# Introduction to Laws, Policies, and Regulations of Pharmaceuticals

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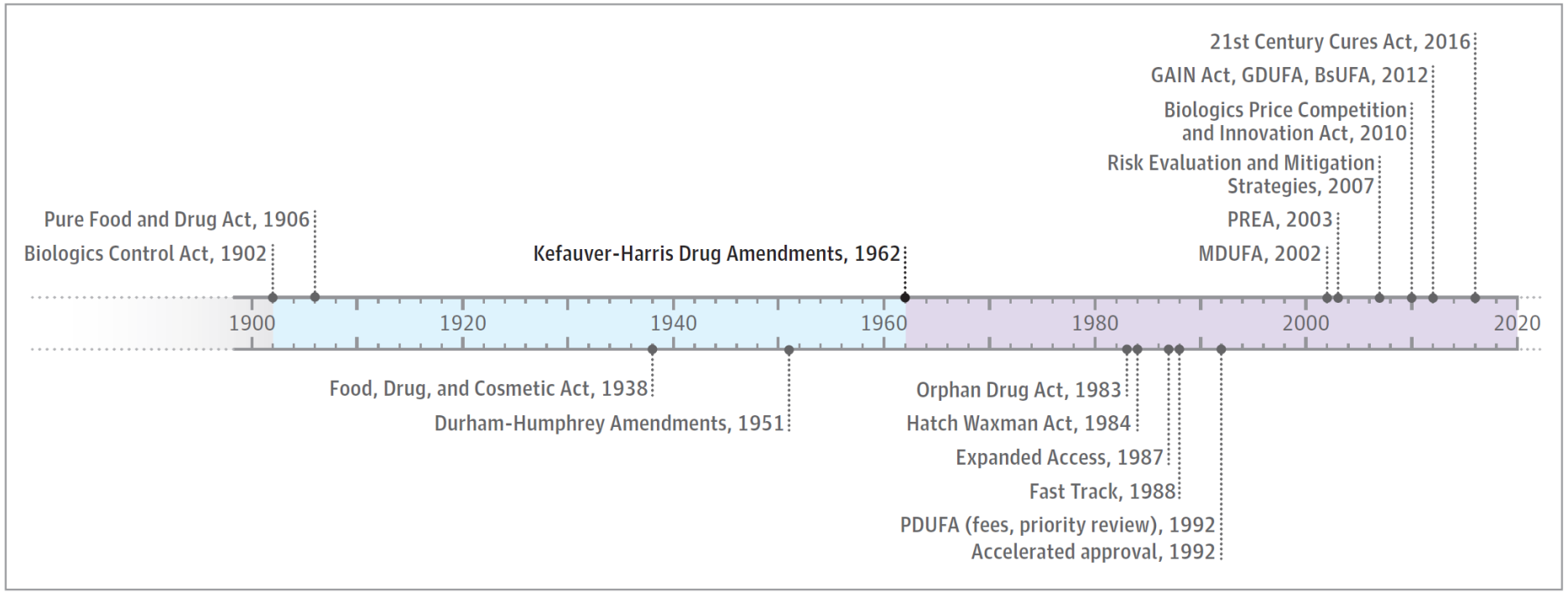
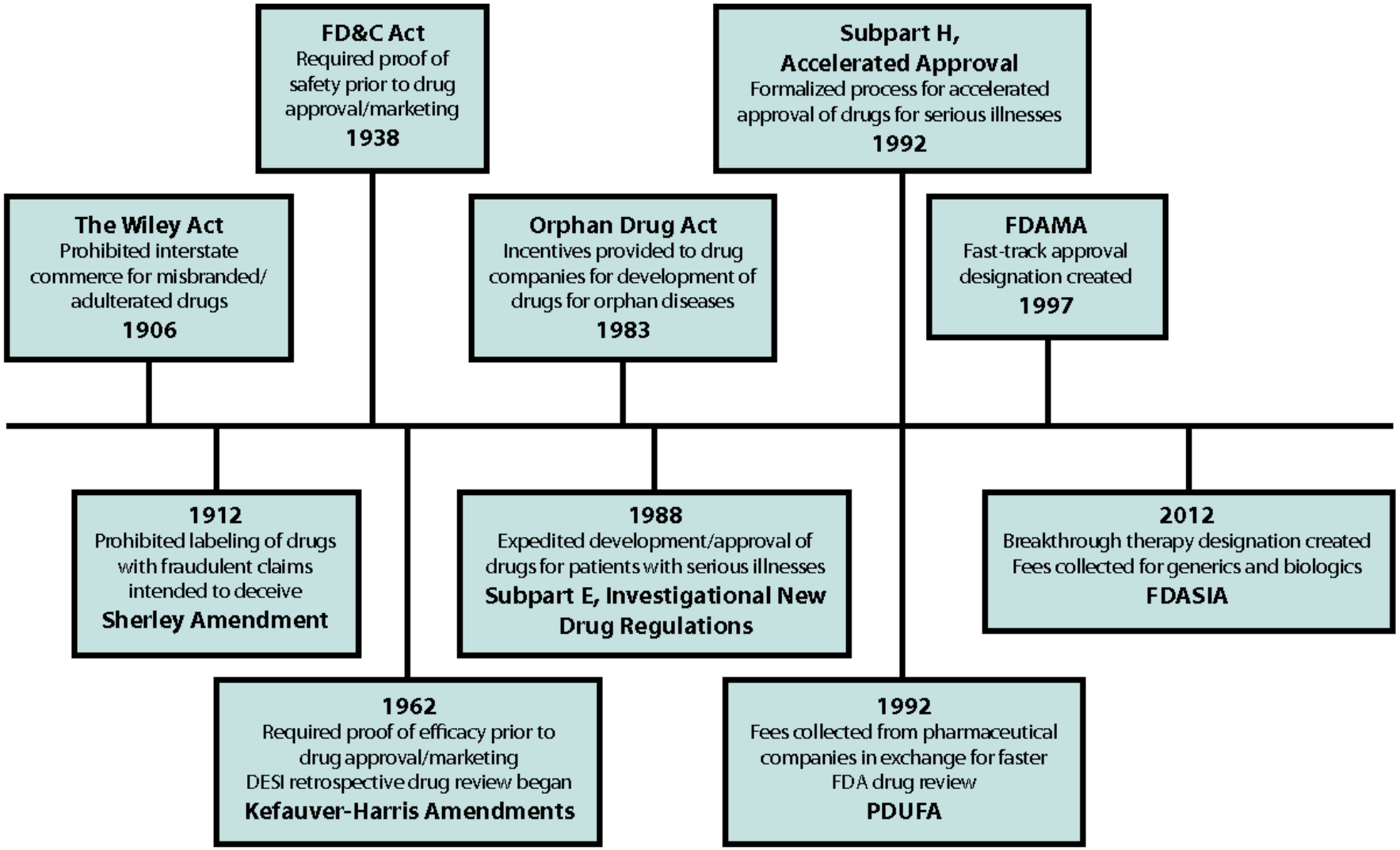
# Timeline (Darrow et al., 2020)

