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Speaker Introduction

Sean Christensen received a Bachelor's degree from Utah State University in biology with an emphasis in human physiology and minor in chemistry. He then received his Doctorate of Pharmacy degree from the University of Utah College of Pharmacy. He completed his PGY1 pharmacy practice residency at University of Utah Health. He is the current Medication-Use Safety and Policy PGY2 pharmacy resident at University of Utah Health. His professional interests include drug information, medication safety, inter-professional team-based patient care, and primary care.

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Sean Christensen, PharmD
November 2021

A Play by Play of the FDA: Insight into the FDA Approval Process

Sean Christensen, PharmD
Medication-Use Safety & Policy Specialty Resident
University of Utah Health
sean.christensen@pharm.utah.edu

Disclosure

- Relevant Financial Conflicts of Interest
  - CE Presenter, Sean Christensen: None
  - CE mentor, Erin Fox: None
- Off-Label Uses of Medications
  - None

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Learning Objectives (Pharmacists)

- **Identify regulatory changes and legislation that have led to changes in the FDA approval process**
- **Distinguish correct minimum evidence required for a specific pathway of approval**
- **Contrast approval processes using specific medication examples**

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Learning Objectives (Technicians)

- **Name different pathways of FDA approval**
- **List 2 regulatory or legislative actions that changed the FDA approval process**
- **Use available resources to determine if a product is FDA approved**

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Abbreviations

- ANDA = Abbreviated New Drug Application
- CDER = Center for Drug Evaluation and Research
- FDA = Food and Drug Administration
- NDA = New Drug Application
- OIG = Office of the Inspector General
- OTC = Over the Counter
- RCT = Randomized Controlled Trial
- Rx = Prescription

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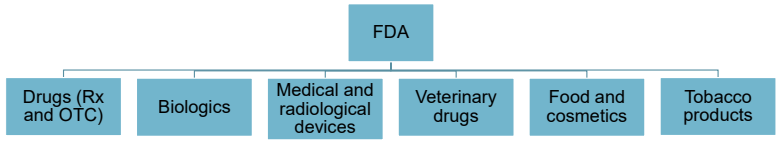
Roadmap

What Does FDA Approved Mean?

- Safe and effective?
- Not all FDA approval pathways are created equal
- Pharmacists and technicians should be aware of the differences between these pathways

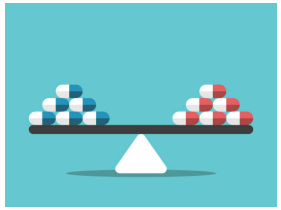
Six FDA Centers



(Center for Drug Evaluation and Research *How drugs are developed and approved*)

Center for Drug Evaluation and Research (CDER)

- Evaluate new medications
- Ensure health benefits outweigh risks
  - Safety and efficacy
  - Prescription, generic, and OTC mediations
- Drug reviews
- Post-marketing risk assessment



(Center for Drug Evaluation and Research *Frequently asked questions about CDER*)

Roadmap

Common Pathways of FDA Approval

- Standard Review
- Fast Track
- Accelerated Approval
- Priority Review
- Breakthrough Therapy
- Orphan Drug

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

Standard Review

Standard Review

- Analysis of condition and available treatments
- Clinical data assesses benefits and risks
- Risk management strategies if needed
- FDA's goal is to review application within 10 months of submission

(Center for Drug Evaluation and Research *Drug development & approval process*)

Fast Track (1988)

Fast Track

Speed up the review of drugs for serious conditions AND that meet an unmet medical need

AIDS	Alzheimer Disease	Heart Failure	Cancer

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

Fast Track

- Either provides a therapy where there isn't one currently OR
- If a current therapy exists:
  - Shows superiority
  - Avoids side effects
  - Improves diagnosis
  - Decreases toxicity
  - Addresses emerging public health need

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

What Does the Fast Track Designation do for Manufacturers?

