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Accelerated Approval Pathways and Ways to Address the Influx of New Drugs

Eastern Medicaid Pharmacy Administrators Association (EMPAA)
Fall 2022 Conference

Neha Kashalikar, PharmD
Manager of Strategic Pharmacy Contracting, MassHealth
University of Massachusetts Chan Medical School

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True or False: The purpose of expedited approval pathways is to allow for earlier access to drugs to treat serious conditions that have an unmet need.

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Which of the following is not true about surrogate endpoints?

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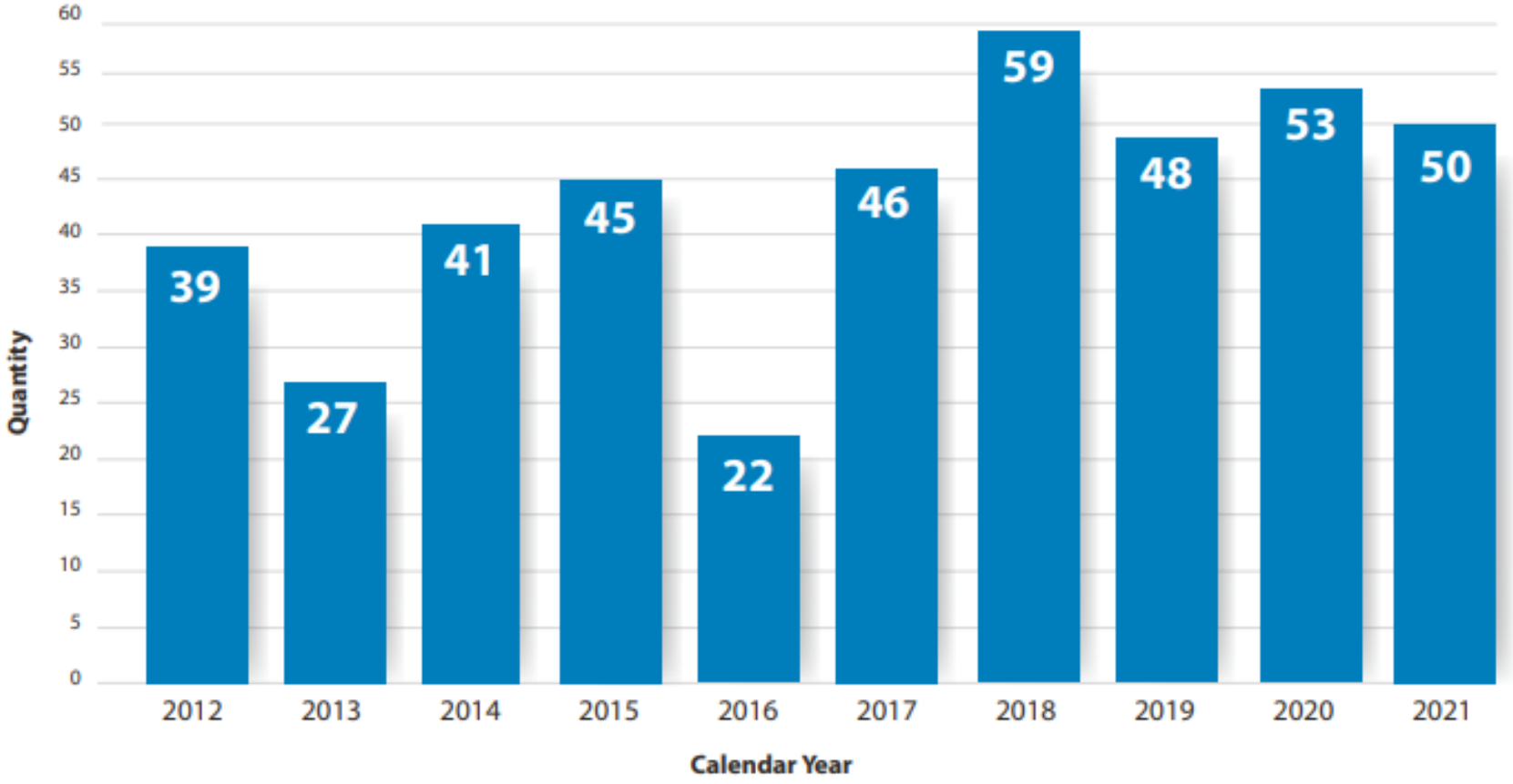
Objectives