Figure 1. Timeline of Landmark Legislation and Regulations Relating to FDA Authority to Regulate Drugs




After the 1962 Kefauver-Harris Drug Amendments (left), a series of legislative enactments and regulatory programs (right) progressively increased the flexibility of evidence requirements and imposed expanding user fees to fund the drug approval process. BsUFA indicates Biosimilar User Fee Act; FDA, US Food and Drug Administration; GAIN, Generating Antibiotic Incentives Now; GDUFA, Generic Drug User Fee Act; MDUFA, Medical Device User Fee Act; PDUFA, Prescription Drug User Fee Act; PREA, Pediatric Research Equity Act. Sources: Hein Online (statutes); Federal Register (FDA regulations).

# U.S


FD&C Act
Required proof of safety prior to drug approval/marketing
1938
Subpart H, Accelerated Approval
Formalized process for accelerated approval of drugs for serious illnesses
1992
The Wiley Act
Prohibited interstate commerce for misbranded/ adulterated drugs
1906
Orphan Drug Act
Incentives provided to drug companies for development of drugs for orphan diseases
1983
FDAMA
Fast-track approval designation created
1997
1912
Prohibited labeling of drugs with fraudulent claims intended to deceive
Sherley Amendment
1988
Expedited development/approval of drugs for patients with serious illnesses
Subpart E, Investigational New Drug Regulations
2012
Breakthrough therapy designation created
Fees collected for generics and biologics
FDASIA
1962
Required proof of efficacy prior to drug approval/marketing
DESI retrospective drug review began
Kefauver-Harris Amendments
1992
Fees collected from pharmaceutical companies in exchange for faster FDA drug review
PDUFA

# Terminology

- **Investigational New Drug Application (IND):** A submission required to be made to the FDA before initiating human drug trials.
- **Abbreviated New Drug Application (ANDA):** Application submitted to the FDA seeking approval of a generic version of previously approved drug.
- **New Drug Application (NDA):** A submission required to be made to the FDA after completion of human drug trials and before marketing
- **New Molecular Entity (NME):** An active ingredients that contains no active moiety that has been previously approved by the FDA or has been previously marketed as a drug in **the USA**
- **Biologics License Application (BLA):** Application submitted to FDA seeking approval of a new biologic product
- **Center for Biologics Evaluation and Research (CBER):** A part of the FDA responsible fore regulating blood products, tissues, vaccines, and cellular and gene therapies.
- **Center for Drug Evaluation and Research (CDER):** A part of the FDA responsible for regulating over-the-counter and prescription drugs, including most therapeutics biologics.
- **Orange Book:** A publication of the FDA that lists approved prescription drug products and patents and nonpatent exclusivities; formally entitled "Approved Drug Products with Therapeutic Equivalence Evaluations“ and available in electronic format

# Terminology - Continued

- **Phase1:** Uncontrolled human studies generally involving 20 to 80 healthy volunteers that are primarily intended to gather information about a drug's pharmacokinetics and pharmacodynamics at varying doses.
- **Phase 2:** Human trials generally involving up to a few hundred participants with the condition intended to be treated; designed to assess the safety and efficacy of a new drug and, like phase 3 trials, often use surrogate measures.
- **Phase 3:** Large-scale human trials generally involving several hundred to several thousand patients that are ideally randomized, controlled, and blinded; intended to form the basis for FDA approval
- **Pivotal Trials:** An informal used to refer to the studies on which the FDA primarily relies in making its approval decision; pivotal trials are usually phase 3 trials, but earlier-phase trials may also serve as the basis for approval at the discretion of the FDA
- **Postmarket requirements (PMRs):** A clinical trial or other study an applicant agrees with the FDA to conduct after approval
- **Postmarket commitments (PMCs):** A clinical trial or other study an applicant agrees with the FDA to conduct after approval

# Biologics Control Act of 1902

- Also known as the Virus-Toxin law
- The first law that implemented federal regulation of biologics such as vaccines.
- It was enacted in response to two incidents involving the deaths of 22 children who had contracted tetanus from contaminated vaccines.
- Contents of the act: Given the board power to issue, suspend, and revoke licenses. Mandated that all products be labeled accurately with the name and license number of manufacturer.
- Led to PFDA of 1906 & FFDCA of 1938
- https://en.wikipedia.org/wiki/Biologics_Control_Act

# Pure Food and Drug Act of 1906

- Enacted to address the widespread use of over-the-counter medications that often included dangerous and undisclosed ingredients like opium, alcohol, or cocaine.
- But this only required medications to accurately list their ingredients, but not the evidence of safety and efficacy.
  - Coca-cola : Caffeine
  - Alcohol, cocaine, heroin, morphine, cannabis: contents and doses

- Main purpose was to ban foreign and interstate traffic in mislabeled food and drug products in US.
- Signed by President Theodore Roosevelt
- Was assigned to the Bureau of Chemistry in US Department of Agriculture which was renamed to FDA in 1930.
- Later largely replaced by FFDCA of 1938
- https://en.wikipedia.org/wiki/Pure_Food_and_Drug_Act

