Primer on Drug Development

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We need safe and effective drugs!

Outline

- FDA and OCE's role in Drug development
- The Drug Development Process
- The Drug Approval Process
- 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

What does FDA regulate?

a) U.S. Marketing of Drugs
b) Drug costs
c) Treatment guidelines
d) All of the above

Key FDA Centers

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

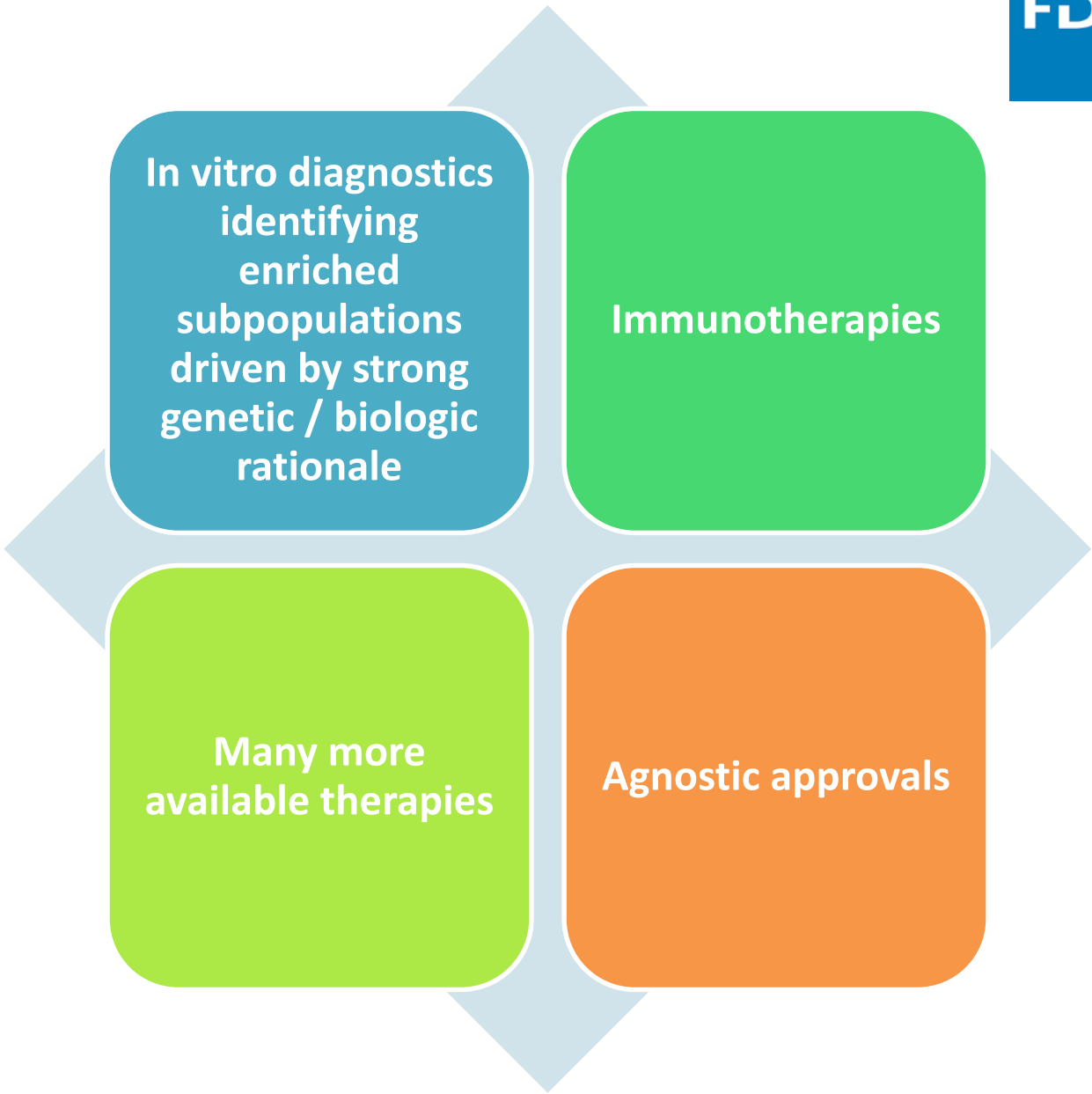
Center for Devices and Radiologic Health (CDRH)

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



Agnostic Approvals

- **Pembrolizumab:** indicated for tumors with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors. Approval 2017.
- **Larotrectinib:** treatment of adult and pediatric patients with solid metastatic tumors that have neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions. Approval 2018.
- **Entrectinib:** treatment of adult and pediatric patients with a variety of tumors that have *NTRK* gene fusions. Also indicated in adults with metastatic NSCLC whose tumors are ROS-1 positive. Approval 2019.

