
- Treatment for many months to years
- Serious toxicities may occur later
- Long-term tolerability, including chronic symptomatic Grade 1-2 toxicities, very important
- No time off treatment

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

Diarrhea

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥7 stools per day over baseline; hospitalization indicated	Life-threatening consequences (e.g., hemodynamic collapse)	Death

DLT

Consequences of Poor Dose Optimization

1. Failure to Bring a Drug to Market

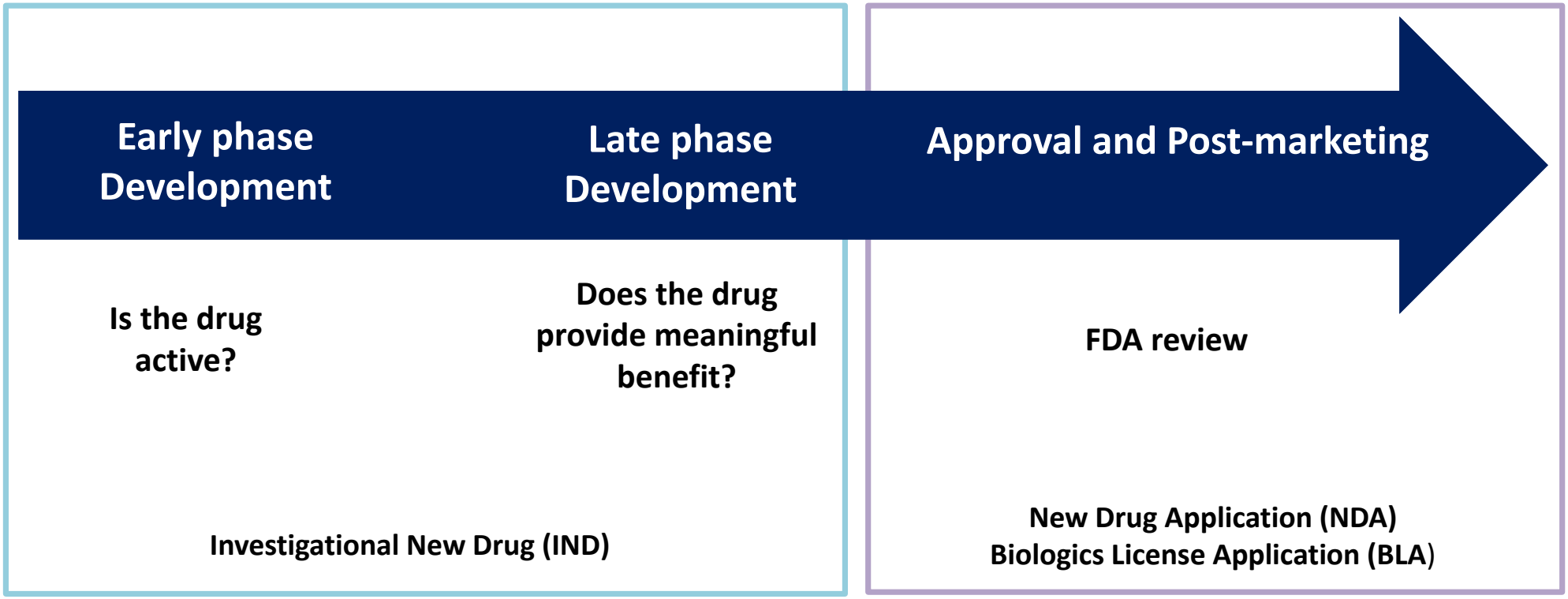
2. High Frequencies of Dose Modifications at Approved Doses

3. Postmarketing Dose Changes for Safety/Tolerability

Right Time for Dose Optimization = Prior to Approval

Clinical Trial Efficacy Endpoints

What question are you asking?



