# FDA Regulatory Review: Implications for Evidence-Based Prescribing

## US Deprescribing Research Network

## January 16, 2024

**Joseph S. Ross, MD, MHS**
Section of General Internal Medicine, School of Medicine
Center for Outcomes Research and Evaluation, Yale-New Haven Hospital

CORE Center for Outcomes Research and Evaluation Yale School of Medicine

**@jsross119**

# Potential Conflicts of Interest

- **Research grant funding through Yale from:**
  - **FDA for the Yale-Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI)**
  - **MDIC to support project collaborations as part of the National Evaluation System for health Technologies (NEST)**
  - **Johnson & Johnson, and formerly from Medtronic Inc., for the Yale Open Data Access (YODA) Project**
  - **NIH/NHLBI, AHRQ**
  - **Laura & John Arnold Foundation**

CERSI
Yale-Mayo Clinic

NEST
Coordinating Center
An initiative of MDIC

the YODA PROJECT
Forging a unified scientific community

CRIT
COLLABORATION FOR REGULATORY RIGOR, INTEGRITY AND TRANSPARENCY

# Outline for Today

- **Brief history of the FDA and prescription drug oversight**
- **Evidentiary standards to secure FDA approval for new drugs**
- **Discuss implications for evidence-based prescribing**



**As clinicians and investigators, our focus is typically on medication use, safety and effectiveness, as opposed to the role FDA's policies play in guiding what evidence is available to inform practice.**


**1906 – Passage of the Federal Food and Drugs Act, prohibited interstate commerce in misbranded food, drink and drugs (basis of the law rested on the regulation of product labeling rather than pre-market approval)**

**1938 – Passage of the Food, Drug and Cosmetic Act, required pre-market safety proof for drugs and prohibition of false therapeutic claims**

**1960s – Passage of the Kefauver-Harris Drug Amendments, required pre-market efficacy proof for drugs: "adequate and well-controlled investigations".**

# Many Roles & Broad Responsibilities

**Responsibilities span research, enforcement, education, and information generation for …**

- **Most food products (other than meat & poultry)**
- **Human and animal drugs**
- **Therapeutic agents of biological origin**
- **Medical devices**
- **Radiation-emitting products for consumer, medical, and occupational use**
- **Food and color additives**
- **Infant formula**
- **Cosmetics**
- **Animal feed**

# Many Roles & Broad Responsibilities

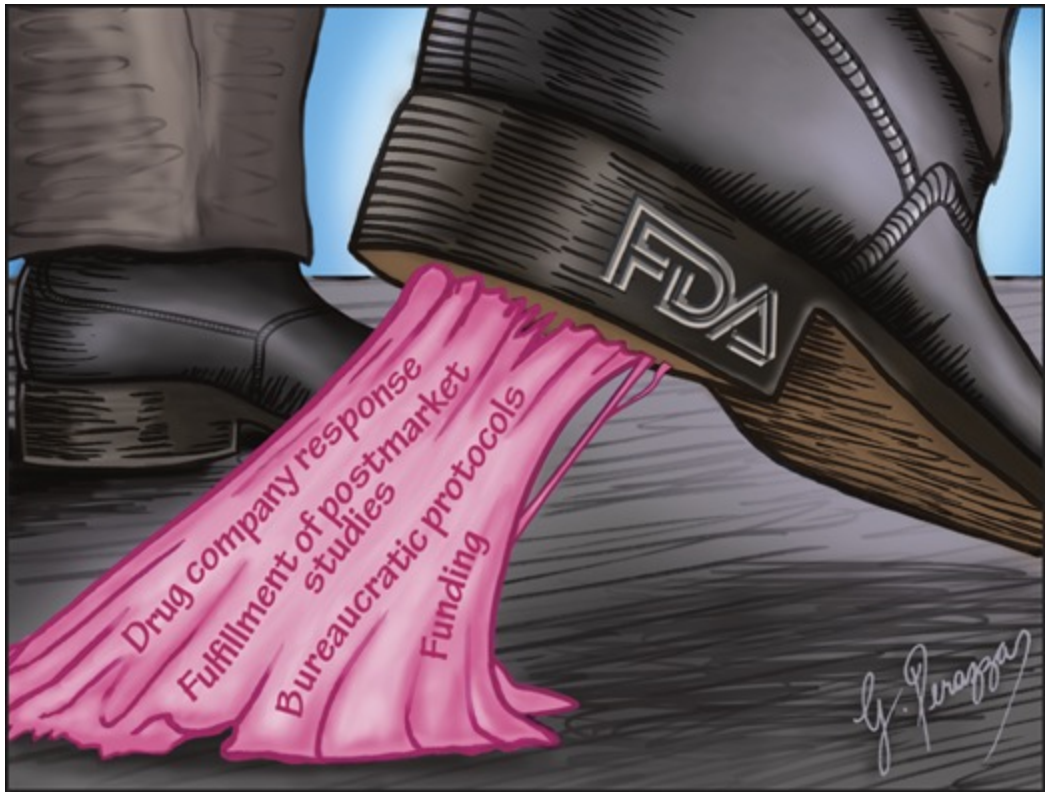
- **Oversees items accounting for 25 cents of every dollar spent by consumers**
- **>15,000 employees**
- **~$5,137,000,000 budget**
- **Monitors the manufacture, import, transport, storage, or sale of about $1 trillion worth of products annually at a cost to taxpayers of about $3 per person**

# Clear Mission, FDA Responsible for

- **Protecting the public health by assuring the safety, efficacy and security of all medical products for which it maintains oversight**
- **Advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable**
- **Helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health**