- Describe the different expedited review pathways through the Food and Drug Administration (FDA)
- Discuss benefits and challenges associated with drugs approved via expedited approval pathways
- Understand strategies being used to manage drugs approved via expedited review pathways

Drug Approval Trends

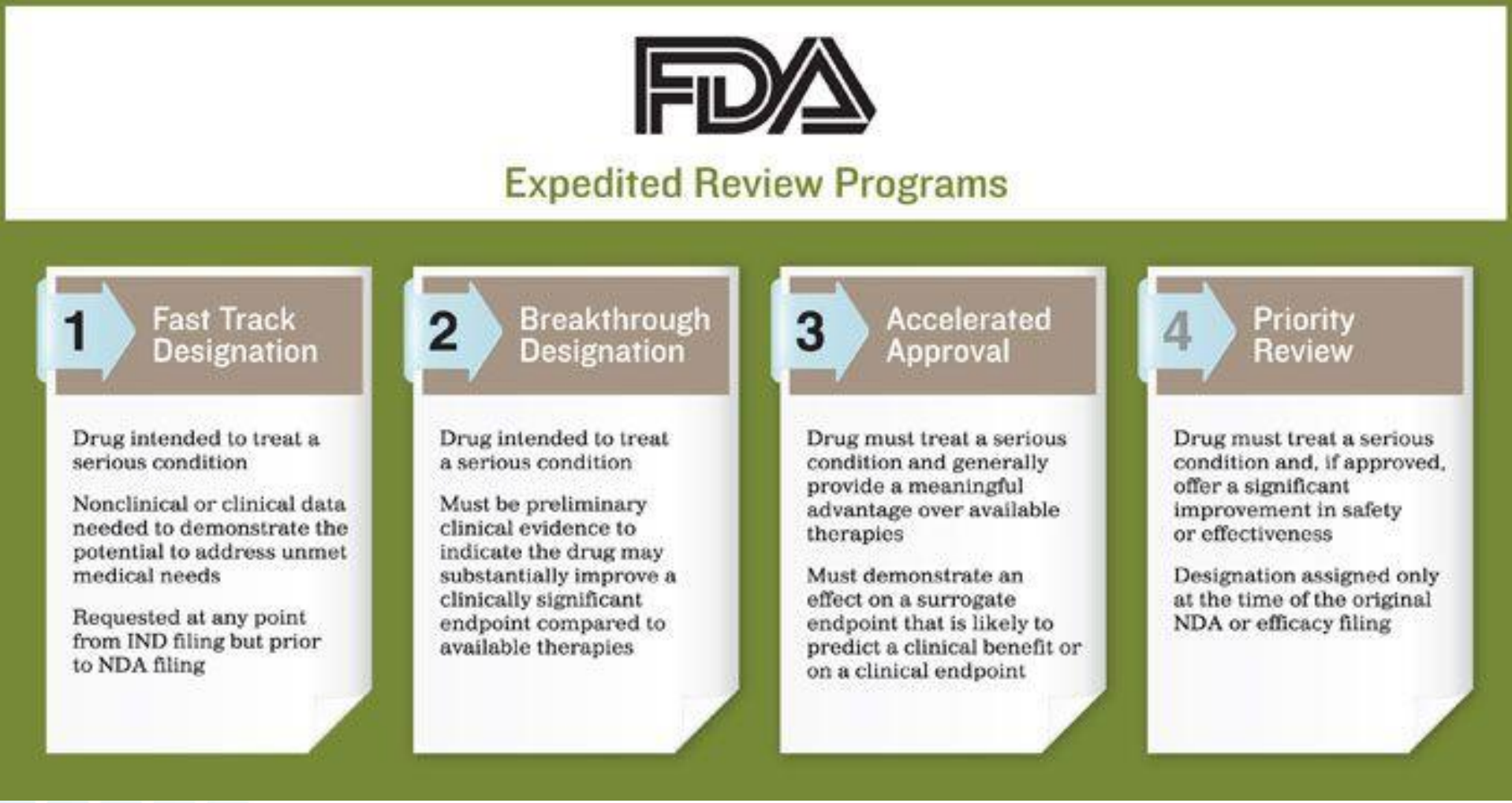
CDER's Annual Novel Drug Approvals: 2012–2021

The 10-year graph below shows that from 2012 through 2021, CDER has averaged 43 novel drug approvals per year.



