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.”
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

OCE
Oncology Center of Excellence

CBER
Center for Biologics Evaluation and Research

CDER
Center for Drug Evaluation and Research

CDRH
Center for Devices and Radiological Health
Outline

- FDA and OCE Background and Mission
- **Cancer Drug Development**
- Clinical Trial Endpoints
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- Conclusions
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

“Too Cautious! Stifling Innovation! Reduce regulatory burden!”

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Consistent, Thorough, Independent
Phase Success and Likelihood of Approval for Oncology Drugs

- **Drug Discovery**: 5,000–10,000 compounds, 3–6 years
- **Preclinical**: 250
- **Clinical Trials**
  - **Phase 1**: Number of Volunteers 20–100, 6–7 years
  - **Phase 2**: Number of Volunteers 100–500
  - **Phase 3**: Number of Volunteers 1,000–5,000
- **FDA Review**: 0.5–2 years
- **Scale-up to MFG.**: Indefinite
- **Post-Marketing Surveillance**: Indefinite

Source: PhRMA
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

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

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

<table>
<thead>
<tr>
<th>Cytotoxic Chemotherapies</th>
<th>Molecularly Targeted Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Steep dose-response, narrow therapeutic index</td>
<td>• Different dose-response, potentially wide therapeutic index</td>
</tr>
<tr>
<td>• MTD reached</td>
<td>• MTD may not be reached (or needed)</td>
</tr>
<tr>
<td>• Fixed number of cycles or short duration of treatment</td>
<td>• Treatment for many months to years</td>
</tr>
<tr>
<td>• Serious toxicities predictable, occur early</td>
<td>• Serious toxicities may occur later</td>
</tr>
<tr>
<td>• Patients recover with time off of treatment</td>
<td>• Long-term tolerability, including chronic symptomatic Grade 1-2 toxicities, very important</td>
</tr>
<tr>
<td></td>
<td>• No time off treatment</td>
</tr>
</tbody>
</table>
## National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

### Diarrhea

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of &lt;4 stools per day over baseline</td>
<td>Increase of 4-6 stools per day over baseline</td>
<td>Increase of ≥7 stools per day over baseline; hospitalization indicated</td>
<td>Life-threatening consequences (e.g., hemodynamic collapse)</td>
<td>Death</td>
</tr>
</tbody>
</table>

[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?

- Early phase Development
  - Is the drug active?
  - Investigational New Drug (IND)

- Late phase Development
  - Does the drug provide meaningful benefit?

- Approval and Post-marketing
  - FDA review
  - New Drug Application (NDA)
  - Biologics License Application (BLA)
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

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

**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)
Direct Measures of Efficacy: Clinical Outcome Assessments (COA)

COAs measure Signs and Symptoms

Observable Concepts (signs): e.g., Diarrhea, Vomiting

Need clinical assessment?

No

Self-report?

No

ObsRO

Yes

ClinRO

Non-Observable Concepts (symptoms): e.g., Pain, Itching

PRO

ClinRO = Clinician-Reported Outcome
PRO = Patient-Reported Outcome
ObsRO = Observer-Reported Outcome
Direct Measures of Efficacy: Clinical Outcome Assessments (COA)

**Strengths**
- COAs directly measure 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

- 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 better 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

<table>
<thead>
<tr>
<th></th>
<th>Accelerated Approval</th>
<th>Regular Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diseases</strong></td>
<td>Serious or life-threatening</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Comparative Efficacy</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Indirect measure of clinical benefit*</td>
<td>Direct clinical benefit</td>
</tr>
<tr>
<td><strong>Confirmatory Trial May Be Required</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* 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
<table>
<thead>
<tr>
<th>Program</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Priority Review</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Designation</td>
<td>Designation</td>
<td>Designation</td>
<td>Approval Pathway</td>
</tr>
</tbody>
</table>

### Qualifying Criteria (condition must be serious)

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<th>Breakthrough Therapy</th>
<th>Priority Review</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclinical or clinical data demonstrate potential to address unmet need</td>
<td>Preliminary clinical evidence demonstrates substantial improvement over available therapies</td>
<td>If approved would result in significant improvement in safety or efficacy</td>
<td>Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies</td>
</tr>
</tbody>
</table>

### When to Submit

<table>
<thead>
<tr>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Priority Review</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND or after</td>
<td>Ideally no later than EOP2</td>
<td>With (s)BLA, (s)NDA</td>
<td>Discuss during development</td>
</tr>
</tbody>
</table>

### Features

<table>
<thead>
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<th>Breakthrough Therapy</th>
<th>Priority Review</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expedite development and review Rolling review</td>
<td>Intensive development guidance Organizational commitment Rolling review</td>
<td>6 month vs. 10 month review clock for regulatory action after filing</td>
<td>Approval based on effect on endpoint that is reasonably likely to predict clinical benefit</td>
</tr>
</tbody>
</table>
Timing of Expedited Programs

- Fast Track
- Breakthrough Therapy
- Priority Review
- Accelerated Approval

- Non-Clinical
- Early Phase Trials
- Late Phase Trials
- NDA/BLA Submission
- FDA Decision
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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.
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

Expedited Pathways
QUESTIONS?