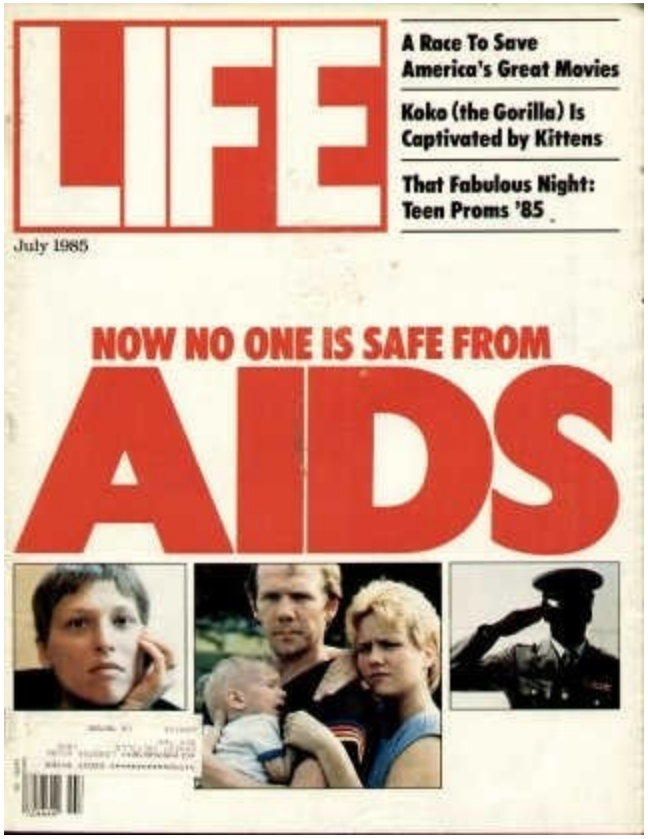

Promote Timely Drug Approval
Assure Drug Safety & Efficacy
Encourage Innovation

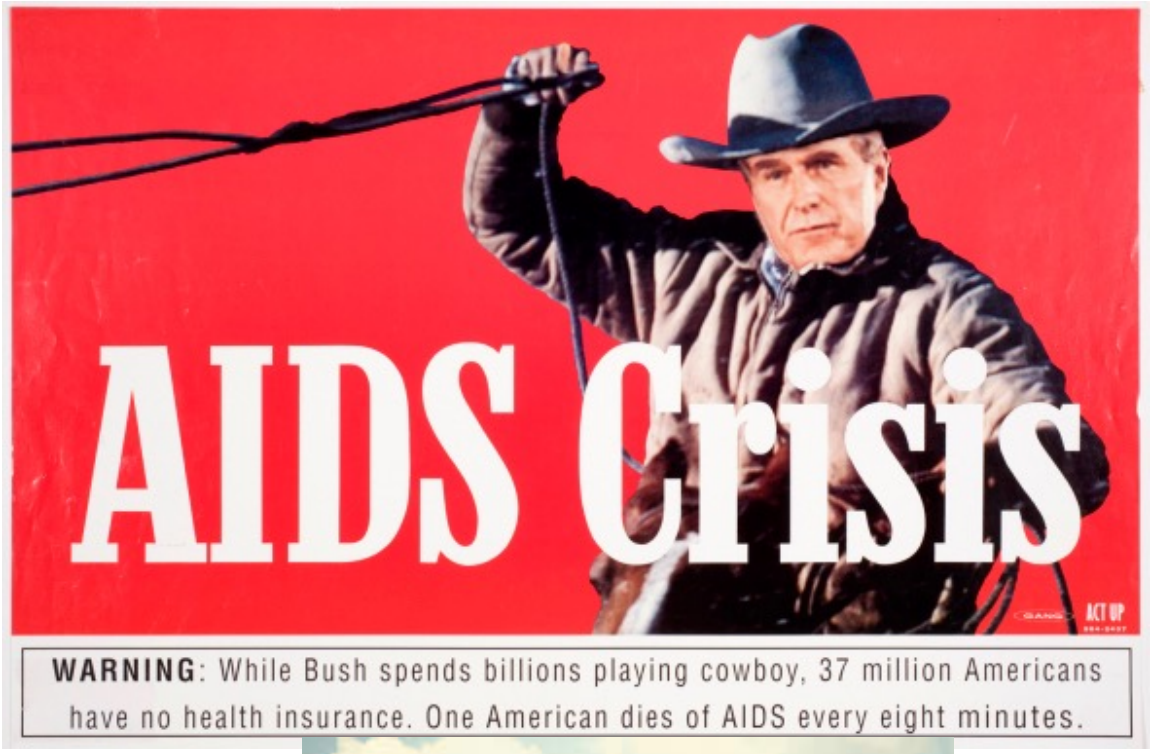
# Need for Timely Approval: Late 1980s



# Need for Timely Approval: Late 1980s

- **Dissatisfaction among patients, industry, and FDA – drug approvals taking too long**
- **Companies wanted to recoup R&D costs; every month of delay cost $10 million (~$25m today)**
- **FDA argued that it needed additional staff to end its back-log of drugs awaiting approval for market, but had not received sufficient appropriations from Congress to hire them**


LIFE
A Race To Save America's Great Movies
Koko (the Gorilla) Is Captivated by Kittens
That Fabulous Night: Teen Proms '85
July 1985
NOW NO ONE IS SAFE FROM
AIDS

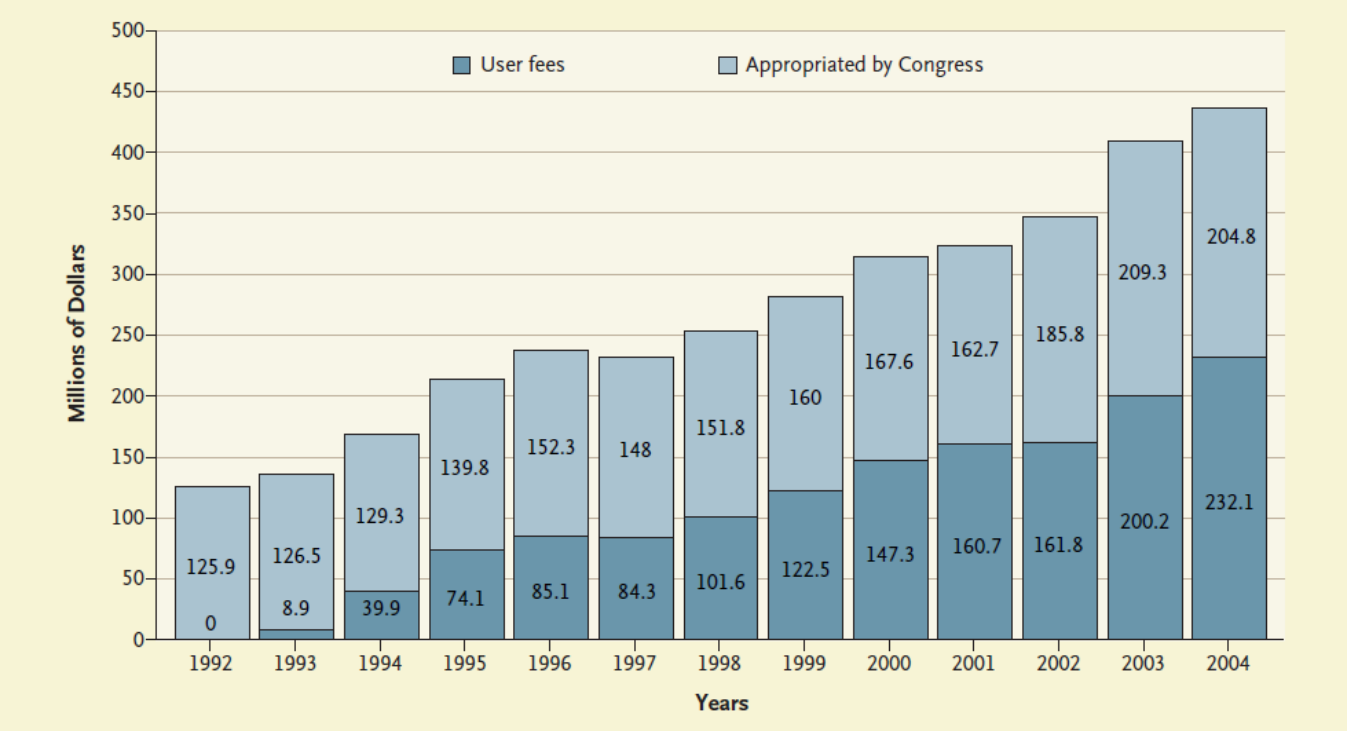

AIDS Crisis
ACT UP
WARNING: While Bush spends billions playing cowboy, 37 million Americans have no health insurance. One American dies of AIDS every eight minutes.


IGNORANCE = FEAR
SILENCE = DEATH
FIGHT AIDS ACT UP


MUSIC FROM AND INSPIRED BY
DALLAS BUYERS CLUB

# Prescription Drug User Fee Act

- **Pharmaceutical companies seeking approval of new drugs charged fees (~$3.5m today) to supplement, but not replace, direct appropriations from Congress**