- More frequent FDA meetings
- More frequent written communication from FDA
- Can pursue Accelerated Approval and Priority Review
- Rolling review

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

Fast Track: Examples

- **Cannabidiol (Epidolex®) – 7/31/2020**
- **Nivolumab (Opdivo®) – 1/22/2021**
- **Carbotegravir and Rilpivirine ER Injection (Cabenuva) – 1/22/21**

(U.S. Food and Drug Administration *CY 2021 CDER fast track calendar year approvals*)

Accelerated Approval (1992)

Accelerated Approval

Speed up approval of drugs for serious conditions AND fill an unmet need based on:

- Surrogate endpoint: measure "thought" to predict benefit (not a measure of benefit in itself) OR
- Intermediate clinical endpoint: "reasonably likely" to predict benefit

Still "need" to undergo phase 4 confirmatory trials

FDA "may" withdraw or change a labeled indication if no benefit

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

Accelerated Approval: Example

- Aducanumab (Aduhelm™)
  - Approved based on the surrogate endpoint of decreased β-amyloid plaque
  - Phase 3 clinical trials were conflicting with only 1 of 2 showing clinical efficacy
  - Also approved amidst some continuing controversy
    - FDA advisory panel did not recommend approval
    - Recent referral to OIG

(*Aduhelm FDA Clinical Review*)

Priority Review (1992)

PRESCRIPTION DRUG USER FEE ACT

Priority Review

May show significant improvements in safety, efficacy, diagnosis, or prevention of serious conditions

Increase efficacy	Decrease existing drug reactions	Increase patient compliance	Efficacy and safety in new subpopulations

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

Priority Review

- Does not affect:
  - Clinical trial period
  - Efficacy standards
  - Safety standards
  - Or quality of evidence required in any way

- FDA makes a goal to review the application and take action within 6 months of submission

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

Priority Review

Capmatanib (Tabrecta®) – 5/6/2021

Atogepant (Qulipta™) – 9/28/21

(*AbbVie's migraine-prevention drug wins FDA approval, FDA speeds up examination of 5 drugs with priority review, DRUGS@FDA: FDA-approved drugs*)

Breakthrough Therapy (2012)

2012 FDA SAFETY AND INNOVATION ACT

Breakthrough Therapy

Speeds up the development and review of drugs for serious conditions AND *preliminary* evidence shows that it *may* be more efficacious than existing therapy

Irreversible morbidity or mortality	Serious symptoms of the disease	Effect on surrogate endpoint	An endpoint reasonably likely to predict clinical benefit	PD biomarker that doesn't meet criteria for an acceptable surrogate endpoint	Improved safety profile

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

What Does the Breakthrough Therapy Designation do for Manufacturers?

- All benefits from Fast Track
- "Intensive guidance" on development of the drug (as early as Phase 1)
- "Organizational commitment involving senior managers"

(U.S. Food and Drug Administration *Fast track, breakthrough therapy, Accelerated Approval, priority review*)

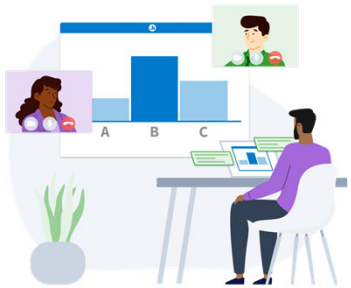
Breakthrough Therapy

Donanemab - still in phase 3 trials

Trastuzumab deruxtecan (Enhurtu®)

(May *Eli Lilly Guns for alzheimer's drug approval with FDA's breakthrough Therapy designation*, Tucker *FDA grants breakthrough therapy designation to trastuzumab Deruxtecan for her2+ MBC*)

Audience Response Question



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Pharmacist Question (Answer)

- Which of the following was approved based on a surrogate endpoint?

A. Aducanumab
B. Capmatanib
C. Donanemab
D. Cannabidiol

Audience Response Question

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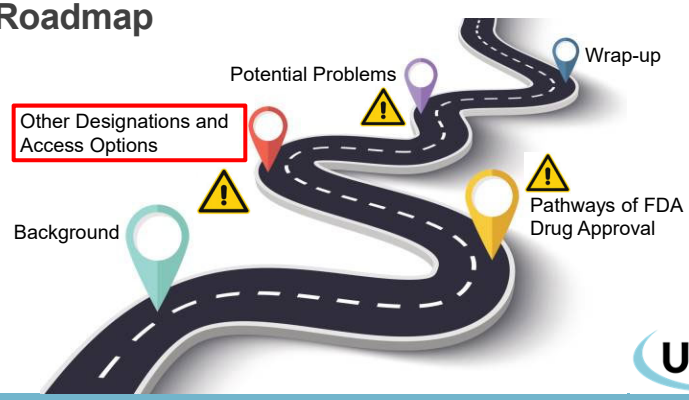
Technician Question (Answer)