Clinical Trial Efficacy Endpoints

"What" you are measuring

Direct Measure of Clinical Benefit

- Directly measures how a patient "feels, functions, or survives"
- Examples: OS, PFS, clinical outcome assessments

Indirect Measures of Clinical Benefit intended to **PREDICT** clinical benefit

- Endpoints (surrogate & intermediate) may not measure clinical benefit in and of themselves
- Examples: DFS, ORR, CR, PFS
- Includes established surrogate endpoints (e.g., HIV viral load, durable complete response in leukemia)

Direct Measures of Efficacy: Overall Survival*

Strengths

- Direct measure of benefit
- Least prone to bias, no interpretation of the event (yes or no)
- Event timing (date of death) typically known to the day
- Includes information regarding safety
  - Deaths due to drug toxicity are part of the endpoint

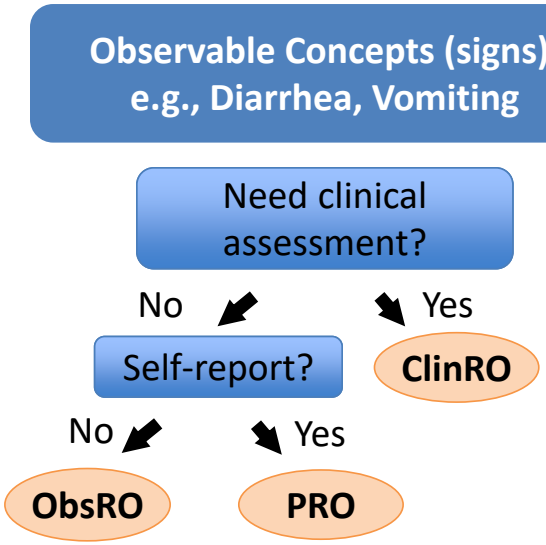
Limitations

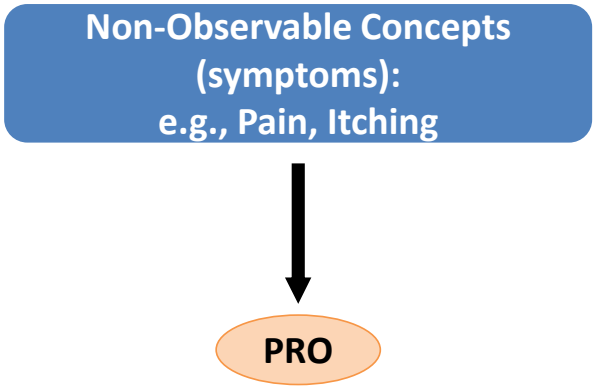
- Last event in a disease's natural history = longer and larger trial
- Requires randomized-controlled trial
- May be confounded by cross-over between treatment arms (depending on magnitude of effect)
- May be confounded subsequent therapies (that may extend life)

*The Gold Standard. However, meaningful clinical benefit of a survival advantage incorporates both toxicity of drug and **magnitude** of OS result.

Direct Measures of Efficacy: Clinical Outcome Assessments (COA)

COAs measure Signs and Symptoms





ClinRO = Clinician-Reported Outcome
PRO = Patient-Reported Outcome
ObsRO = Observer-Reported Outcome

Direct Measures of Efficacy: Clinical Outcome Assessments (COA)

Strengths

- COAs directly measures how a patient feels or functions: e.g., symptom improvement is direct clinical benefit
- COAs, if done well, may serve as important endpoints to support approval.

Limitations

- Hard to identify appropriate instruments (difficulty in measuring broad concepts such as QoL)
- Must define clinically-meaningful score changes and pre-specify them in the statistical analysis plan
- Determine the appropriate recall period
- Reporting bias possible in open-label and single-arm trials
- Handling missing data

Indirect Measures of Efficacy: Radiographic Evidence of Anti-Tumor Effect*

Response Rate (RR, ORR)

- Decrease in tumor by predefined threshold
- Important factors: tumor location, number of CRs, duration of response
- Interpretable in single-arm trials as evidence of treatment effect

Progression Free Survival (PFS)

- Time from randomization to growth of tumor (predefined threshold)
- PFS counts death as a progression event
- Requires randomized trial to be meaningful

* = in certain clinical settings, these endpoints can also provide evidence of direct clinical benefit