*All received accelerated approvals

Who Reviews Cancer Drugs?

- Clinical reviewers: hematologists, oncologists, NPs, PAs, PharmDs
- Nonclinical: pharmacology/toxicology reviewers
- Chemistry, Manufacturing, Controls reviewers
- Clinical pharmacology reviewers
- Biostatisticians
- Microbiologists

Striking the Balance

Flexible, Efficient, Interactive

Consistent, Thorough, Independent

PRE-CLINICAL

Drug Sponsor's Discovery and Screening Phase

Drug Developed

Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

1

Animals Tested

Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

2

IND Application

The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from intial testing that include, the drug's composition and manufacturing, and develops a plan for testing the drug on humans.

IND REVIEW

FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protection.

FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold.

The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, are effective and their health benefits outweigh their known risks.

CLINICAL

Drug Sponsor's Clinical Studies/Trials

3

PHASE 1

20-80

The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.

4

PHASE 2

100's

The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

5

PHASE 3

1000's

The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

NDA REVIEW

FDA's New Drug Application (NDA)Review

10 Drug Labeling

FDA reviews the drug's professional labeling and assures appropriate information is communicated to health care professionals and consumers.

8-9 Application Reviewed

After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA Review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.

7 NDA Application

The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

6 Review Meeting

FDA meets with a drug sponsor prior to submission of a New Drug Application.

11 Facility Inspection

FDA inspects the facilities where the drug will be manufactured.

FASTER APPROVALS

The **Accelerated Approval** program allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. The approval is faster because FDA can base the drug's effectiveness on a "surrogate endpoint," such as a blood test or X-ray result, rather than waiting for results from a clinical trial.

The **Fast Track** program helps reduce the time for FDA's review of products that treat serious or life-threatening diseases and those that have the potential to address an unmet medical need. Drug sponsors can submit portions of an application as the information becomes available ("rolling submission") instead of having to wait until all information is available.

12 FDA Drug Approval

FDA reviewers will approve the application or issue a response letter.

POST-MARKETING

FDA's Post-Approval Risk Assessment Systems

PHASE 4

Because it's not possible to predict all of a drug's effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA's post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

www.fda.gov/medwatch
(800) FDA-1088 (322-1088) phone
(800) FDA-0178 (322-0178) fax

MEDWATCH

FDA's MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories, and other education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.

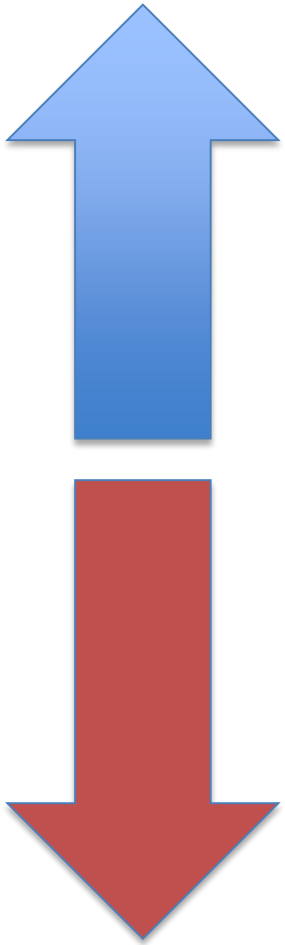
PDUFA

Prescription Drug User Fee Act

Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.

PDUFA has enabled the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process. Under PDUFA, drug companies agree to pay fees that boost FDA resources, and FDA agrees to time frames for its review of new drug applications.

Benefit/Risk



Overall Survival: Will I live 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

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)

Accelerated Approval

Benefits:

- Use of an 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 approvals in oncology have been withdrawn for failure to confirm a benefit

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

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 (10 month)
- Priority review (6 month)
  - NDA or BLA for a drug that treats a **serious condition**
  - If approved would provide a **significant improvement in safety or effectiveness**
  - **4 month** review clock advantage
  - Real-time Oncology Review (RTOR)

How Can I Find a Trial?

The **National Cancer Institute (NCI)** sponsors most government-funded cancer clinical trials.

- www.cancer.gov/clinicaltrials/ or by calling 1-800-4-CANCER (1-800-422-6237).
- Search by type and stage of cancer, by type of study (ex. treatment or prevention), or by zip code

The **National Institutes of Health (NIH)** has a large database of clinical trials at www.clinicaltrials.gov

- Note: All studies listed are not cancer trials

Treating patients: Not just the disease

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FDA
U.S. FOOD & DRUG
ADMINISTRATION