Advancing Health Through Innovation: New Drug Therapy Approvals 2021 (fda.gov)

Expediated Review Pathways



Accelerated Change: Understanding the FDA's Expedited Pathways (pharmexec.com)

Purpose

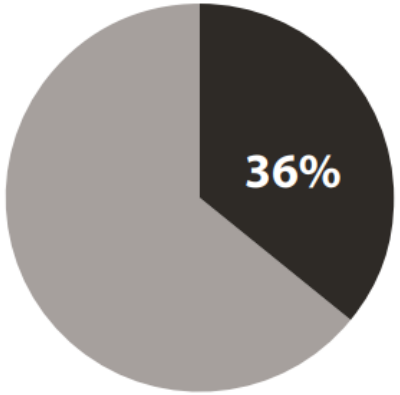
"All four expedited programs represent efforts to address an **unmet medical need** in the treatment of a **serious condition**…"

- U.S. Department of Health and Human Services Food and Drug Administration (*Guidance Document*)

Fast Track Designation

- Qualifying Criteria:
  - A drug that is intended to treat a serious condition AND
  - One of the following:
    - nonclinical or clinical data demonstrate the potential to address unmet medical need
    - A drug that has been designated as a qualified infectious disease product
- In 2021, 18 of the 50 novel drugs (36%) were designated as Fast Track status.

Examples: Aduhelm, Amondys 45, Brexafemme, Bylvay, Cabenuva, Cytalux, Empaveli, Exkivity, Kerendia, Lumakras, Lupkynis, Nexviazyme, Rylaze, Saphnelo, Scemblix, Truseltiq, Verquvo, Vyvgart



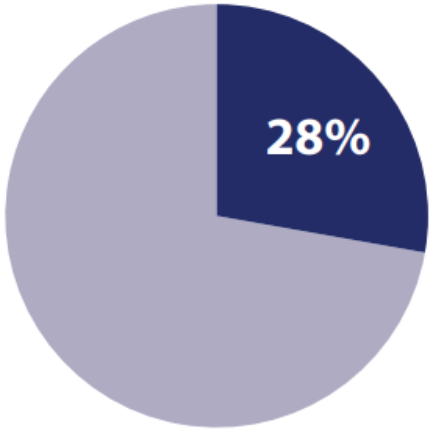
Fast Track Designation

- Operational Process:
  - Request should be submitted with Investigational New Drug (IND) process
  - FDA response may be expected within 60 calendar days of receipt of the request
- Features:
  - Actions to expedite development and review
  - Rolling review
- Other:
  - A Fast Track designation does not need clinical evidence and can be obtained very early in drug development based just on animal data (distinguishes from other expeditated programs)
  - Designation may be rescinded if it no longer meets the qualifying criteria for fast track

Breakthrough Therapy Designation

- Qualifying Criteria:
  - A drug that is intended to treat a serious condition AND
  - preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
- In 2021, 14 of the 50 novel drugs (28%) were designated as Breakthrough Therapies.

Examples: Cosela, Evkeeza, Exkivity, Jemperli, Korsuva, Livmarli, Livtencity, Lumakras, Nexviazyme, Nulibry, Rezurock, Rybrevant, Scemblix, Ukoniq