Indirect Measures of Efficacy: Radiographic Evidence of Anti-Tumor Effect

Strengths

- Earlier events than survival = smaller, shorter trial
- Radiographs can be captured and stored to verify the event
- Not confounded by cross-over or subsequent therapies (because the event, i.e., progression, occurs prior to crossover)

Limitations

- Uncertainty regarding clinical benefit: Will a given change in an asymptomatic radiographic finding predict true clinical benefit?
- Missing, incomplete, or infrequent assessments
- Difficult to measure in some instances (ill-defined lesions, bone metastases, peritoneal carcinomatosis) and subjective in all instances
- Often recommend Blinded Central Review (or audit) to address potential bias

To Summarize Endpoints…

Direct Measure of Clinical Benefit, “Feels, Functions, Survives”

- For example: OS, COA (measures of symptomatic or functional changes), PFS in certain clinical settings

Established Indirect Measure of Clinical Benefit

- High degree of certainty that the surrogate predicts clinical benefit (e.g., HIV viral load for anti-viral therapies)
- Is disease/indication-specific

Unestablished Indirect Measure of Clinical Benefit

- Limited existing data
- Lower certainty that the surrogate or intermediate endpoint is predicting true clinical benefit

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Approval Pathways

Two Pathways to U.S. Approval of Drugs and Biologics:

1. Regular Approval

2. Accelerated Approval

Regular Approval

Regular Approval

- Substantial evidence of Safety and Efficacy
- Well-controlled clinical trials (usually 2 or more)
- based on **a direct measure** of clinical benefit

No comparative efficacy

- As safe and effective as existing therapies, allowing for non-inferiority designs

Accelerated Approval

ALSO requires Substantial Evidence of Safety and Efficacy

Only for serious or life-threatening diseases

Benefits:

- Can be based on an **indirect measure** of clinical benefit, i.e., "an endpoint… reasonably likely… to predict clinical benefit"
- Usually provides for earlier events and smaller, quicker trials

Risks:

- Must demonstrate product is <u>better</u> than existing therapy (unlike regular approval, there is an implied comparative efficacy requirement here)
- May be required to complete post-marketing trials and confirm meaningful clinical benefit

Comparing Accelerated Approval to Regular Approval

	Accelerated Approval	Regular Approval
Diseases	Serious or life-threatening	Any
Comparative Efficacy	Yes	No
Endpoint	Indirect measure of clinical benefit*	Direct clinical benefit
Confirmatory Trial May Be Required	Yes	No

*** Accelerated approval uses an endpoint (often ORR) that is *reasonably likely to predict clinical benefit*.**

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Expedited Programs

One goal: to expedite the approval of safe and effective therapies to treat serious and life-threatening conditions

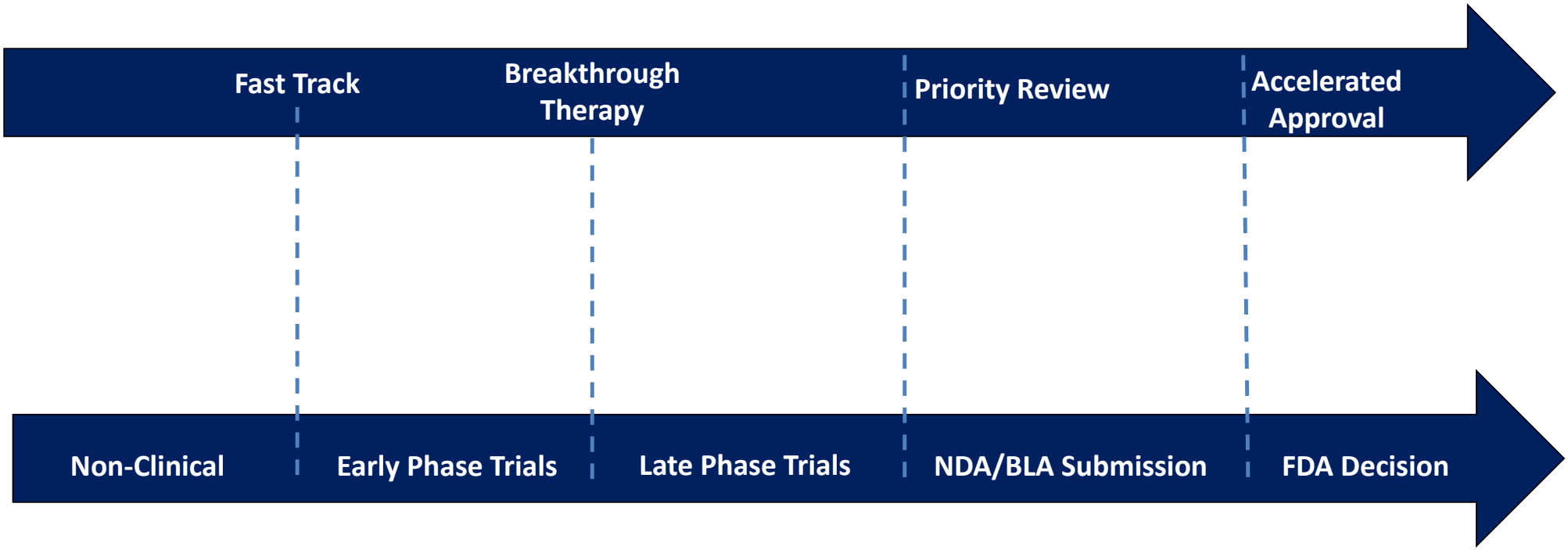
For drugs:
- Fast Track Designation
- Breakthrough Therapy Designation
- Priority Review
- Accelerated Approval