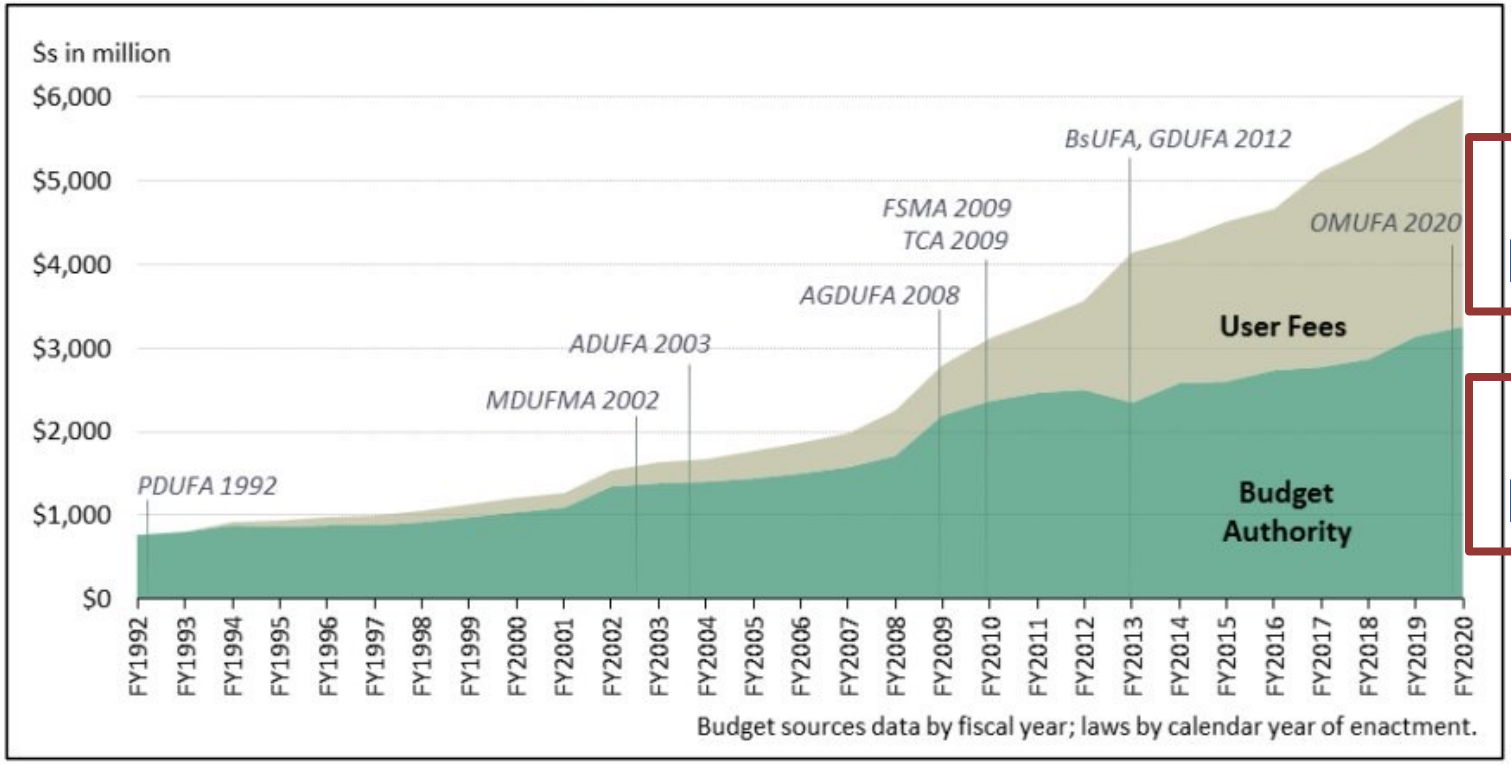



Source: Avorn, NEJM 2007;356:1697-1700.

# FDA User Fee Acts

**Figure 1. FDA Spending, by Source, FY1992-FY2020**

(in millions of dollars)




**Source:** Figure created by CRS using the FY1992 through FY2022 FDA CJs.

**$2.9 billion**

**$3.4 billion**

Source: Congressional Research Service, R44576.

# COUNTERTHINK


ART: DAN BERGER
CONCEPT BY: MIKE ADAMS

www.NewsTarget.com

# PDUFA: Review Times 27→14 months

## FY 2021 ~3,200 actions

- Priority NDA/BLA (98%)
- Standard NDA/BLA (92%)
- Class 1 resubs (80%)
- Class 2 resubs (94%)
- NDA/BLA manufacturing supp rq approval (96%)
- NDA/BLA manufacturing supp not rq approval (96%)

## Met 11 of 12 Goals

- Priority NME (91%)
- Standard NME (93%)
- Priority efficacy supp (90%)
- Standard efficacy sup (93%)
- Class 1 resub efficacy supp (100%)
- Class 2 resub efficacy supp (100%)

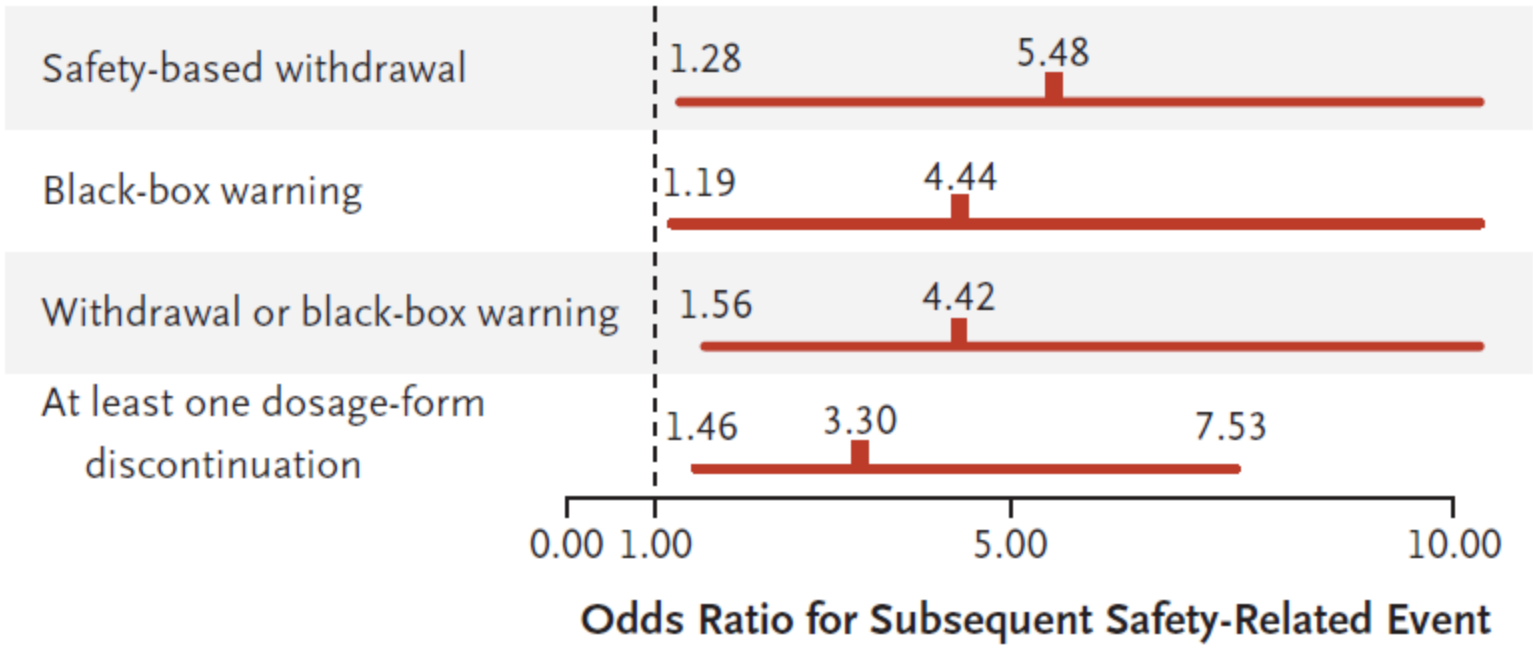



**Figure 2. Likelihood of Subsequent Safety-Related Problem for Drugs Approved in the Last 2 Months before the Review Deadline as Compared with All Other Drugs, 1993–2004.**

The bars indicate odds ratios, and the horizontal lines 95% confidence intervals.

Source: Carpenter et. al., NEJM 2008;358:1354-1361.


THE WALL STREET JOURNAL.
WSJ


## The FDA Nixes a Pathbreaking Drug for MS

**Thirty developed nations have approved Lemtrada. The U.S. refusal to do so shows the need for regulatory reform.**

## How the FDA Could Cost You Your Life

**An aortic valve approved in Europe four years ago will soon be approved in the U.S. Meanwhile, thousands who may have benefited from the device have died.**

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

# Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies

Nicholas S. Downing, A.B., Jenerius A. Aminawung, M.D., M.P.H.,
Nilay D. Shah, Ph.D., Joel B. Braunstein, M.D., M.B.A.,
Harlan M. Krumholz, M.D., and Joseph S. Ross, M.D., M.H.S.

