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PDUFA Reauthorization: Achieving Efficiency and Evidence Generation in Drug Approvals

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Prescription Drug User Fee Act

- Ensure FDA has sufficient funding to conduct its essential activities effectively and efficiently
- User-fee legislation has contributed to the more rapid evaluation and approval of new drugs and funds the generation of important additional evidence after drug approval

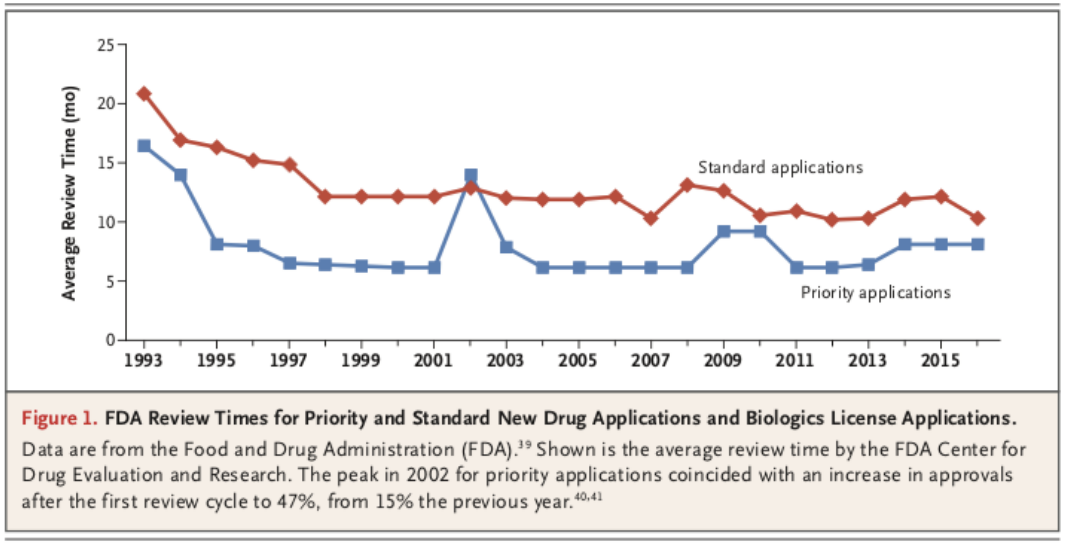

Figure 1. FDA Review Times for Priority and Standard New Drug Applications and Biologics License Applications.
Data are from the Food and Drug Administration (FDA).[39] Shown is the average review time by the FDA Center for Drug Evaluation and Research. The peak in 2002 for priority applications coincided with an increase in approvals after the first review cycle to 47%, from 15% the previous year.[40,41]

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Darrow, Avorn, Kesselheim, NEJM, 2017

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Expedited development & approval pathways

A. Fast Track (added 1988; FDAMA/PDUFA II in 1997)

- One Phase 2 (biomarker-based) trial sufficient
- Life-threatening or severely debilitating diseases

B. Accelerated Approval (added in regs 1992; FDASIA/PDUFA V in 2012)

- Approval based on biomarker or intermediate measure "reasonably likely to predict clinical benefit"
- Serious/life-threatening illnesses providing meaningful therapeutic benefit over existing treatments