For biologics: Regenerative Medicine Advanced Therapy Designation (RMAT)

For devices: Breakthrough Devices Program

	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Program	Designation	Designation	Designation	Approval Pathway
Qualifying Criteria (condition must be serious)	Nonclinical or clinical data demonstrate potential to address unmet need	Preliminary clinical evidence demonstrates substantial improvement over available therapies	If approved would result in significant improvement in safety or efficacy	Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies
When to Submit	IND or after	Ideally no later than EOP2	With (s)BLA, (s)NDA	Discuss during development
Features	Expedite development and review Rolling review	Intensive development guidance Organizational commitment Rolling review	6 month vs. 10 month review clock for regulatory action after filing	Approval based on effect on endpoint that is reasonably likely to predict clinical benefit

Timing of Expedited Programs



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Conclusions (I)

- Review of cancer therapeutics involves severe and life-threatening diseases: an active area of research with many new drugs in development.
- Safety and efficacy data are examined to assess for meaningful clinical benefit.
- Direct measures of clinical benefit endpoints address how patients feel, function, or survive.
- Indirect measures of clinical benefit endpoints are used to *predict* clinical benefit.

Conclusions (II)

- Regular approval normally is based on measures of direct clinical benefit or an *established* surrogate.

- Accelerated approval is often based on intermediate or surrogate endpoints and confirmatory trials may be required to provide evidence of clinical benefit.

- Ultimately, the appropriateness of particular trial endpoints for the different approval pathways are context-specific (disease, stage, availability of other therapies, trial design) and are also driven by the state of the science of tumor biology.

- Early interaction with FDA is encouraged to enable feedback regarding trial design and endpoints.

FDA U.S. FOOD & DRUG ADMINISTRATION

ONCOLOGY CENTER OF EXCELLENCE

PROJECT FACILITATE

Assisting healthcare providers with requests for access to investigational oncology products

DO YOU NEED HELP SUBMITTING A SINGLE PATIENT IND EXPANDED ACCESS (EA) REQUEST (ALSO KNOWN AS COMPASSIONATE USE) FOR A PATIENT WITH CANCER?

...FDA's Oncology Center of Excellence (OCE) can help:

- Locate IRB resources
- Find an EA contact for a drug/biotech company
- Complete Form FDA 3926

Phone: (240) 402-0004

Email: OncProjectFacilitate@fda.hhs.gov

www.fda.gov/oce

Patients: Talk to your healthcare provider to discuss whether expanded access is an appropriate option.

Resources

https://www.fda.gov/

https://www.fda.gov/regulatoryinformation/guidances/

Endpoints

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071590.pdf

Expedited Pathways

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm358301.pdf

QUESTIONS?