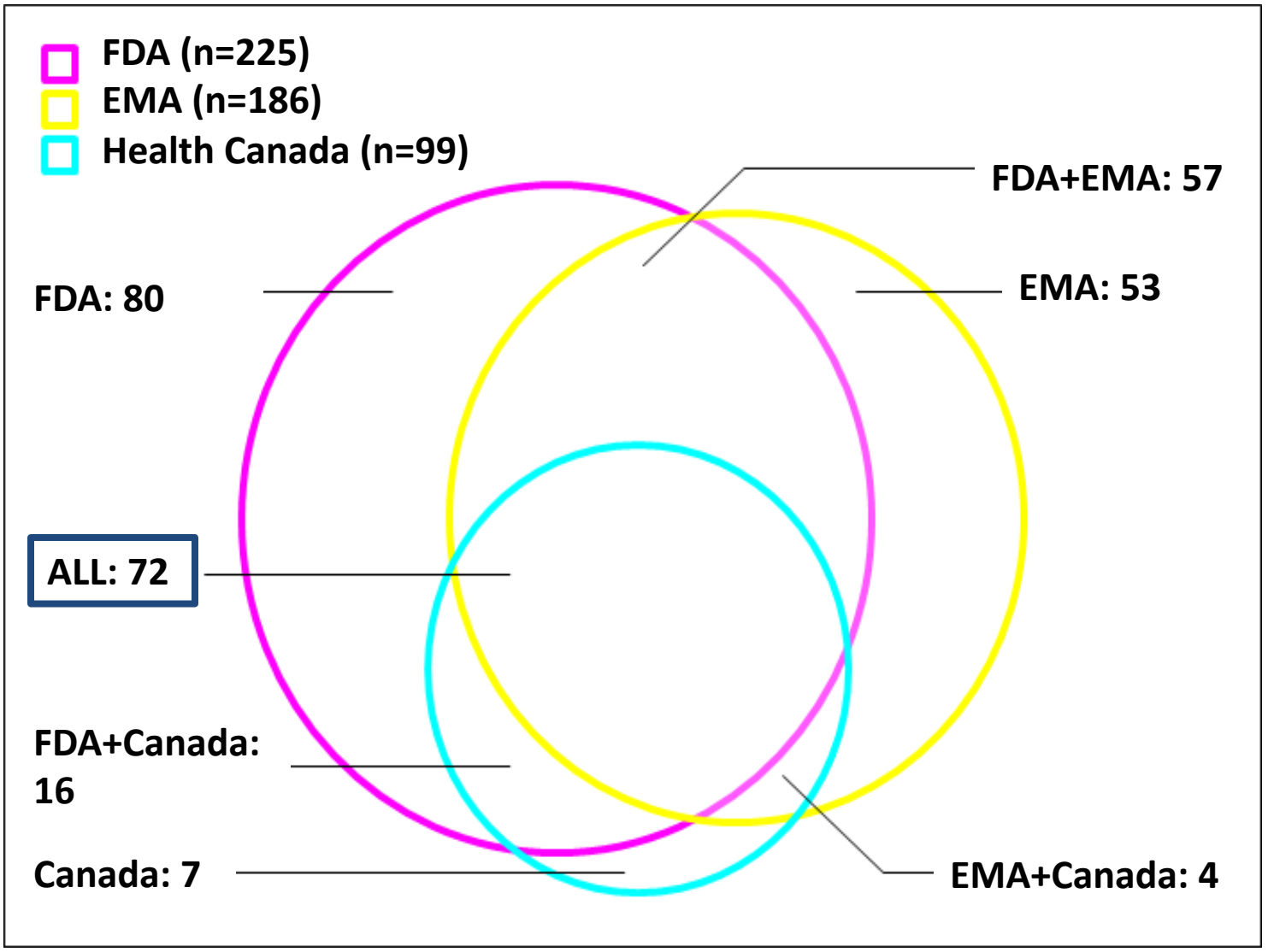
Source: Downing et. al., NEJM 2012;366:2284-2293.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

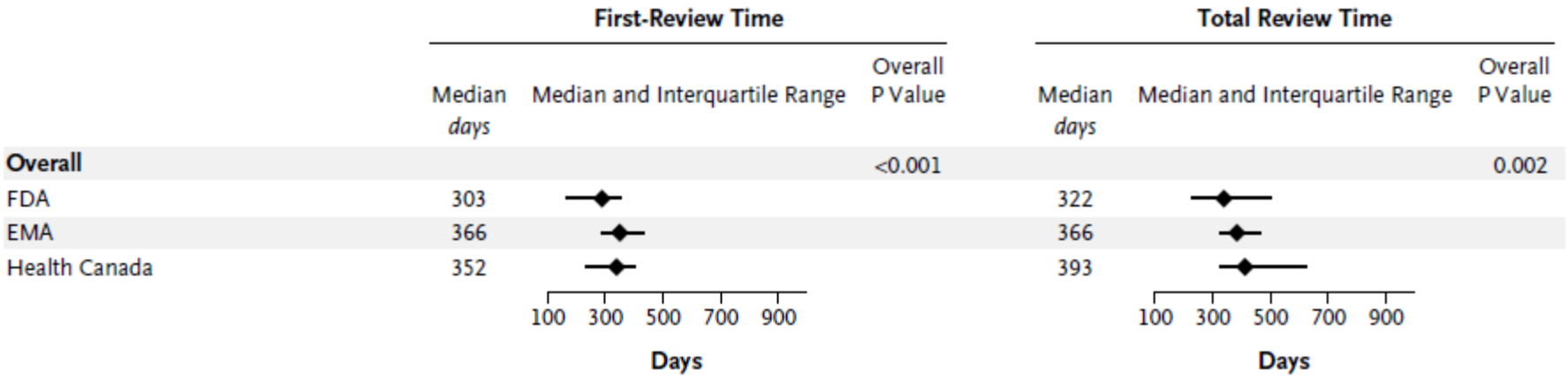
Source: Downing et. al., NEJM 2012;366:2284-2293.

# Agency Approvals, 2001-2010




Source: Downing et. al., NEJM 2012;366:2284-2293.

# All Medications Approved by 3 Agencies




- **Overall, FDA reviews ~2 months faster**
- **Results consistent when comparing**
  - **PDUFA submission periods**
  - **Drug vs. biologic**
  - **Orphan designation**
  - **Priority review status**

Source: Downing et. al., NEJM 2012;366:2284-2293.

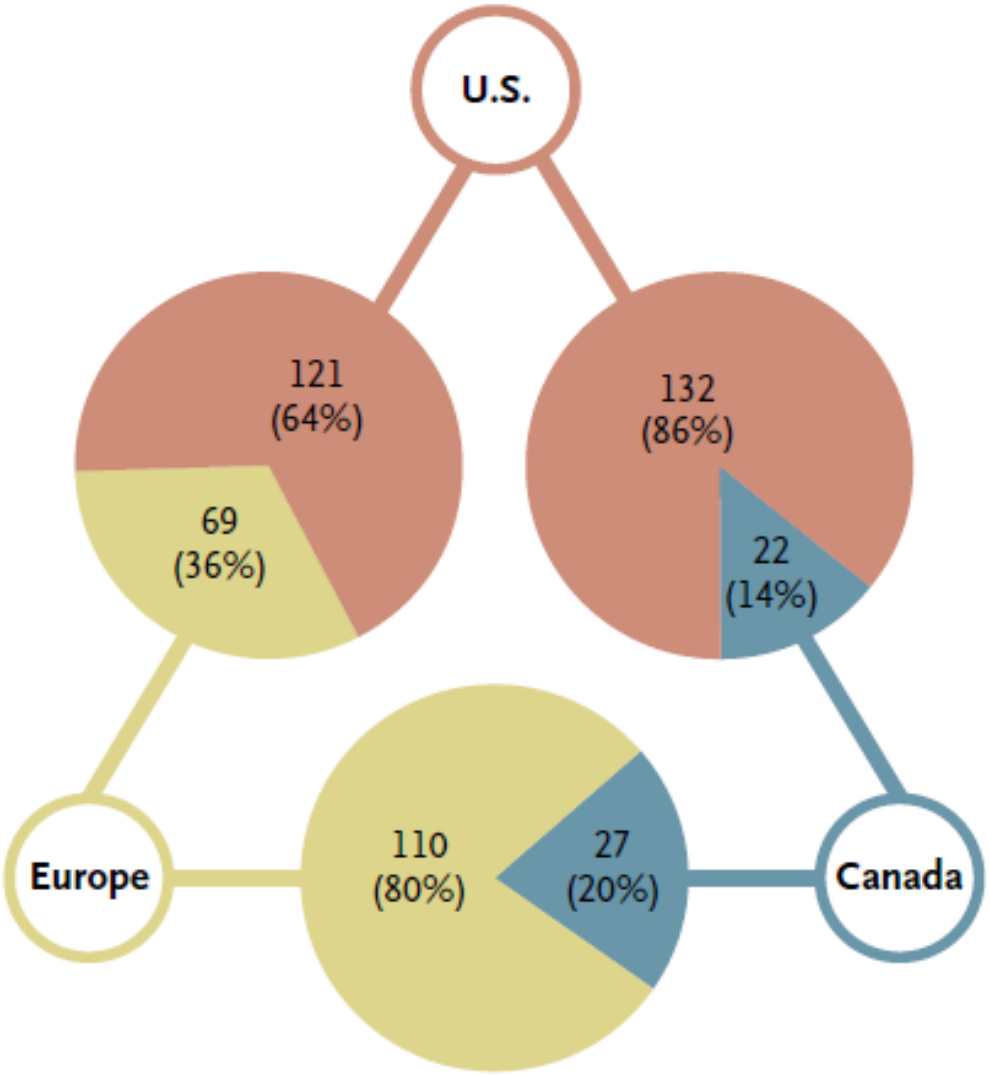
# Medications Approved by All 3 Agencies

| Approved by all 3 agencies (n=72) | FIRST REVIEW TIME | | | TOTAL REVIEW TIME | | |
|---|---|---|---|---|---|---|
| | Median | IQR | P value | Median | IQR | P value |
| FDA | 254 | 182-307 | 0.001 | 268 | 182-384 | 0.001 |
| EMA | 356 | 302-410 | | 356 | 302-419 | |
| Health Canada | 346 | 228-424 | | 266 | 255-588 | |

**Differences more substantial, FDA reviews ~3 months faster than EMA and Canada**

Source: Downing et. al., NEJM 2012;366:2284-2293.