# Food, Drug, and Cosmetic Act of 1938

- FFDCA required that a drug be shown to be non-toxic, but the act still had no explicit efficacy requirement.
- Giving authority to US FDA to oversee the safety of food, drugs, medical devices, and cosmetics.
- Influenced by the death of more than 100 patients due to sulfanilamide medication
- Replaced PFDA of 1906
- Included regulation for medical devices (Class I / II / III)
- https://en.wikipedia.org/wiki/Federal_Food,_Drug,_and_Cosmetic_Act

# Durham-Humphrey Amendments of 1951

- Explicitly defined two specific categories of medications: prescription and over-the-counter.
- Required any drug that is habit-forming or potentially harmful to have the caution statement.
- https://en.wikipedia.org/wiki/Durham-Humphrey_Amendment

# Kefauver-Harris Drug Amendments of 1962

- “Thalidomide crisis”
- The KHDA or “Drug Efficacy Amendment of 1962” is a an amendment to Federal Food, Drug, and Cosmetic Act of 1938
- Signed by John F Kennedy
- Required drug manufacturers
  - to provide proof of effectiveness and safety of their drugs before approval – “proof-of-efficacy” for the first time
  - With advertising to disclose accurate information about side effects
  - Stopped cheap generic drugs being marketed as expensive drugs under new trade name
- Drug Efficacy Study Implementation was to begun to classify all pre-1962 drugs as effective, ineffective, or needing further study
- https://en.wikipedia.org/wiki/Kefauver_Harris_Amendment

# Orphan Drug Act of 1983

- ODA is a law passed in the US to facilitate development of orphan drugs
- Orphan drug designation does not indicate that the therapeutic is either safe and effective or legal for marketing
  - Designation only means that the sponsors qualify for certain benefits from the federal government such as marketing exclusivity and reduced taxes
- In 1982, National Organization for Rare Disorders (NORD) was formed and they succeed in getting approval.
- https://en.wikipedia.org/wiki/Orphan_Drug_Act_of_1983

# Hatch Waxman Act of 1984 (Drug Price Competition and Patent Term Restoration Act)

- Landmark legislation responsible for catalyzing the modern generic drug industry by authorizing an Abbreviated New Drug Application pathway for drugs approved after 1862 and creating special challenge process for brand-name drug patents
  - More protection and incentives for companies to file ANDAs
- Patent Term Restoration: A provision allowing extensions of up to 5 years (but in no case extending more than 14 years after approval) for 1 patent for each product subject to a regulatory review period, to compensate for patent time lost because of the conduct of clinical trials and regulatory review
- Incentivized litigation
- Summary
  - New five-year period of data exclusivity for a new chemical entity
  - During that period the FDA cannot approve a generic version
  - Life of patens covering a drug to be extended by the portion of time the drug is under regulatory review
  - Required generics to only prove bioequivalence
- https://en.wikipedia.org/wiki/Drug_Price_Competition_and_Patent_Term_Restoration_Act

# Prescription Drug Marketing Act of 1987

- “It establishes legal safeguards for prescription drug distribution to ensure safe and effective pharmaceuticals and is designed to discourage the sale of counterfeit, adulterated, misbranded, subpotent, and expired prescription drugs. It was passed in response to the development of a wholesale sub-market (known as the "diversion market") for prescription drugs.”
- https://en.wikipedia.org/wiki/Prescription_Drug_Marketing_Act

# Prescription Drug User Fee Act (PDUFA) of 1992

- US legislation authorizing the FDA to collect “user fees” from drug manufacturers to help fund FDA drug review activities; later expanded to medical devices, generic drugs, and biosimilar products; also started priority-review
- Spurred by AIDS activist complaining the drug development is taking too long!
- PDUFA I (1992): Application review fees, establishment fees, product fees
- PDUFA II (1997): Stricter performance goals, required increased transparency in drug review process
  - 1st chapter of FDA Modernization Act
- PDUFA III (2002): Increased postmarket monitoring of new product
  - part of Public Health and Bioterrorism Preparedness Act
- PDUFA IV (2007) : Fee increase
  - FDA Amendments Act of 2007
- PDUFA V (2012)

- https://en.wikipedia.org/wiki/Prescription_Drug_User_Fee_Act

# Medical Device User Fee Act of 2002

- PDUFA for Medical Device Product Reviews
- https://www.fda.gov/medical-devices/premarket-submissions/medical-device-user-fees

# Best Pharmaceuticals for Children Act of 2002

- To encourage the pharmaceutical industry to perform pediatric studies to improve labeling for patented drug products used in children, by granting an additional 6 months patent exclusivity
- For NIH to prioritize therapeutic areas and sponsor clinical trials and other research for off-patent drug products that need further study in children

- https://www.nichd.nih.gov/research/supported/bpca

# Pediatric Research Equity Act (PREA) of 2003

- US Legislation requiring results from pediatric assessments to be submitted as part of new drug applications (NDA) unless granted a waiver by the FDA.
- https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea

# FDA Amendments Act of 2007

- US legislation renewing user fees for drugs and devices, creating the Risk Evaluation and Mitigation Strategies program, and authorizing Sentinel Initiative (Signed by Bush)
- Risk Evaluation and Mitigation Strategies (REMS) Program
  - A program created in 2007 that authorizes the FDA to restrict the distribution of high-risk new drugs to certain facilities or health care providers, or to take other measure to ensure that the benefit of new drug outweigh its risk.
- Sentinel Initiative
  - An FDA program created in 2007 that uses electronic health data, including insurance claim data, to engage in active post-market surveillance and risk identification
- https://en.wikipedia.org/wiki/Food_and_Drug_Administration_Amendments_Act_of_2007

# Biologics Price Competition and Innovation Act of 2010

- Enacted a s part of the US Patient Protection and Affordable Care Act, the BPCIA created an abbreviated pathway for follow-on biologic products analogous to the Hatch-Waxman abbreviated NDA pathway for small-molecule drugs
- Patient Protection and Affordability Care Act (PPACA) of 2010
- https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009

# FDA Safety and Innovation Act of 2012

- “Expands FDA authorities to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products; promotes innovation to speed patient access to safe and effective products; increases stakeholder involvement in FDA processes, and enhances the safety of the drug supply chain”
- Breakthrough Therapy Designation: Created and applicable to experimental drugs that based on preliminary clinical evidence, any demonstrate substantial improvements over existing therapies on 1 or more clinically significant endpoints
- https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-safety-and-innovation-act-fdasia

# Generating Antibiotic Incentives Now (GAIN) of 2012

- As part of 2012 FDA Safety and Innovation Act, GAIN authorized an extension by 5 years of existing 3-, 5-, and 7-year non-patent exclusivities, for certain antibacterial and antifungal products.