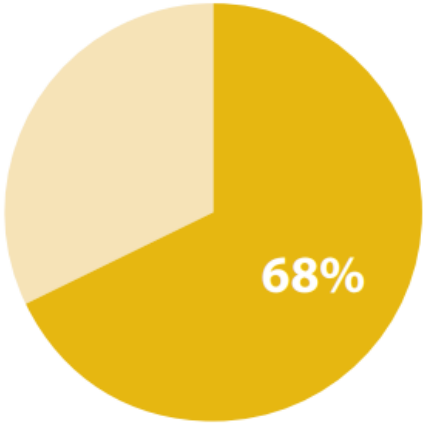
Breakthrough Therapy Designation

- Operational Process
  - Request should be submitted with IND
  - FDA response may be expected within 60 calendar days of receipt of the request
- Features:
  - Intensive guidance on efficient drug development
  - Organizational commitment
  - Rolling review
  - Other actions to expediate review
- Other: Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy

Priority Review

- Qualifying Criteria:
  - An application for a drug that treats a serious condition AND
  - One of the following:
    - If approved, would provide a significant improvement in safety or effectiveness
    - Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A
    - An application for a drug that has been designated as a qualified infectious disease product
    - Any application or supplement for a drug submitted with a priority review voucher
- In 2021, 34 of the 50 novel drugs approved (68%) were designated
- Priority Review.

Examples: Aduhelm, Amondys 45, Brexafemme, Bylvay, Cabenuva, Cosela, Cytalux, Empaveli, Evkeeza, Exkivity, fexinidazole, Jemperli, Kerendia, Korsuva, Livmarli, Livtencity, Lumakras, Lupkynis, Nexviazyme, Nulibry, Pepaxto, Pylarify, Rezurock, Rybrevant, Scemblix, Tepmetko, Tezspire, Tivdak, Truseltiq, Ukoniq, Verquvo, Voxzogo, Welireg, Zynlonta*



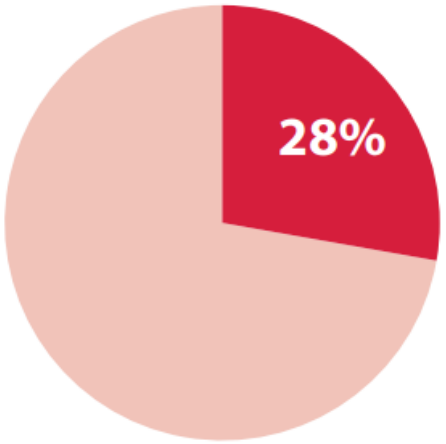
Priority Review

- Operational Process
  - Request should be submitted with original IND or efficacy supplement
  - FDA response may be expected within 60 calendar days of receipt of INDor efficacy supplement
- Features:
  - Shorter clock for review of marketing application (6 months compared with the 10-month standard review)
- Other:
  - Drug developers may redeem these vouchers or vouchers may be sold to other developers at varying market values

Accelerated Approval

- Qualifying Criteria:
  - A drug that treats a serious condition AND
  - provides a meaningful advantage over available therapies AND
  - demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is reasonably likely to predict clinical benefit
- In 2021, 14 of the 50 novel drugs (28%) were approved under Accelerated Approval.

Examples: Aduhelm, Amondys 45, Exkivity, Jemperli, Lumakras, Pepaxto, Rybrevant, Scemblix, Tepmetko, Tivdak, Truseltiq, Ukoniq, Voxzogo, Zynlonta



Accelerated Approval

- Operational Process
  - The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development
- Features:
  - Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
- Other:
  - Given the Accelerated Approval program relies on surrogate endpoints, companies must follow up with data from confirmatory trials demonstrating the positive outcome of their surrogate studies with post-approval trials that assess clinical endpoints and confirms a clinical benefit
  - Subject to expedited withdrawal

Clinical vs. Surrogate Endpoints

Clinical Endpoints:

- Gold standard for traditional FDA review pathway
- Endpoints may measure patient response, function, or survival after treatment with a drug
- Endpoints may require larger patient population or longer tracking
- *Example: Overall survival as a measure of a novel treatment's outcomes*

Surrogate Endpoints

- Indicators of disease change predicted to be correlated with clinical benefit
- Provide an estimate of how well a drug may treat a condition
- *Example: Tumor size as a stand-in to measure cancer progression*

Benefits

- Address unmet needs and increase availability of new therapies to patients with serious conditions
- Each of these distinct pathways is intended to reduce the time to market for drug candidates
  - Patient Impact: Quality of Life
  - Manufacturer Impact: Market access
  - Payer Impact: Lower costs?