# Majority First Approved for U.S. Market




Source: Downing et. al., NEJM 2012;366:2284-2293.

# FDA & EMA Review Time Differences Consistent for 2011-2015 Approvals

| | New Therapeutic Agents Approved *no. (%)* | Median Total Review Time (Interquartile Range) *days* | P Value |
|---|---|---|---|
| Overall | | | <0.001 |
| FDA | 170 (100) | 306 | |
| EMA | 144 (100) | 383 | |

Source: Downing et. al., NEJM 2017;376:1386-1387.


Promote Timely Drug Approval
Assure Drug Safety & Efficacy
Encourage Innovation

# Efficacy Must be Proven for Approval

- **Key provision of 1962 amendment was requirement that, in addition to pre-market safety demonstrations required under 1938 Food, Drug and Cosmetic Act, new drugs would also have to be demonstrated "efficacious".**

ORIGINAL INVESTIGATION

LESS IS MORE

# Communicating Uncertainties About Prescription Drugs to the Public

- **39% of patients believe FDA only approves "extremely effective" drugs, 25% only drugs without serious side effects**

# Physicians' Perspectives On FDA Regulation Of Drugs And Medical Devices: A National Survey

- **39% of physicians believe FDA only approves drugs "more effective than alternatives", 31% only drugs "safer than alternatives"**

Source: Schwartz and Woloshin, Arch Intern Med 2011;171:1463-1468 and Dhruva et al. Health Aff 2024;43:27-35.

# Efficacy Must be Proven for Approval

- Key provision of 1962 amendments was requirement that, in addition to pre-market safety demonstrations required under 1938 Food, Drug and Cosmetic Act, new drugs would also have to be demonstrated "efficacious".
- **Required “adequate and well-controlled investigations” (ie, clinical trials) that could provide “substantial evidence” to support claims of efficacy.**
  - **Suggests 2 or more pivotal efficacy trials …**

# Clinical Trial Phases

| Phase | Trial Objective | Typical Dose | Typical Size |
|---|---|---|---|
| Preclinical | Non-human toxicity & pharmacodynamics | Unrestricted | In Vitro/Animal |
| 0 | Pharmacodynamics / Pharmacokinetics | Sub-therapeutic | ~10 healthy volunteers |
| I | Dose-ranging | Ascending doses | 20-100 healthy volunteers |
| II | Preliminary clinical testing of efficacy and safety | Therapeutic dose | 100-300 patients |
| III | Robust clinical testing of efficacy and safety | Therapeutic dose | 1000-2000 patients |
| IV | Post-market surveillance focused on safety | Therapeutic dose | As Many As Possible |

Research

Original Investigation

# Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012

Nicholas S. Downing, AB; Jenerius A. Aminawung, MD, MPH; Nilay D. Shah, PhD; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

Source: Downing et. al., JAMA 2014;311:368-377.

# 184 Novel Therapeutics Approved for 201 Indications based on 448 Pivotal Trials

| Trial Design Features | |
|---|---|
| Randomized, % | 89% |
| Double-blinded, % | 80% |
| Comparator, % | |
| Active | 32% |
| Placebo | 55% |
| None | 13% |
| End Point, % | |
| Surrogate Marker of Disease | 49% |
| Clinical Outcome or Scale | 51% |
| Overall Patients, Median (IQR) | 446 (205-678) |
| Intervention Patients, Median (IQR) | 271 (133-426) |
| Duration, Median (IQR) | 14.0 (6.0-26.0) |

Source: Downing et. al., JAMA 2014;311:368-377.

# Aggregated Trials by Indication (n=201)

| Agent/Indication Characteristic (Indications) | Median (IQR), No. | | | |
|---|---|---|---|---|
| | Pivotal Efficacy Trials | Patients in Aggregated Pivotal Efficacy Trials | | Total Safety Population[b] |
| | | Overall | Intervention Group | |
| All indications (N = 201) | 2.0 (1.0-2.5) | 760 (270-1550) | 445 (169-936) | 1143 (503-2600) |
| Therapeutic area | | | | |
| Cancer (n = 41) | 1.0 (1.0-1.0) | 397 (180-634) | 277 (159-414) | 511 (295-1100) |
| Infectious disease (n = 27) | 2.0 (2.0-2.0) | 1171 (763-1408) | 605 (462-817) | 1408 (840-1979) |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | 3.0 (1.0-5.0) | 3645 (1446-5942) | 2291 (832-3947) | 3422 (1579-6570) |
| Neurology (n = 17) | 2.0 (2.0-3.0) | 1088 (448-1394) | 661 (279-877) | 2315 (1729-3145) |
| Dermatology (n = 15) | 2.0 (1.0-2.0) | 374 (233-1005) | 187 (127-376) | 1193 (1048-2228) |
| Autoimmune/musculoskeletal (n = 13) | 2.0 (2.0-3.0) | 1209 (289-2893) | 804 (223-1906) | 1955 (379-3233) |
| Psychiatry (n = 10) | 4.0 (2.0-5.5) | 1492 (947-3000) | 878 (417-1812) | 3290 (1596-4099) |
| Other (n = 55) | 2.0 (1.0-2.0) | 418 (105-1608) | 238 (78-968) | 700 (296-1781) |
| *P* value | <.001 | <.001 | <.001 | <.001 |
| Expected length of treatment | | | | |
| Acute (n = 36) | 2.0 (2.0-2.0) | 586 (305-1194) | 349 (155-613) | 889 (471-1560) |
| Intermediate (n = 57) | 1.0 (1.0-2.0) | 435 (192-787) | 290 (159-507) | 645 (365-1319) |
| Chronic (n = 108) | 2.0 (1.0-3.0) | 1203 (361-2062) | 694 (234-1407) | 1857 (698-3262) |
| *P* value | <.001 | <.001 | <.001 | <.001 |
| Agent type | | | | |
| Pharmacologic (n = 164) | 2.0 (1.0-3.0) | 825 (322-1607) | 503 (209-956) | 1206 (554-2806) |
| Biologic (n = 37) | 1.0 (1.0-2.0) | 374 (105-1213) | 229 (70-683) | 890 (288-1839) |
| *P* value | .01 | .009 | .003 | .05 |

Source: Downing et. al., JAMA 2014;311:368-377.