C. Priority Review (added in PDUFA 1992)

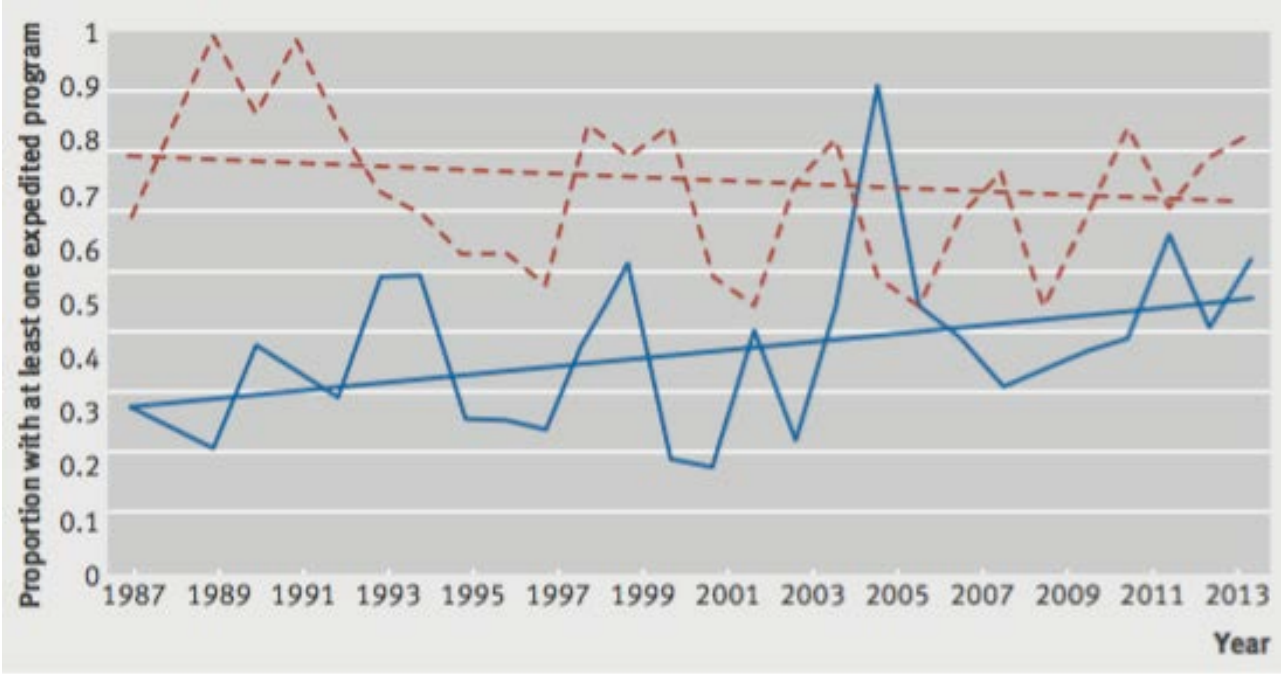
- Shorter FDA review (6 mos) for "therapeutic advance"

D. Breakthrough Therapy (added in FDASIA/PDUFA V in 2012)

- Treating serious or life-threatening disease with preliminary clinical evidence of substantial improvement over existing therapies on clinically significant endpoints
- Effects can be seen in biomarkers, predictive toxicology, and results from accelerated clinical trial design strategies

Darrow et al., NEJM, 2014; Darrow et al., NEJM, 2015; Kramer & Kesselheim, NEJM, 2012

Trends in use of expedited development pathways



Proportion of newly-approved first-in-class (dotted line) and other (solid line) NMEs granted at least one of the designations