- All of the following are examples of FDA approval pathways except:

A. Accelerated Approval
B. Priority Review
C. Fast Track
D. Clinically Exempt Review

Roadmap



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Other Designations and Access Options

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Orphan Drug Act (1983)

For drugs or biologics that prevent, diagnose, or treat rare conditions (<200,000 cases in the United States).

Tax credits for clinical trials	Exempt from certain fees	Seven year market exclusivity (potentially)	Same requirements for safety and efficacy as the standard pathway

(U.S. Food and Drug Administration *Designating an orphan drug or biologic*)

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Orphan Drug Designation - Examples

Adalimumab (Humira®)

Sebelipase alfa (Kanuma®)

(U.S. Food and Drug Administration *List of FDA Orphan Drugs*)

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Other Avenues of Access

- Expanded Access Regulations – AKA compassionate use (1987)
  - Terminally ill patients
  - No satisfactory or comparable alternatives available
  - Unable to participate in a clinical trial
  - Access to investigational medication outside of clinical trials

- Right to Try (2014)
  - Life threatening illness
  - Have tried all approved therapy options
  - Unable to participate in a clinical trial
  - Access to investigational medication

(U.S. Food and Drug Administration *Expanded access*, U.S. Food and Drug Administration *Right to try*)

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Emergency Use Authorization

- Authorizes the following during public health emergencies when there are no available, approved, or adequate alternatives:
  - Unapproved products or devices
  - Unapproved uses for approved products or devices

(U.S. Food and Drug Administration *Emergency use authorization*)

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Generic vs. Authorized Generic

- Generic:
  - Same active ingredient, form, route, strength, labeling, conditions of use, and is bioequivalent
  - Company submits an ANDA

- Authorized generic: exact same as the branded product in ALL aspects (ie. is the branded product)
  - Does not use the brand name
  - Not listed in the Orange book (still marketed under the brand name NDA)

(Karen Berger *The FDA, generics and differentiating authorized from branded types*)

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But Wait, There's More: Branded Generic

- A generic drug, submits an ANDA, assigned a name that is not the chemical name
  - Can be done by a generic company or the branded company after the expiration of the patent
  - Owned by company
  - Must be bioequivalent to brand product
    - Oral contraceptives often use this method

(Karen Berger *The FDA, generics and differentiating authorized from branded types*)

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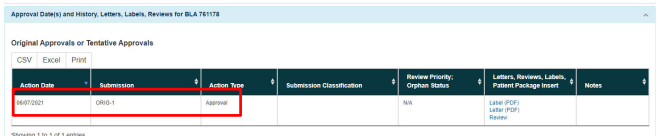
How Can I Tell if a Drug is FDA Approved?

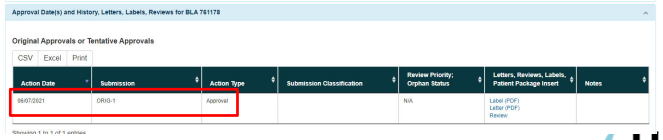
- Drugs@FDA
  - Select the drug of interest
    - Expand the “Approval Date(s) and History, Letters, Labels, Reviews for NDA” tile
      - Click on the letter PDF



(*DRUGS@FDA: FDA-approved drugs*)

Technician Participation Question

- Now you try! - Drugs@FDA
  - https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
    - Select the drug of interest
      - Expand the “Approval Date(s) and History, Letters, Labels, Reviews for NDA” tile