# Aggregated Trials by Indication (n=201)

| Agent/Indication Characteristic (Indications) | Median (IQR), No. | | | |
|---|---|---|---|---|
| | Pivotal Efficacy Trials | Patients in Aggregated Pivotal Efficacy Trials | | Total Safety Population[b] |
| | | Overall | Intervention Group | |
| All indications (N = 201) | 2.0 (1.0-2.5) | 760 (270-1550) | 445 (169-936) | 1143 (503-2600) |
| Therapeutic area | | | | |
| Cancer (n = 41) | 1.0 (1.0-1.0) | 397 (180-634) | 277 (159-414) | 511 (295-1100) |
| Infectious disease (n = 27) | 2.0 (2.0-2.0) | 1171 (763-1408) | 605 (462-817) | 1408 (840-1979) |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | 3.0 (1.0-5.0) | | | 3422 (1579-6570) |
| Neurology (n = 17) | 2.0 (2.0-3.0) | | | 2315 (1729-3145) |
| Dermatology (n = 15) | 2.0 (1.0-2.0) | | | 1193 (1048-2228) |
| Autoimmune/musculoskeletal (n = 13) | 2.0 (2.0-3.0) | | | 1955 (379-3233) |
| Psychiatry (n = 10) | 4.0 (2.0-5.5) | | | 3290 (1596-4099) |
| Other (n = 55) | 2.0 (1.0-2.0) | 418 (105-1608) | 238 (78-968) | 700 (296-1781) |
| *P* value | <.001 | <.001 | <.001 | <.001 |
| Expected length of treatment | | | | |
| Acute (n = 36) | 2.0 (2.0-2.0) | 586 (305-1194) | 349 (155-613) | 889 (471-1560) |
| Intermediate (n = 57) | 1.0 (1.0-2.0) | 435 (192-787) | 290 (159-507) | 645 (365-1319) |
| Chronic (n = 108) | 2.0 (1.0-3.0) | 1203 (361-2062) | 694 (234-1407) | 1857 (698-3262) |
| *P* value | <.001 | <.001 | <.001 | <.001 |
| Agent type | | | | |
| Pharmacologic (n = 164) | 2.0 (1.0-3.0) | 825 (322-1607) | 503 (209-956) | 1206 (554-2806) |
| Biologic (n = 37) | 1.0 (1.0-2.0) | 374 (105-1213) | 229 (70-683) | 890 (288-1839) |
| *P* value | .01 | .009 | .003 | .05 |

**~37% approved on basis of a single pivotal trial**

Source: Downing et. al., JAMA 2014;311:368-377.

# Aggregated Trials by Indication (n=201)

| Agent/Indication Characteristic (Indications) | Median (IQR), No. | | | |
|---|---|---|---|---|
| | Pivotal Efficacy Trials | Patients in Aggregated Pivotal Efficacy Trials | | Total Safety Population[b] |
| | | Overall | Intervention Group | |
| All indications (N = 201) | 2.0 (1.0-2.5) | 760 (270-1550) | 445 (169-936) | 1143 (503-2600) |
| Therapeutic area | | | | |
| Cancer (n = 41) | 1.0 (1.0-1.0) | 397 (180-634) | 277 (159-414) | 511 (295-1100) |
| Infectious disease (n = 27) | 2.0 (2.0-2.0) | 1171 (763-1408) | 605 (462-817) | 1408 (840-1979) |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | 3.0 (1.0-5.0) | 3645 (1446-5942) | 2291 (832-3947) | 3422 (1579-6570) |
| Neurology (n = 17) | 2.0 (2.0-3.0) | 1088 (448-1394) | 661 (279-877) | 2315 (1729-3145) |
| Dermatology (n = 15) | 2.0 (1.0-2.0) | 374 (233-1005) | 187 (127-376) | 1193 (1048-2228) |
| Autoimmune/musculoskeletal (n = 13) | 2.0 (2.0-3.0) | 1209 (289-2893) | 804 (223-1906) | 1955 (379-3233) |
| Psychiatry (n = 10) | 4.0 (2.0-5.5) | 1492 (947-3000) | 878 (417-1812) | 3290 (1596-4099) |
| Other (n = 55) | 2.0 (1.0-2.0) | 418 (105-1608) | 238 (78-968) | 700 (296-1781) |
| *P* value | <.001 | <.001 | <.001 | <.001 |
| Expected length of treat | | | | |
| Acute (n = 36) | | | | -1560) |
| Intermediate (n = 57) | | | | -1319) |
| Chronic (n = 108) | | | | -3262) |
| *P* value | | | | |
| Agent type | | | | |
| Pharmacologic (n = 16 | | | | -2806) |
| Biologic (n = 37) | | | | -1839) |
| *P* value | | | | |

**Drugs indicated for treatment of cancer frequently approved on basis of a single, small pivotal trial; drugs for treatment of CV/DM/Lipids, multiple, larger pivotal trials**

Source: Downing et. al., JAMA 2014;311:368-377.

| Agent/Indication Characteristic (Indications) | No. (%) [95% CI] | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Trial Duration | | Comparator | | End Point | |
| | ≥2 Pivotal Trials[b] | ≥6 mo | ≥12 mo | Active | Placebo | Clinical Outcome | Clinical Scale |
| All indications (N = 201) | 127 (63.2) [56.5-69.9] | 68 (33.8) [27.2-40.4] | 17 (8.5) [4.6-12.3] | 79 (39.3) [32.5-46.1] | 119 (59.2) [52.4-66.0] | 73 (36.3) [29.6-43.0] | 39 (19.4) [13.9-24.9] |
| Therapeutic area | | | | | | | |
| Cancer (n = 41) | 8 (19.5) [6.8-32.1] | 16 (39.0) [23.4-54.6] | 2 (4.9) [0.0-11.8] | 10 (24.4) [10.7-38.1] | 15 (36.6) [21.2-52.0] | 9 (22.0) [8.7-35.2] | 0 |
| Infectious disease (n = 27) | 21 (77.8) [61.0-94.5] | 5 (18.5) [2.9-34.1] | 1 (3.7) [0.0-11.3] | 21 (77.8) [61.1-94.5] | 7 (25.9) [8.3-43.6] | 13 (48.1) [28.0-68.3] | 0 |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | 16 (69.6) [49.2-90.0] | 12 (52.2) [30.0-74.3] | 4 (17.4) [0.0-34.2 | | | | |
| Neurology (n = 17) | 15 (88.2) [71.1-100.0] | 4 (23.5) [1.0-46.0] | 2 (11.8) [0.0-28.8 | | | | |
| Dermatology (n = 15) | 11 (73.3) [48.0-98.6] | 2 (13.3) [0.0-32.8] | 0 | | | | |
| Autoimmune/ musculoskeletal (n = 13) | 11 (84.6) [61.9-100.0] | 6 (46.2) [14.8-77.5] | 1 (7.7) [0.0-24.5 | | | | |
| Psychiatry (n = 10) | 10 (100.0) [100.0-100.0] | 0 | 0 | | | | |
| Other (n = 55) | 35 (63.6) [50.5-76.8] | 23 (41.8) [28.4-55.3] | 7 (12.7) [3.6-21.8] | | | | |
| *P* value | <.001 | .01 | .36 | <.001 | <.001 | .008 | <.001 |
| Expected length of treatment | | | | | | | |
| Acute (n = 36) | 28 (77.8) [63.5-92.0] | 1 (2.8) [0.0-8.4] | 0 | 20 (55.6) [38.5-72.6] | 17 (47.2) [30.0-64.4] | 22 (61.1) [44.4-77.8] | 3 (8.3) [0.0-17.8] |
| Intermediate (n = 57) | 21 (36.8) [23.9-49.8] | 19 (33.3) [20.7-46.0] | 4 (7.0) [0.0-13.8] | 17 (29.8) [17.6-42.1] | 25 (43.9) [30.6-57.1] | 14 (24.6) [13.0-36.1] | 10 (17.5) [7.4-27.7] |
| Chronic (n = 108) | 78 (72.2) [63.6-80.8] | 48 (44.4) [34.9-54.0] | 13 (12.0) [5.8-18.3] | 42 (38.9) [29.5-48.2] | 77 (71.3) [62.6-80.0] | 37 (34.3) [25.2-43.4] | 26 (24.1) [15.9-32.3] |
| *P* value | <.001 | <.001 | .07 | .05 | .001 | .001 | .11 |
| Agent type | | | | | | | |
| Pharmacologic (n = 164) | 110 (67.1) [59.8-74.3] | 52 (31.7) [24.5-38.9] | 15 (9.1) [4.7-13.6] | 71 (43.3) [35.6-51.0] | 92 (56.1) [48.4-63.8] | 66 (40.2) [32.7-47.8] | 23 (14.0) [8.7-19.4] |
| Biologic (n = 37) | 17 (45.9) [29.1-62.8] | 16 (43.2) [26.5-60.0] | 2 (5.4) [0.0-13.0] | 8 (21.6) [7.7-35.5] | 27 (73.0) [58.0-88.0] | 7 (18.9) [5.7-32.2] | 16 (43.2) [26.5-60.0] |
| *P* value | .02 | .18 | .46 | .01 | .06 | .01 | <.001 |

