Primer on Drug Development

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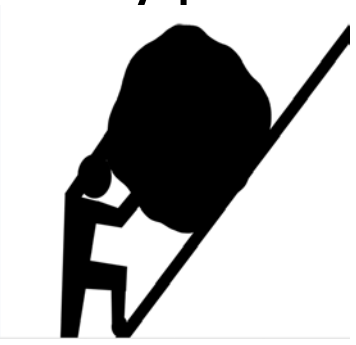
We need safe & effective drugs!

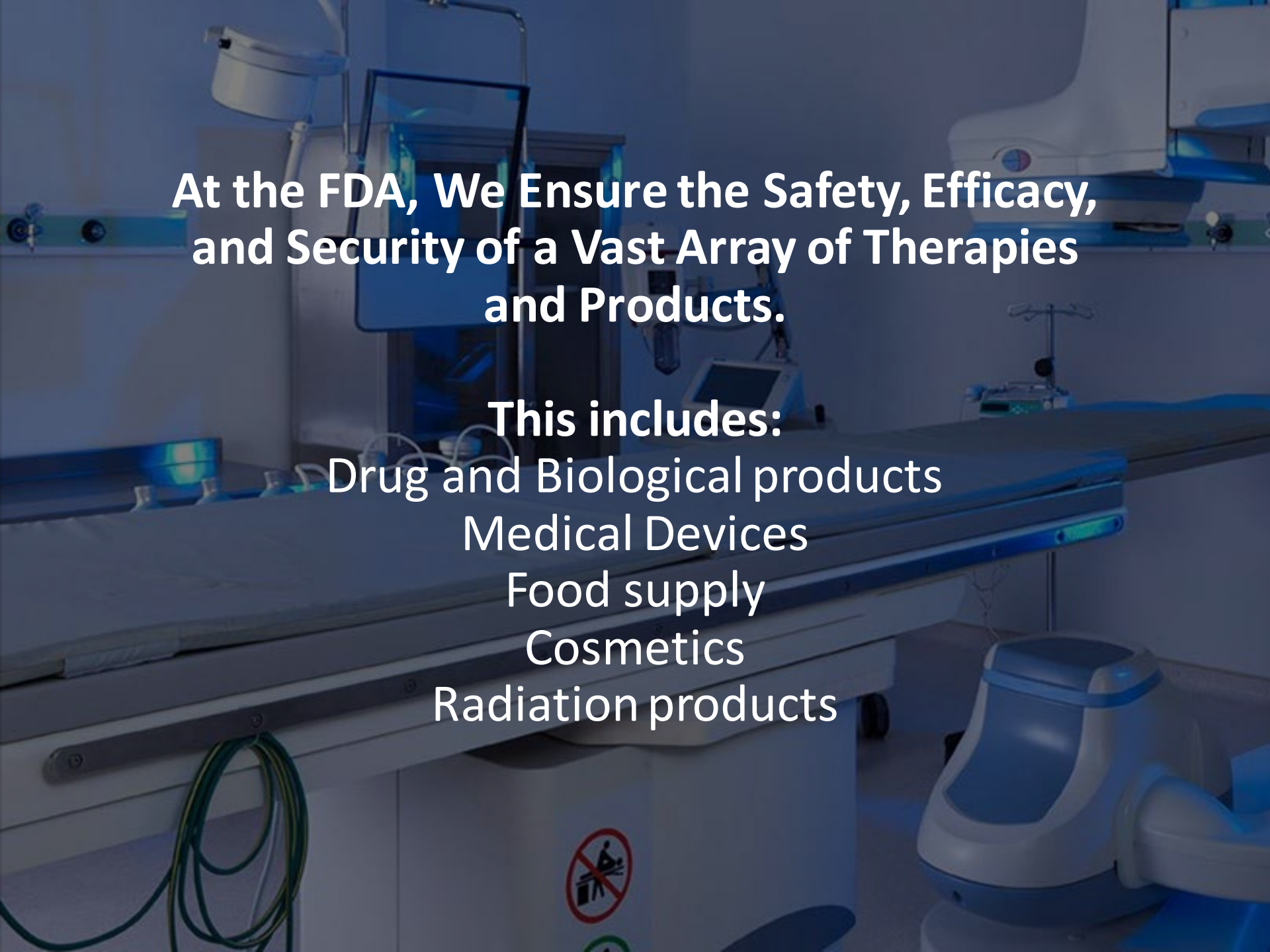
Outline

- FDA and OCE's role in Drug development
- Regulatory Pathways for drug approval
- Measurement of Symptoms and Function
- FDA programs to expedite drug development