# Generic Drug User Fee Act (GDUFA) of 2012

- Enacted to accelerate the access of safe and effective generic drugs to the public.
- Required user fees for generic drugs

# Biosimilar User Fee Act (BsUFA) of 2012

- User fee for Biosimilar

# Pandemics and All-Hazards Preparedness Reauthorization Act of 2013

- “The Act amends the Public Health Service Act in order to extend, fund, and improve several programs designed to prepare the United States and health professionals in the event of a pandemic, epidemic, or biological, chemical, radiological, or nuclear accident or attack. The Act clarifies the authority of different American officials, makes it easier to temporarily reassign personnel to respond to emergency situations, and alters the process for testing and producing medical countermeasures. The Act is focused on improving preparedness for any public health emergency.”

- https://en.wikipedia.org/wiki/Pandemic_and_All-Hazards_Preparedness_Reauthorization_Act_of_2013

# 21st Century Cures Act of 2016

- US Legislation authorizing funds for the Precision Medicine Initiative and Cancer Moonshot; encouraging the use of patient-reported outcomes, surrogate measures, and real world evidence in drug approval; and creating a limited population pathway for antibiotics, among other initiatives
- Authorized $6.3B Funding mostly for National Institutes of Health
- https://en.wikipedia.org/wiki/21st_Century_Cures_Act

# The 21st Century Cures Bill (Lupkin, 2016, KHN)

- Winners
  - Pharmaceutical and Medical Device Companies
  - Medical schools, hospital, and doctors
  - Advocates for metnal helath and substance
  - Patient Groups
  - Health information technology and software companies
- Losers
  - Public health
  - Consumer and patient safety groups
  - Medicaid patients seeking hair growth
  - FDA

# Darrow, Avorn & Kesselheim (2020)

## History & Statistics

# User Fees & Approval Time

- In 2017, FDA spent $1.55B to regulate drugs & biologics and collected $1.22B (79%) user fees ($837M for branded drug, $356M for generics, and $29M for biosimilar).

- History
  - After 1962 KHDA, budget limitations became salient. The FDA review time became 30 months in early 1980s. => Demonstrations by AIDS activists
  - Led to 1992 PDUFA; start collecting fees; most NDA review times within 12 months (10 months by 2002); priority NDAs reviewed in 6 months; Total drug user fees increased from $0.3B in 93-97 to $4.1B in 13-17
  - Review time decline sharply as well; 28.3 years in 86-92 to 1.5 years in 93-05 to 1.2 years in 06-17.
  - In 15-18, FDA approved 90% of 172 drugs after just 1 review cycle
  - However, the total time from the IND to approval has increased.

# User Fees & Approval Time

Figure 2. Fees Collected by the FDA Under the Prescription Drug User Fee Act

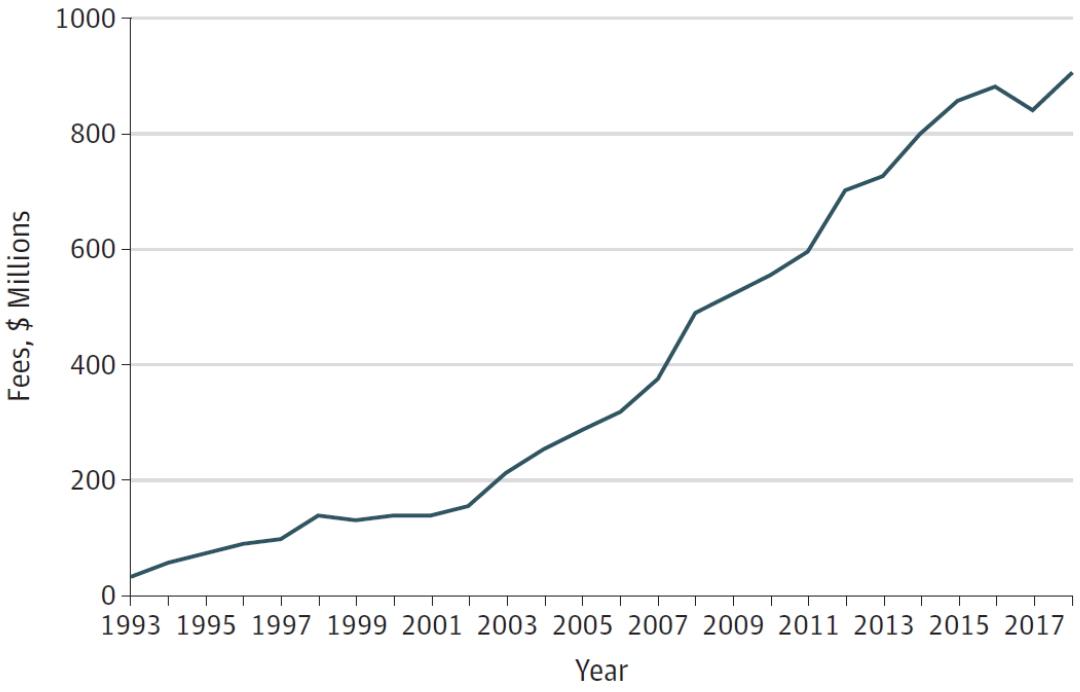
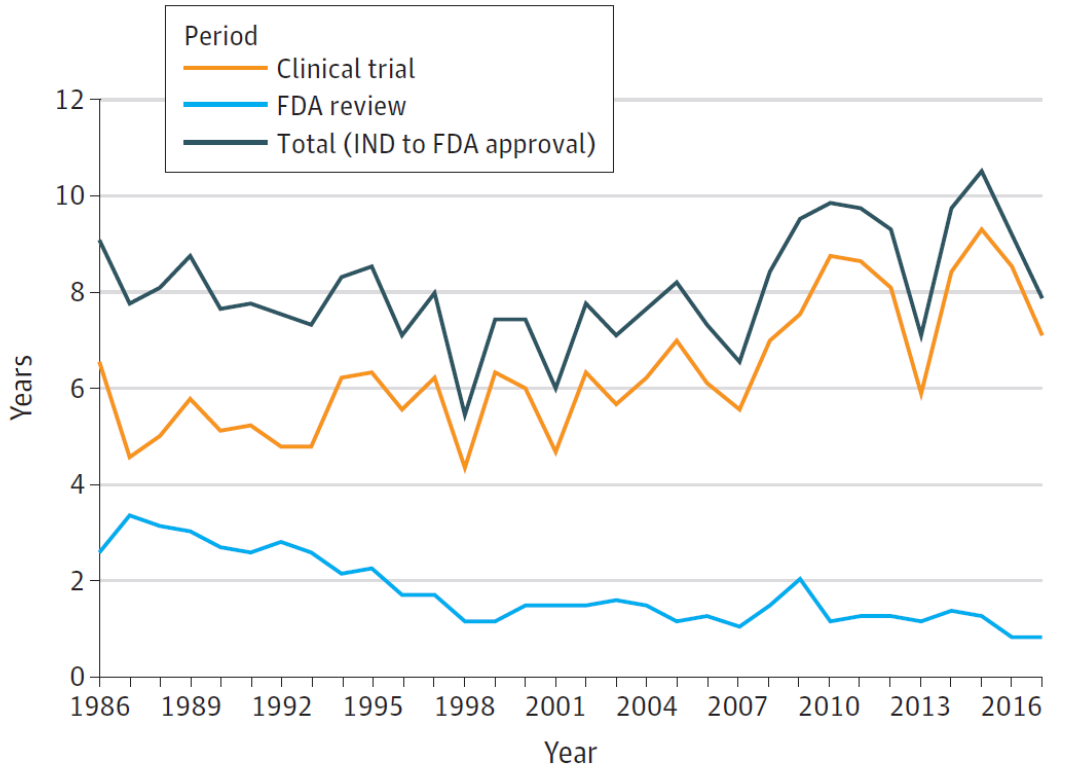