**~33% approved on basis of at least one pivotal trial of 6 months or longer**

Source: Downing et. al., JAMA 2014;311:368-377.

| Agent/Indication Characteristic (Indications) | No. (%) [95% CI] | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Trial Duration | | Comparator | | End Point | |
| | ≥2 Pivotal Trials[b] | ≥6 mo | ≥12 mo | Active | Placebo | Clinical Outcome | Clinical Scale |
| All indications (N = 201) | 127 (63.2) [56.5-69.9] | 68 (33.8) [27.2-40.4] | 17 (8.5) [4.6-12.3] | 79 (39.3) [32.5-46.1] | 119 (59.2) [52.4-66.0] | 73 (36.3) [29.6-43.0] | 39 (19.4) [13.9-24.9] |
| Therapeutic area | | | | | | | |
| Cancer (n = 41) | 8 (19.5) [6.8-32.1] | 16 (39.0) [23.4-54.6] | 2 (4.9) [0.0-11.8] | 10 (24.4) [10.7-38.1] | 15 (36.6) [21.2-52.0] | 9 (22.0) [8.7-35.2] | 0 |
| Infectious disease (n = 27) | | | | | | | |
| Cardiovascular disea diabetes mellitus, hyperlipidemia (n = | | | | | | | |
| Neurology (n = 17) | | | | | | | |
| Dermatology (n = 1 | | | | | | | |
| Autoimmune/ musculoskeletal (n = | | | | | | | |
| Psychiatry (n = 10) | [100.0-100.0] | | | [ 8-100.0] | [35.4-100.0] | [0.0-50.2] | [49.8-100.0] |
| Other (n = 55) | 35 (63.6) [50.5-76.8] | 23 (41.8) [28.4-55.3] | 7 (12.7) [3.6-21.8] | 13 (23.6) [12.0-35.2] | 37 (67.3) [54.5-80.0] | 21 (38.2) [24.9-51.4] | 9 (16.4) [6.3-26.5] |
| *P* value | <.001 | .01 | .36 | <.001 | <.001 | .008 | <.001 |
| Expected length of treatment | | | | | | | |
| Acute (n = 36) | 28 (77.8) [63.5-92.0] | 1 (2.8) [0.0-8.4] | 0 | 20 (55.6) [38.5-72.6] | 17 (47.2) [30.0-64.4] | 22 (61.1) [44.4-77.8] | 3 (8.3) [0.0-17.8] |
| Intermediate (n = 57) | 21 (36.8) [23.9-49.8] | 19 (33.3) [20.7-46.0] | 4 (7.0) [0.0-13.8] | 17 (29.8) [17.6-42.1] | 25 (43.9) [30.6-57.1] | 14 (24.6) [13.0-36.1] | 10 (17.5) [7.4-27.7] |
| Chronic (n = 108) | 78 (72.2) [63.6-80.8] | 48 (44.4) [34.9-54.0] | 13 (12.0) [5.8-18.3] | 42 (38.9) [29.5-48.2] | 77 (71.3) [62.6-80.0] | 37 (34.3) [25.2-43.4] | 26 (24.1) [15.9-32.3] |
| *P* value | <.001 | <.001 | .07 | .05 | .001 | .001 | .11 |
| Agent type | | | | | | | |
| Pharmacologic (n = 164) | 110 (67.1) [59.8-74.3] | 52 (31.7) [24.5-38.9] | 15 (9.1) [4.7-13.6] | 71 (43.3) [35.6-51.0] | 92 (56.1) [48.4-63.8] | 66 (40.2) [32.7-47.8] | 23 (14.0) [8.7-19.4] |
| Biologic (n = 37) | 17 (45.9) [29.1-62.8] | 16 (43.2) [26.5-60.0] | 2 (5.4) [0.0-13.0] | 8 (21.6) [7.7-35.5] | 27 (73.0) [58.0-88.0] | 7 (18.9) [5.7-32.2] | 16 (43.2) [26.5-60.0] |
| *P* value | .02 | .18 | .46 | .01 | .06 | .01 | <.001 |

**44% of drugs indicated for chronic treatment approved on basis of at least one pivotal trial of 6 months or longer, 12% on one 12 months or longer**

Source: Downing et. al., JAMA 2014;311:368-377.

| Agent/Indication Characteristic (Indications) | No. (%) [95% CI] | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Trial Duration | | Comparator | | End Point | |
| | ≥2 Pivotal Trials[b] | ≥6 mo | ≥12 mo | Active | Placebo | Clinical Outcome | Clinical Scale |
| All indications (N = 201) | 127 (63.2) [56.5-69.9] | 68 (33.8) [27.2-40.4] | 17 (8.5) [4.6-12.3] | 79 (39.3) [32.5-46.1] | 119 (59.2) [52.4-66.0] | 73 (36.3) [29.6-43.0] | 39 (19.4) [13.9-24.9] |
| Therapeutic area | | | | | | | |
| Cancer (n = 41) | 8 (19.5) [6.8-32.1] | 16 (39.0) [23.4-54.6] | 2 (4.9) [0.0-11.8] | 10 (24.4) [10.7-38.1] | 15 (36.6) [21.2-52.0] | 9 (22.0) [8.7-35.2] | 0 |
| Infectious disease (n = 27) | 21 (77.8) [61.0-94.5] | 5 (18.5) [2.9-34.1] | 1 (3.7) [0.0-11.3] | 21 (77.8) [61.1-94.5] | 7 (25.9) [8.3-43.6] | 13 (48.1) [28.0-68.3] | 0 |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | | | | | 6 (69.6) 9.2-89.9] | 8 (34.8) [13.7-55.8] | 0 |
| Neurology (n = 17) | | | | | 5 (88.2) .1-100.0] | 11 (64.7) [39.4-90.0] | 7 (41.2) [15.1-67.2] |
| Dermatology (n = 15) | | | | | 1 (73.3) 8.0-98.7] | 8 (53.3) [24.7-81.9] | 5 (33.3) [6.3-60.3] |
| Autoimmune/ musculoskeletal (n = 13) | | | | | 1 (84.6) .9-100.0] | 1 (7.7) [0.0-24.5] | 10 (76.9) [50.4-100.0] |
| Psychiatry (n = 10) | | | | | 7 (70.0) .4-100.0] | 2 (20.0) [0.0-50.2] | 8 (80.0) [49.8-100.0] |
| Other (n = 55) | | | | | 7 (67.3) 4.5-80.0] | 21 (38.2) [24.9-51.4] | 9 (16.4) [6.3-26.5] |
| *P* value | <.001 | .01 | .36 | <.001 | <.001 | .008 | <.001 |
| Expected length of treatment | | | | | | | |
| Acute (n = 36) | 28 (77.8) [63.5-92.0] | 1 (2.8) [0.0-8.4] | 0 | 20 (55.6) [38.5-72.6] | 17 (47.2) [30.0-64.4] | 22 (61.1) [44.4-77.8] | 3 (8.3) [0.0-17.8] |
| Intermediate (n = 57) | 21 (36.8) [23.9-49.8] | 19 (33.3) [20.7-46.0] | 4 (7.0) [0.0-13.8] | 17 (29.8) [17.6-42.1] | 25 (43.9) [30.6-57.1] | 14 (24.6) [13.0-36.1] | 10 (17.5) [7.4-27.7] |
| Chronic (n = 108) | 78 (72.2) [63.6-80.8] | 48 (44.4) [34.9-54.0] | 13 (12.0) [5.8-18.3] | 42 (38.9) [29.5-48.2] | 77 (71.3) [62.6-80.0] | 37 (34.3) [25.2-43.4] | 26 (24.1) [15.9-32.3] |
| *P* value | <.001 | <.001 | .07 | .05 | .001 | .001 | .11 |
| Agent type | | | | | | | |
| Pharmacologic (n = 164) | 110 (67.1) [59.8-74.3] | 52 (31.7) [24.5-38.9] | 15 (9.1) [4.7-13.6] | 71 (43.3) [35.6-51.0] | 92 (56.1) [48.4-63.8] | 66 (40.2) [32.7-47.8] | 23 (14.0) [8.7-19.4] |
| Biologic (n = 37) | 17 (45.9) [29.1-62.8] | 16 (43.2) [26.5-60.0] | 2 (5.4) [0.0-13.0] | 8 (21.6) [7.7-35.5] | 27 (73.0) [58.0-88.0] | 7 (18.9) [5.7-32.2] | 16 (43.2) [26.5-60.0] |
| *P* value | .02 | .18 | .46 | .01 | .06 | .01 | <.001 |