Audience Response Question

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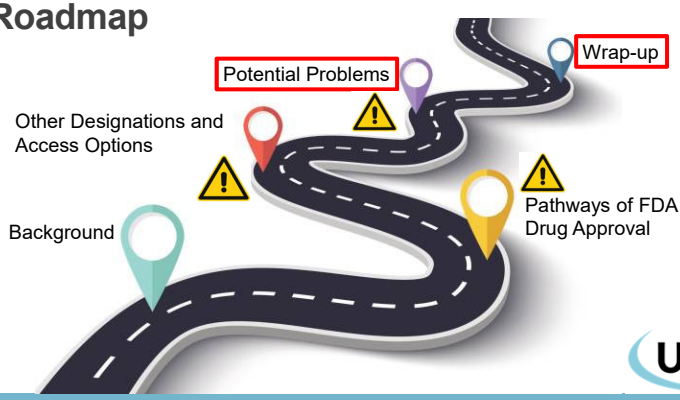
Pharmacist Question

Free response: RetroAgeron, an agent that recently finished phase 3 clinical trials to slow the process of aging, has a Breakthrough Therapy designation. As you begin to dive into the literature, what are some potential limitations to look for knowing its pathway of approval?

Roadmap



Should We be Worried?

- Many changes to legislation and regulation since 1983
- 81% of new drugs in 2018 benefited from at least 1 expedited FDA approval process
- Orphan Drug designation has increased from 18% from 1984-1995 to 41% from 2008-2018
- New approvals with support from ≥ 2 clinical trials have decreased from 80.6% (1995-1997) to 52.8% (2015-2017)

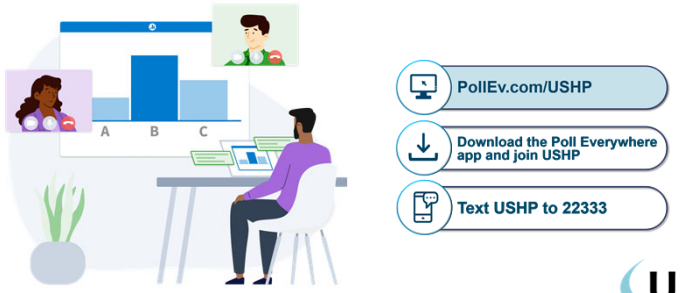
(Darrow et al. *FDA approval and regulation of pharmaceuticals, 1983-2018*)

21st Century Cures Act – 2016

- Passed to accelerate and streamline development and approval of new drug to those who need them
- Incorporates patient perspective in the FDA's approval process
- Encourages use of
  - Biomarkers and surrogate measures
  - Patient experience
  - "Real world evidence" – observational data from daily use vs RCTs

(U.S. Food and Drug Administration *21st Century cures act*)

Audience Response Question



Pharmacist and Technician Question

- **Free response: What are some regulatory or legislative actions that changed the FDA approval process?**

Should We be Worried?

112 of 253 drugs approved through the Accelerated Approval pathway have not been shown to be clinically effective

24 of these have been on the market for more than 5 years

- 6 of these have been approved, postponed or withdrawn from market
- Manufacturers of 4 have started recruiting for confirmatory trials
- Manufacturers of 2 are still in discussion about trial design
- Manufacturers of 12 did not respond to the inquirer

16 of the 253 drugs have been removed from the market

(Mahase *FDA allows drugs without proven clinical benefit to languish for years on Accelerated pathway*)

Should we be Worried?

- There are some problems
- All of these pathways are well intentioned
- Increased awareness of these pathways = increased use
- Can facilitate development and approval of medications for patients in dire need
- Highlights the need for pharmacists and technicians to be aware of the different pathways of approval

Summary

- There are many pathways for FDA approval of drugs
- Common pathways include: Standard, Fast-Track, Accelerated Approval, Breakthrough Therapy, Priority Review, and Orphan Drug
- Each pathway has a different set of nuances
- Pharmacists and technicians should be aware of the different pathways to ensure they can provide appropriate recommendations and counseling to patients and providers

Learning Objectives (Pharmacists)

- Identify regulatory changes and legislation that have led to changes in the FDA approval process
- Distinguish correct minimum evidence required for a specific pathway of approval
- Contrast approval processes using specific medication examples

Learning Objectives (Technicians)

- Name different pathways of FDA approval
- List 2 regulatory or legislative actions that changed the FDA approval process
- Use available resources to determine if a product is FDA approved

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CE Code: (USHP will fill in)

Sean Christensen, PharmD
Medication-Use Safety & Policy Specialty Resident
University of Utah Health
sean.christensen@pharm.utah.edu