Challenges

- Drugs approved based on surrogate endpoints or biomarkers may have limited real-world data
- Increase in safety-related labeling changes compared to drugs approved through traditional review pathways
  - i.e. Boxed warnings and Contraindications

Challenges

- Difficulty enforcing confirmatory trials for drugs approved through accelerated approval pathways
- Challenges around withdrawal of accelerated approval indications
- Payers are at risk for paying for products with unknown value

Case Example: Makena

- In 2011, Makena was granted accelerated approval for the prevention of pre-term birth
- Clinical trials demonstrated reduction in pre-term birth but did not evaluate clinical endpoint of improved neonatal outcomes
  - FDA required that the manufacturer confirm these outcomes in a post-marketing study
- In 2019, subsequent trial failed to demonstrate improvement in neonatal outcomes or in pre-term births and it is recommended that approval be withdrawn
- After reviewing additional evidence from the manufacturer, the FDA review committee reiterated its recommendation that the drug be withdrawn
- In October 2022, The FDA advisory group voted to recommend Makena be removed from market (14-1)
- To date, Makena remains on the market

Management Strategies

Direct Negotiations Authority

In July 2019, MassHealth was granted authority for greater negotiating leverage for prescription drug prices without impacting access to medically necessary prescription drugs for members

1. **Direct Negotiations:** Negotiate supplemental rebates and cost-effective, outcomes-based contracts directly with drug manufacturers.

2. **Public Process:** If negotiations are stalled, MassHealth can establish a target value for a given high-cost* drug through a public process, similar to the rate-setting process that exists for most other services that MassHealth covers.

3. **Health Policy Commission (HPC) Accountability Process:** If negotiations are unsuccessful, MassHealth may refer high-cost* drug manufacturers to the HPC

**High-Cost Drug Threshold: Drug costs at least $25K person/year after rebate or $10M after rebate in the aggregate annually*

Direct Negotiations: Target Price Development

- Pharmacoeconomist team has developed a customized process to calculate target prices for high-cost drugs with contracting constructs under negotiations
  - Variety of economic models
  - MassHealth specific utilization data
  - Evidence-based medicine (consensus guidelines/clinical literature)
  - Market landscape and trend considerations
  - Pipeline
  - Outreach to stakeholders (including clinical specialists)
- Target price and methodology posted for public comment and/or public hearing

Value-Based Contracting (VBC)

- In July 2019, MassHealth was also granted the authority to engage in value-based or outcomes-based contracting with pharmaceutical manufacturers
- In these arrangements, the amount reimbursed to the payer is linked to clinical, utilization, or other intermediary endpoints.
- Drugs that approved based on surrogate endpoints or biomarkers may be well suited for VBC, as there may be questions around the efficacy of the drug in clinical practice
    - VBC may allow manufacturers to stand behind the expected outcome of a drug.

VBC Endpoint Selection

It is important payers and manufacturers work together to select the best endpoint for a VBC

- It is crucial the selected endpoint be clinically relevant and tied directly to clinical outcomes
- The contract should be structured in a manner that is operationable, such as an objective endpoint that can be tracked on a PA form or in claims
- The endpoint should be tracked as a part of routine patient care, and it may be helpful to reach out to clinical specialist to ensure alignment around proposed VBC end points
- And along those same lines, the endpoint should be reported by the provider or office staff with minimal additional education required, such as a standard clinical scale used in practice.

Essential Features of MassHealth's Program

- Utilization Management
  - Formulary decisions based on evidence-based medicine
- Pipeline monitoring program
  - New drugs and indications and anticipated generics
- Budget Impact Forecasting
- Pharmacoeconomics team
- Clinical Monitoring Programs
- Data analytics team

Conclusions

- Expediated approval pathways were developed to provide early access to patients with serious conditions that fill an unmet medical need
- These well-intended policies may introduce challenges for payers and providers, particularly when drugs approvals are based on surrogate endpoints
- Payers should consider various management strategies to address challenges with drugs approved through expediated approval pathways

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Questions?

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