Drug and Device Development

- **Expensive**: estimated $0.6B to $2.7B to develop a drug
- **Takes Time**: average of a decade from first in human to FDA approval
- **Risky:** <10% of drugs entering trials are eventually approved
- **Increasing complexity**: gene therapy, massively parallel genetic sequencing, immunotherapy





At the FDA, We Ensure the Safety, Efficacy, and Security of a Vast Array of Therapies and Products.

This includes:

Drug and Biological products

Medical Devices

Food supply

Cosmetics

Radiation products

Key FDA Centers

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

Center for Devices and Radiologic Health (CDRH)

Oncology Center of Excellence

- FDA Inter-center Institute as Part of 21st Century Cures Act
- Integrated approach to clinical evaluation of cancer products
- Leverages combined skills of regulatory scientists and reviewers from the 3 key centers who review cancer products

High Emotion and Public Interest

Changing Landscape for Oncology Drug Development

- In vitro diagnostics identifying enriched subpopulations driven by strong genetic / biologic rationale
- Immunotherapies
- Many more available therapies
- Beyond incremental benefits…combination regimens to overcome resistance and really move survival out to cure?

Treating patients – not just the disease

Striking the Balance

Flexible, Efficient, Interactive

Consistent, Thorough, Independent

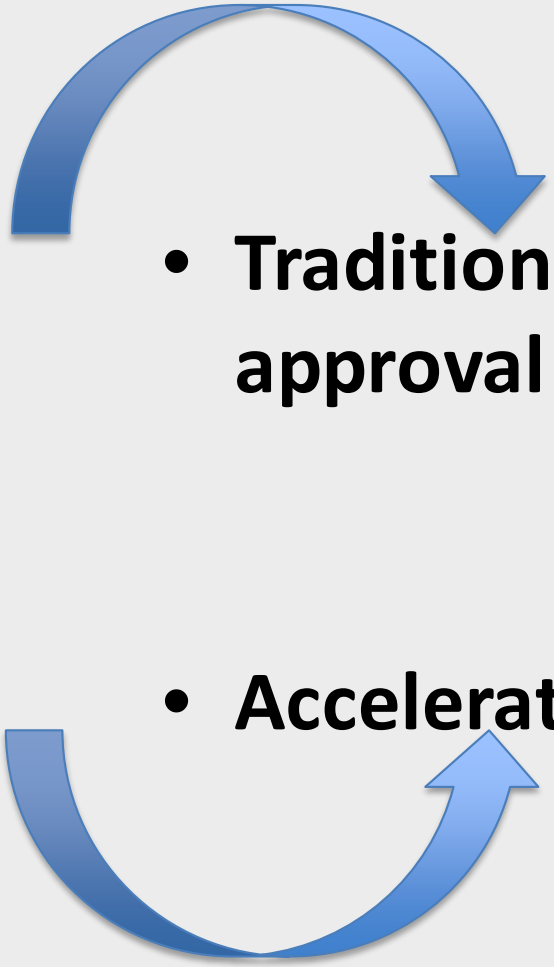
Regulatory Framework

Safety and Efficacy Requirements:
Drugs (FD&C Act) & Biologics (PHS Act)

- The Food Drug and Cosmetics Act
- The Public Health Services Act

Similar evidentiary framework

Two Pathways to Approval of Drugs and Biologics



- **Traditional (or regular) approval**
- **Accelerated approval**

Traditional or "Regular" Approval

- Traditional approval requires
  - Substantial evidence of Safety and Efficacy
  - Well-controlled clinical trials (usually 2 or more)
  - based on **prolongation of life, a better life or an established surrogate for either of the above**

- No comparative efficacy requirement
  - As safe and effective as existing therapies, allowing for non-inferiority designs

Direct Clinical Benefit Endpoint:

Overall Survival:

Strengths:

- Least prone to bias (death yes or no)
- Event timing typically known to the day
- Includes information regarding safety
- Includes deaths due to drug toxicity

Limitations

- Longer and Larger Trial needed
- Requires randomized controlled trial
- Comparison with historical control limited
- May be confounded by cross-over and subsequent therapies if given unequally between arms

Measuring Symptoms and Function

- **Research Collaboration with Kaiser Permanente Northern California- Real-World Physical Function**
- **Friends of Cancer Research Collaboration on Comparative Tolerability**
- **Annual FDA Workshops to Advance the Measurement and Analysis of PRO**
- **SPIRIT-PRO Standardizing Protocols**
- **SISAQOL Standardizing Analytic Methods**

What questions can PRO answer?