P=0.03 for interaction

Kesselheim et al, BMJ, 2015

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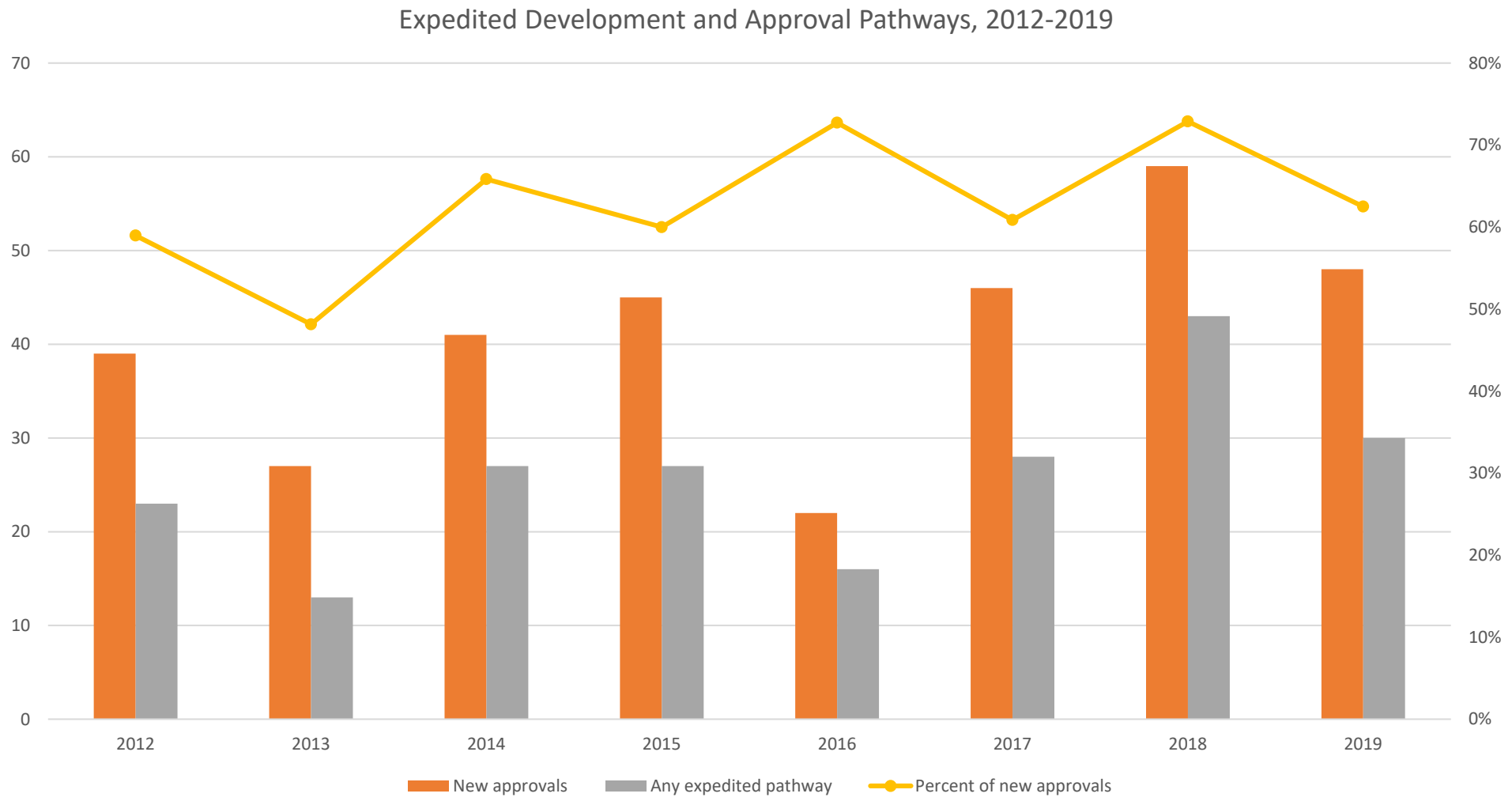
Trends continue with PDUFA VI



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Greater reliance on surrogate measures

- PDUFA VI: Support increased used of new biomarkers and surrogate endpoints

- Advantages of using surrogate measures:
  - Identifying drug safety problems earlier
  - Predicting efficacy
  - Directing treatments to patients more precisely
  - Incentivizing drug development by predicting likely efficacy years earlier

Broader use of unvalidated surrogate measures

- If not validated, then can lead to approval of drugs that do not work as intended, or have safety issues that outweigh any benefits
- Review of FDA's Table of Surrogate Endpoints
  - List disease, surrogate endpoint, type of relevant approval, "mechanism of action"
  - *Breast cancer*: objective response rate, progression-free survival (PFS), disease-free survival (DFS), event-free survival (EFS), pathologic complete response
  - Association between endpoints and actual clinical endpoints is not strongly correlated in most cases
    - Strong only for DFS and HER-positive cases (R^2=0.75)
    - EFS not validated at all

Gyawali et al., EClinicalMedicine, 2020

Limitations of confirmatory trials

- May be delayed
  - Challenges in requiring them to be completed in a timely fashion

- Review of accelerated approval cancer drugs
  - 51/93 (55%) confirm benefit (5 did not), but …
  - Only 15 of the 51 tested a clinical outcome (17 tested a surrogate measure and 19 tested a surrogate measure that was the *same as the preapproval study*)

Gyawali and Kesselheim, JAMA IM, 2019

Summary and Recommendations

- Important to provide adequate funding to ensure drug regulatory system serves the public effectively
  - In a different political climate, adequate public funding in place of user fees would allow the FDA to continue its current performance levels while promoting maximum confidence from public
- Need to make sure we have process for identifying promising drugs in development and getting them to patients who need them
  - Multiple expedited pathways are inefficient and confusing and should be streamlined to a single pathway
- Be vigilant about possibility that expedited development and review will lead to drugs that may actually have risks that outweigh benefits
  - Increased chance when approved based on unvalidated biomarkers or surrogate endpoints
  - Opportunity for thoughtful use of ‘real-world’ evidence
- **Need formal re-assessment of efficacy and safety for new drugs approved based on surrogate measures after 3 years on market**