Figure 3. Clinical Trial and FDA Review Periods, 1986-2017



# Preapproval Testing

- 1962 KHDA required IND before human trials, which later was divided into 3 phases.

- New drugs supported by at least 2 pivotal trials decreased from 80.6% in 95-97 to 52.8% in 15-17 based on 124 and 106 approvals.
- Also those supported by at least 1 pivotal trial that used an active comparator (as opposed to placebo or historical controls) decreased from 44% to 29%.
- And, those based on non-randomized studies with only a single intervention group increased from 4% to 17%.

- However, the length of trials increased: approvals based on at least 1 pivotal trial of at least 6 month increased from 26% to 46%

# Expanded Access

- In 1987, AIDS epidemic led to “expanded access” regulations formalized
- FDA approves almost all such requests, but access to experimental drugs can be denied by manufactures
- In 2014, “right-to-try” laws enacted: has had a little documented effect

- # of EA requests increased from 1165 in 10-13 to 1746 in 14-17.
- FDA approved 98-99% of them within few days
- 30% of 408 drugs were provided via EA

# History

- After 1962 KHDA, (unlike the before) now the increasing time and cost required to obtain approval was the concern.
- 1983: Orphan Drug Act
- 1988: Fast-track program
  - Approval on the basis of phase 2
- 1992: Accelerated Approval
  - Surrogate measures “reasonably likely.. To predict clinical benefit”
  - Required post-approval studies
- 2012: Breakthrough Therapy (by Congress)
  - Similar to Fast-track, but with more formalized internal review process
  - On the basis of “alternative clinical trial designs” that may be smaller and require less time to complete
- 2016: 21st CCA
  - Maximize use of such measures

# Special Approval Programs

**Box 2. Special Approval Programs**

**Orphan Drug Act (1983)**. US legislation creating incentives for the development of rare disease treatments, defined in 1984 as diseases or conditions affecting fewer than 200 000 people in the United States.

**Fast-Track (1987)**. A program intended to expedite the development, evaluation, and marketing of new therapies for serious and life-threatening conditions by, among other things, eliminating phase 3 trials.

**Accelerated approval (1992)**. A program intended to expedite the development and marketing of new therapies for serious and life-threatening conditions by allowing the use of surrogate measures only reasonably likely to predict clinical benefit as end points for the pivotal clinical trials forming the basis for drug approval.

**Priority review (1992)**. Under the Prescription Drug User Fee Act, the FDA committed to first-cycle review deadlines for new drug applications of 6 months for priority applications and 12 months for standard applications (shortened to 10 months by 2002).

**Breakthrough Therapy (2012)**. Experimental therapies designated in this program are eligible for greater FDA attention and expedited response timelines during the clinical development process.