Efficacy:

- Like OS, PROs can be a direct measure of clinical benefit *if it accurately measures how a patient feels or functions*
- Does the drug improve disease related symptoms or functional deficits**?**

Tolerability: How do patients feel while on therapy?

- Tolerance/ Symptoms
- Like AE data, more descriptive in nature
- Work underway to standardize analysis and presentation to complement traditional safety and efficacy results

Example of Disease Symptom Benefit

- **Ruxolitinib (Jakafi™) for myelofibrosis**
  - Primary endpoint: Radiographic Surrogate Endpoint
    - Reduction in spleen size by (MRI) (Splenic Response Rate)
  - Key secondary endpoint: PRO **Total Symptom Score**
    - Abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety

- Is shrinking a patient's spleen clinical benefit? The total symptom score was very helpful in correlating the anti-tumor effect with improvements in how patients were feeling (symptoms) and Jakafi™ was granted traditional approval.

Advancing PRO in Oncology

Proactive Efforts to Standardize and Optimize the PRO effort in Oncology

- FDA Oncology PRO lead reviewers in each division
- Monthly meetings between FDA Oncology Office and Clinical Outcomes Assessment Staff
- Multiple regulatory science projects analyzing in-house PRO data
- Active interaction with multiple PRO stakeholders

Accelerated Approval

- ALSO requires Substantial Evidence of Safety and Efficacy
- "Provide meaningful therapeutic benefit… over existing therapies"
- *Can be based on a* ***"Surrogate endpoint… reasonably likely… to predict clinical benefit" or a "Clinical endpoint other than survival or irreversible morbidity"***

Surrogate Endpoints:

Response Rate (RR)

- Shrinking a tumor

Progression Free Survival (PFS)

- PFS counts death as a progression event and is preferred

Accelerated Approval:

Benefits:

- Use of an unestablished surrogate endpoint
- Usually provides for earlier events and smaller, quicker trials

Risks:

- Must demonstrate product is better than existing therapy
- Post-marketing trials required to confirm meaningful clinical benefit

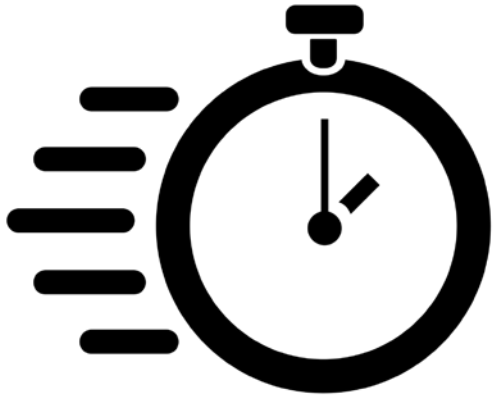
5% of Accelerated Approval

indications in malignant hematology and oncology have been withdrawn for failure to confirm a benefit **NOT** a failure of the accelerated approval program

Expedited Programs

Accelerated approval **plus** -

- Fast track designation
- Breakthrough therapy
- Priority review



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

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

Review Timelines

- Standard 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**
  - **4 m**onth review clock advantage
- Expedited review

In Conclusion:

Rapidly changing landscape for oncology drug development

FDA is committed to promoting the development of safe and effective drugs and biologics

Expedited Programs are available to facilitate approval of treatments for cancer

Surrogate endpoints and innovative study design can make trials more efficient

Commitment to improving measurement of symptoms and function

Acknowledgements

- Paul Kluetz
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Questions

Slides Courtesy of Paul Kluetz

For information on how a drug is approved, review the FDA label and the clinical reviews at Drugs@FDA.

Resources

FDA Drug Review

- Provides details of Agency's assessment of drug application
- Includes full review by each FDA 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.