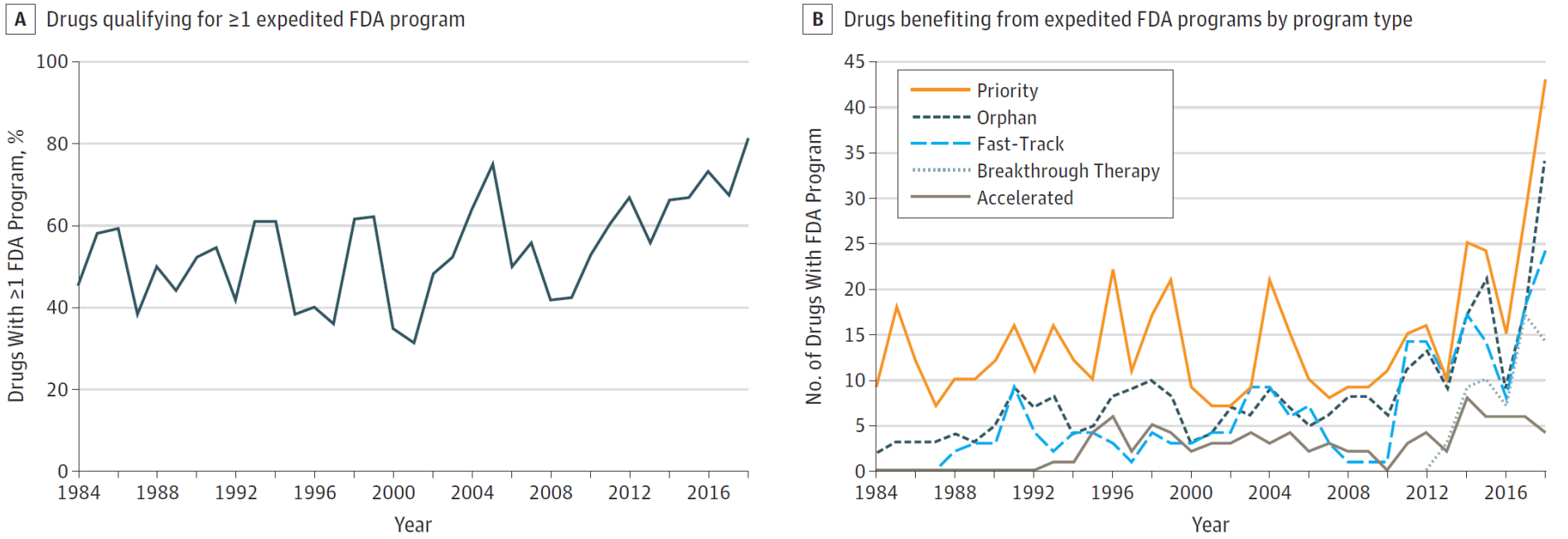
Abbreviation: FDA, US Food and Drug Administration.

# Statistics

- Orphan Drug
  - Drug approved with ODA designation increased from 18% in 84-95 to 41% in 08-18.
  - Trials for orphan drugs are much smaller (96 vs. 290); less likely to be randomized (30% vs. 80%); less likely to be double-blinded (4% vs. 33%); and more likely to assess surrogate endpoints (68% vs. 27%) rather than survival (8% vs. 27%)
- Expedited Development
  - Increased from 11% in 89-98 to 34% in 09-18
  - Approvals based on AA increased from 9% in 93-01 to 13% in 11-18.
  - 27% of new drugs approval in 14-18 were breakthrough designated
  - Breakthrough The pray resulted in significantly shorter total development time (4 years vs 8 years)
    - Misinterpreted by physicians as implying higher levels of efficacy than has necessarily been demonstrated
  - 52% of all breakthrough designated drugs approved in 13-16 were approved on the bases of phase 1 or phase 2; 45% on the basis of single trial; 42% w/o using either placebo or control
    - These figures were higher for oncology
    - However, follow-up study of 33 breakthrough and 25 non-break through cancer medicines, no significant differences in response rates, novel mechanisms, rates of death, or serious side effects.
- 48% qualified for at least expedited program in 86-96 while 64% in 08-18.

# # of Drugs benefiting from Expedited Programs 84-18

**Figure 4. Number of Drugs Benefiting From Expedited Programs, 1984 to 2018**




A, Forty-eight percent of drugs (150/313) qualified for at least 1 expedited program from 1986-1996, 51% (163/319) from 1997-2007, and 64% (243/380) from 2008-2018. B, Drugs may benefit from more than 1 program. Before the establishment of the 2-tiered priority review classification system in 1992, the US Food and Drug Administration (FDA) used a 3-tiered classification system. For drugs approved between 1984 and 1992, types A (important therapeutic gain) and B (modest therapeutic gain) were considered to correspond to priority review and type C (little or no therapeutic gain) to standard review. Drugs were categorized as subpart E (fast-track) drugs using the FDA's annual summaries, other public reports, and information provided by the FDA under the Freedom of Information Act. Accelerated approvals were identified using FDA documents and the FDA's annual summaries of novel new drugs. Drugs were categorized as having an Orphan Drug Act designation using the FDA's monthly drug approval reports database and the FDA's orphan drug database (expanded access not included).

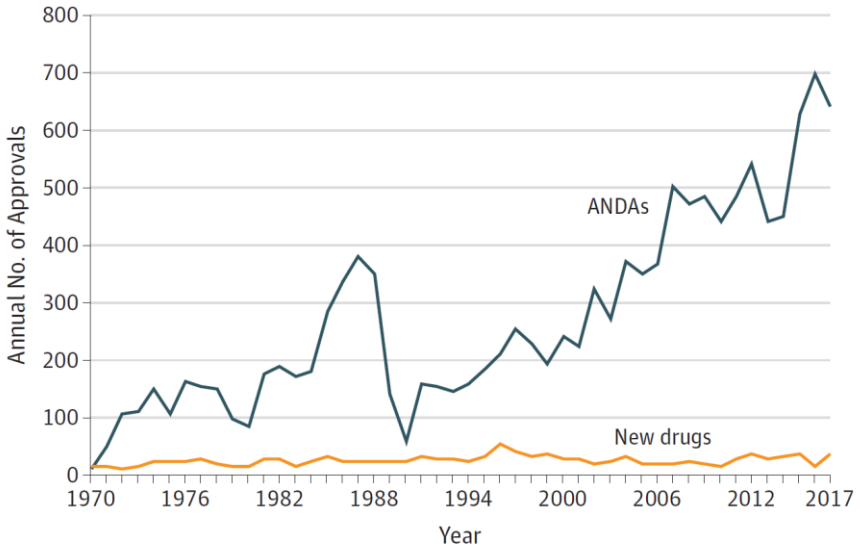
# History

- 1962 KHDA increased costs on pharmaceutical manufacturers
  - Branded manufacturers worked hard to recoup these cost during the exclusivity
  - However, generic manufacturers couldn’t’ afford clinical trials
- In 1970, FDA began to allow the submission and ANDAs for generic versions of drugs approved before 1962
  - Submit paper NDAs relied in part on published literature but such published reports were not so available -> by early 80s, 150 drugs approved after 1962 were off-patent and not had generics
- 1984 HWA: expanded ANDA pathway to encompass drugs approved after 1962
  - The law provided that a generic drug can be approved if pharmacokinetic testing showed that the generic drug achieved blood levels comparable to those of branded product w/o the need to independently demonstrate its own clinical outcomes.
  - Generic drugs have to be identical in active ingredient, strength, dosage form, and route of administration but could differ in :”inactive ingredients and appearance”

# Statistics

- 136 generic drugs approved in 70-84 to 588 in 13-18
- Annual # of potential new drugs on generic manufacturers could rely to produce ANDA products changed
- Proportion of prescription filled with generic drugs have increased 9% in 70 to 90% in 17.
- But it only represents 22% of drug expenditure. (still results in $1TR saving in costs)

Figure 5. Annual Number of Abbreviated New Drug Applications and New Drug Approvals, 1970 to 2018



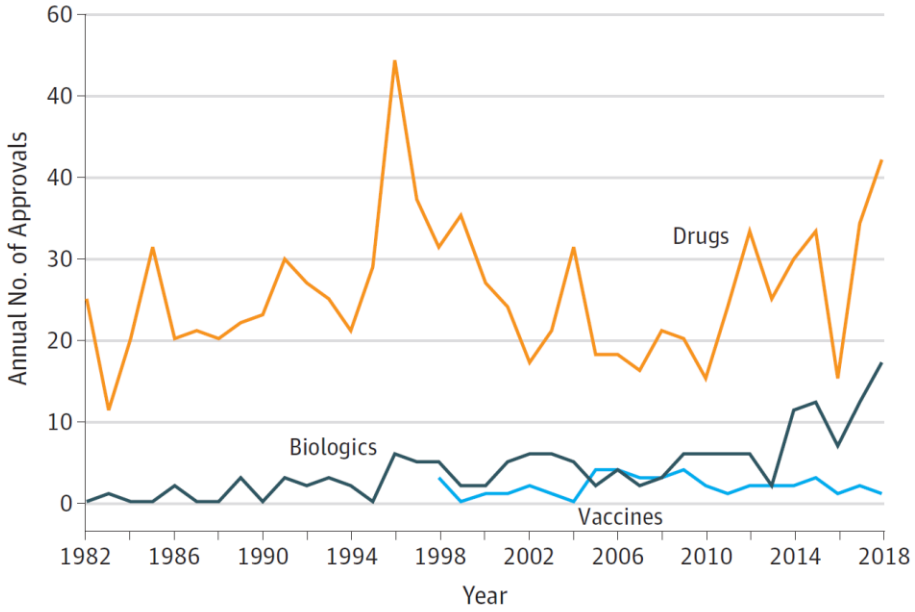
# Biosimilar Biologics

- ANDA does not cover biologics; biologics were about 29% of new drug approvals in 2018.
- In 2010, Biologics Price Competition and Innovation Act was enacted as part of the ACA; provided an abbreviated pathway for so-called biosimilars.
- Biosimiar: This term reflects the complexity of these large, cell-manufactured proteins, it is considered impossible for other companies to produce an identical version – just a similar one.
  - But still requires no clinically meaningful differences of safety, purity, and potency compared to the original medication
- FDA approved 73 biologics between 84 – 09 and few were off-patent when BPCIA took effect
- The first true biosimilar approved was CSF “Zarxio” in 2015 (e years after FDA issued draft biosimilar guidance
- So far 20 biosimilars for 9 distinct drug products have been approved

# Approval Period

- Mean annual # of approvals including biologics was 34 in 90-99, 25 in 00-09, and 41 in 10-18.
- The peak in 96 generally attributed to FDA';s hiring of additional review personnel enabled by 1992 PDUFA
- 21 biologics approved by CDER in 86-96 and they were transfer erred to CBER in 2003; 44 from 97 – 08; 88 from 08-18.
- 42 vaccines have been approved form 98 to 18.

Figure 6. Annual Number of Drug, Biologic, Device, and Vaccine Approvals



# History

- Patent laws in 1790
- Challenges in pharmaceuticals
  - Difficult to ascertain the value of a new product compared with that of its predecessor, causing physicians and patients to embrace heavily promoted, newly patented variations that may have little additional value
  - Insurance coverage of such patented but low-value drugs has allowed drug prices to increase, even after patent expires
  - Government price negotiation in US is limited
- Patent applications on active ingredients are generally filed early in drug development process
- So 1962 amendments reduced the average patent term remaining after approval from 13.8 years in 66 to 8.9 years in 77.
- To compensate for lost patent exclusivity, HWA granted brand-name manufactures “ patent term restoration” an opportunity to extend 1 patent per drug yb up to 5 years as long as the total time from initial FDA drug approval to patent expiration did not exceed 14 years

# History - Continued

- HWA also created additional exclusivities
  - Prevents a competitor from filing a generic drug application until at least 4 years after a new chemical entity is approved
  - In 1997, after companies showing reluctance to voluntarily test their products in children if there was no specific pediatric indication, Congress authorized a 6 month extension of exclusivity to companies that agree to study in children if requested by the FDA
  - IN 2012, GAIN Act authorized t-year extensions of nonpatent exclusivity to incentivize the development of certain new antibacterial and antifungal drugs added to the periods of HW and ODA
- The average exclusivity period before generic entry has remained approximately 13.5 years since the 1990s.
  - Manufacturers came up with clever ways to extend exclusivity
    - Single-enantiomer versions of racemic products
    - Newly patented fixed-dose combination drugs
    - Drug-device combinations
    - Slight modifications

# Statistics

- Among 170 top selling drugs with market exclusivity that expired in 00 – 02, 49% benefited from patent term restoration, which accounted for median extension of 2.75 years.
- From 12-17, FDA awarded 12 products an additional 5 years of exclusivity under GAIN Act
- From 98 to 18, 242 grants of 6 month pediatric exclusivity were awarded
  - Cost of conducting pediatric clinical trial is far less ($36.4M vs. 221.7M)
- Including patent and nonpatent exclusivities, generic entry for small molecule drugs continue to occur on average 13.5 years after the FDA approval

# Statistics

| Category | Exclusivity Period | Enacted |
|---|---|---|
| Orphan Drug | 7 years | 1983 |
| New Drug | 4-5 years | 1984 |
| Modifications to existing drugs | 3 years | 1984 |
| Pediatric research | 6 months | 1997 |
| Biologics | 12 years | 2012 |
| Antibacterials and Antifunglas | 5 years | 2012 |

# Post Approvals

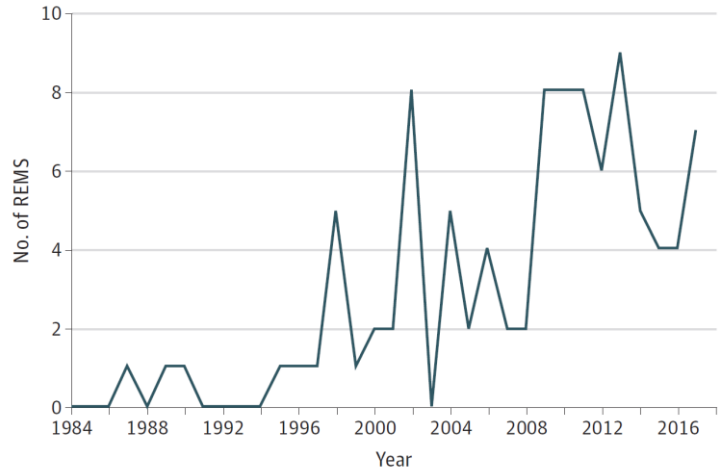
- Sponsors of drugs approved under the AA program are obliged by law to engage in postapproval study to verity and describe the clinical benefit.
- Under 2003 PREA, FDA may require postmarket pediatric studies for drugs with new active ingredients, indications, and dosage forms

- B/c FDA's influence becomes weaker after approval, the rate of completion of these post-approval studies is inadequate.
- FDA data on postmarketing requirement and commitments that were closed in 2016 indicated that 72% of postmarketing requirements and 82% of postmarketing commitment were fulfilled
- By contract, a study of 614 postapproval requirement and commitment imposed in 09 and 10 around that by the end of 15, 20% had not been started, 25% were delayed and only 54% were closed

# Risk Evaluation and Mitigation Strategies

- Congress carefully avoided authorizing the FDA to engage in activities that regulate the practice of medicine
- Practice of medicine vs. Regulation of drugs
  - Practice of medicine: Safety and efficacy of drug may dependent on how it is used by a prescriber or patient such as off-label or in conjunction with another drug
- 2007 FDA Amendments Act granted FDA the authority to require REMS
  - May be required as a condition for approval or for an already approved drug, and to both brand name and generics
    - Medication guide
    - Communication plan
    - Elements to ensure safe such as requiring patient to enroll in a registry
- REMS have served to limit overall prescribing, risky prescribing, and off-label prescribing
- Case
  - Fentanly decrease in outpatient dispensing from 14,400 in 12 to 4700 in 2017
  - REMS for opioids

Figure 7. Risk Evaluation and Mitigation Strategies With Elements to Ensure Safe Use, by Year of Drug Approval




Source: US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) data files. A REMS was applied to 1 drug approved before 1984 (methadone [Dolophine], 1947).

# Active Postmarket Monitoring

- Real-world setting
  - Comorbidities
  - Polypharmacy
  - Rare adverse events
    - Rofecoxib
      - Congress questioning FDA

- 2007 FDA Amendments Act to establish a system to conduct active postmarket risk surveillance by lking and analyzing the safety data of at least 100M patients
- Sentinel Initiatve

# Other Laws, Policies, and Regulations

## Healthcare / Insurance / Physicians

# Patient Protection and Affordability Care Act (PPACA) of 2010

- “Obamacare”

- https://en.wikipedia.org/wiki/Patient_Protection_and_Affordable_Care_Act

# PPPCA - Medicare Part D

- Medicare drug benefit (Part D) (Source: Wikipedia)
  - Medicare Part D participants received a 50% discount on brand name drugs purchased after exhausting their initial coverage and before reaching the catastrophic-coverage threshold.[101] By 2020, the "doughnut hole" would be completely filled.[102]

- *"Medicare Part D is a voluntary federal prescription drug program that provides subsidized outpatient prescription drug coverage for the elderly and disabled. This program was enacted as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), and coverage began in January 2006."*
- "We demonstrate that the passage of Medicare Part D was associated with significantly higher pharmaceutical R&D for drug classes with higher Medicare market share, and for firms specializing in higher-Medicare-share drugs." (Blume-Kohout & Sood, 2008)
- "We show that–counter to the predictions of frictionless models–firms respond to a plausibly exogenous positive shock to their net worth by developing more of these riskier novel candidates." (Kriegeret al. 2019)

# Physician Payments Sunshine Act of 2010

- Goal: To increase transparency of financial relationship between healthcare providers and pharmaceutical manufacturers
- Perlis & Perlis (2016)
  - “While distribution and amount of payments differed widely across medical specialties, for each of the 12 specialties examined the receipt of payments was associated with greater prescribing costs per patient, and greater proportion of branded medication prescribing. We cannot infer a causal relationship, but interventions aimed at those physicians receiving the most payments may present an opportunity to address prescribing costs in the US.”

- https://www.policymed.com/2014/04/physician-payment-sunshine-act-effect-on-smaller-companies.html
- https://en.wikipedia.org/wiki/Physician_Payments_Sunshine_Act

# References


- Darrow JJ, Avorn J, Kesselheim AS. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA*. 2020;323(2):164-176. doi:10.1001/jama.2019.20288
- Perlis, Roy H.; Perlis, Clifford S. (2016-05-16). "Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs". *PLoS ONE*. **11** (5): e0155474.
- Wikipedia webpages cited in slides where needed

# Useful Links / Further Reading

- Milestones in US FDA Law History
  - https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history
- Laws Enforced by FDA
  - https://www.fda.gov/regulatory-information/laws-enforced-fda
- Selected Amendments to the FD&C Act
  - https://www.fda.gov/regulatory-information/laws-enforced-fda/selected-amendments-fdc-act
- Brochure: “The History of Drug Regulation in the United States”
  - https://www.fda.gov/about-fda/fda-leadership-1907-today/brochure-history-drug-regulation-united-states
- FDA Glossary of terms
  - https://www.fda.gov/patients/clinical-trials-what-patients-need-know/glossary-terms