**~39% approved on basis of at least one pivotal trial using an active comparator**

Source: Downing et. al., JAMA 2014;311:368-377.

| Agent/Indication Characteristic (Indications) | No. (%) [95% CI] | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Trial Duration | | Comparator | | End Point | |
| | ≥2 Pivotal Trials[b] | ≥6 mo | ≥12 mo | Active | Placebo | Clinical Outcome | Clinical Scale |
| All indications (N = 201) | 127 (63.2) [56.5-69.9] | 68 (33.8) [27.2-40.4] | 17 (8.5) [4.6-12.3] | 79 (39.3) [32.5-46.1] | 119 (59.2) [52.4-66.0] | 73 (36.3) [29.6-43.0] | 39 (19.4) [13.9-24.9] |
| Therapeutic area | | | | | | | |
| Cancer (n = 41) | 8 (19.5) [6.8-32.1] | 16 (39.0) [23.4-54.6] | 2 (4.9) [0.0-11.8] | 10 (24.4) [10.7-38.1] | 15 (36.6) [21.2-52.0] | 9 (22.0) [8.7-35.2] | 0 |
| Infectious disease (n = 27) | 21 (77.8) [61.0-94.5] | 5 (18.5) [2.9-34.1] | 1 (3.7) [0.0-11.3] | 21 (77.8) [61.1-94.5] | 7 (25.9) [8.[illegible]43.6] | 13 (48.1) [28.0-68.3] | 0 |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | | | | | [illegible]6 (69.6) [illegible]9.2-89.9] | 8 (34.8) [13.7-55.8] | 0 |
| Neurology (n = 17) | | | | | [illegible]5 (88.2) [illegible].1-100.0] | 11 (64.7) [39.4-90.0] | 7 (41.2) [15.1-67.2] |
| Dermatology (n = 15) | | | | | [illegible]1 (73.3) [illegible]8.0-98.7] | 8 (53.3) [24.7-81.9] | 5 (33.3) [6.3-60.3] |
| Autoimmune/ musculoskeletal (n = 13) | | | | | [illegible]1 (84.6) [illegible].9-100.0] | 1 (7.7) [0.0-24.5] | 10 (76.9) [50.4-100.0] |
| Psychiatry (n = 10) | | | | | [illegible]7 (70.0) [illegible].4-100.0] | 2 (20.0) [0.0-50.2] | 8 (80.0) [49.8-100.0] |
| Other (n = 55) | | | | | [illegible]7 (67.3) [illegible]4.5-80.0] | 21 (38.2) [24.9-51.4] | 9 (16.4) [6.3-26.5] |
| *P* value | <.001 | .01 | .36 | <.001 | <.001 | .008 | <.001 |
| Expected length of treatment | | | | | | | |
| Acute (n = 36) | 28 (77.8) [63.5-92.0] | 1 (2.8) [0.0-8.4] | 0 | 20 (55.6) [38.5-72.6] | 17 (47.2) [30.0-64.4] | 22 (61.1) [44.4-77.8] | 3 (8.3) [0.0-17.8] |
| Intermediate (n = 57) | 21 (36.8) [23.9-49.8] | 19 (33.3) [20.7-46.0] | 4 (7.0) [0.0-13.8] | 17 (29.8) [17.6-42.1] | 25 (43.9) [30.6-57.1] | 14 (24.6) [13.0-36.1] | 10 (17.5) [7.4-27.7] |
| Chronic (n = 108) | 78 (72.2) [63.6-80.8] | 48 (44.4) [34.9-54.0] | 13 (12.0) [5.8-18.3] | 42 (38.9) [29.5-48.2] | 77 (71.3) [62.6-80.0] | 37 (34.3) [25.2-43.4] | 26 (24.1) [15.9-32.3] |
| *P* value | <.001 | <.001 | .07 | .05 | .001 | .001 | .11 |
| Agent type | | | | | | | |
| Pharmacologic (n = 164) | 110 (67.1) [59.8-74.3] | 52 (31.7) [24.5-38.9] | 15 (9.1) [4.7-13.6] | 71 (43.3) [35.6-51.0] | 92 (56.1) [48.4-63.8] | 66 (40.2) [32.7-47.8] | 23 (14.0) [8.7-19.4] |
| Biologic (n = 37) | 17 (45.9) [29.1-62.8] | 16 (43.2) [26.5-60.0] | 2 (5.4) [0.0-13.0] | 8 (21.6) [7.7-35.5] | 27 (73.0) [58.0-88.0] | 7 (18.9) [5.7-32.2] | 16 (43.2) [26.5-60.0] |
| *P* value | .02 | .18 | .46 | .01 | .06 | .01 | <.001 |

**~45% approved exclusively on basis of pivotal trials using surrogate endpoints**

Source: Downing et. al., JAMA 2014;311:368-377.

| Agent/Indication Characteristic (Indications) | No. (%) [95% CI] | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Trial Duration | | Comparator | | End Point | |
| | ≥2 Pivotal Trials[b] | ≥6 mo | ≥12 mo | Active | Placebo | Clinical Outcome | Clinical Scale |
| All indications (N = 201) | 127 (63.2) [56.5-69.9] | 68 (33.8) [27.2-40.4] | 17 (8.5) [4.6-12.3] | 79 (39.3) [32.5-46.1] | 119 (59.2) [52.4-66.0] | 73 (36.3) [29.6-43.0] | 39 (19.4) [13.9-24.9] |
| Therapeutic area | | | | | | | |
| Cancer (n = 41) | 8 (19.5) [6.8-32.1] | 16 (39.0) [23.4-54.6] | 2 (4.9) [0.0-11.8] | 10 (24.4) [10.7-38.1] | 15 (36.6) [21.2-52.0] | 9 (22.0) [8.7-35.2] | 0 |
| Infectious disease (n = 27) | 21 (77.8) [61.0-94.5] | 5 (18.5) [2.9-34.1] | 1 (3.7) [0.0-11.3] | 21 (77.8) [61.1-94.5] | 7 (25.9) [8.3-43.6] | 13 (48.1) [28.0-68.3] | 0 |
| Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23) | 16 (69.6) [49.2-90.0] | 12 (52.2) [30.0-74.3] | 4 (17.4) [0.0-34.2] | 13 (56.5) [34.6-78.4] | 16 (69.6) [49.2-89.9] | 8 (34.8) [13.7-55.8] | 0 |
| Neurology (n = 17) | 15 (88.2) [71.1-100.0] | 4 (23.5) [1.0-46.0] | 2 (11.8) [0.0-28.8] | 5 (29.4) [5.3-53.6] | 15 (88.2) [71.1-100.0] | 11 (64.7) [39.4-90.0] | 7 (41.2) [15.1-67.2] |
| Dermatology (n = 15) | 11 (73.3) [48.0-98.6] | 2 (13.3) [0.0-32.8] | 0 | 3 (20.0) [0.0-42.9] | 11 (73.3) [48.0-98.7] | 8 (53.3) [24.7-81.9] | 5 (33.3) [6.3-60.3] |
| Autoimmune/ musculoskeletal (n = 13) | 11 (84.6) [61.9-100.0] | 6 (46.2) [14.8-77.5] | 1 (7.7) [0.0-24.5] | 6 (46.2) [14.8-77.5] | 11 (84.6) [61.9-100.0] | 1 (7.7) [0.0-24.5] | 10 (76.9) [50.4-100.0] |
| Psychiatry (n = 10) | 10 (100.0) [100.0-100.0] | 0 | 0 | 8 (80.0) [49.8-100.0] | 7 (70.0) [35.4-100.0] | 2 (20.0) [0.0-50.2] | 8 (80.0) [49.8-100.0] |
| Other (n = 55) | 35 (63.6) [50.5-76.8] | 23 (41.8) [28.4-55.3] | 7 (12.7) [3.6-21.8] | 13 (23.6) [12.0-35.2] | 37 (67.3) [54.5-80.0] | 21 (38.2) [24.9-51.4] | 9 (16.4) [6.3-26.5] |
| *P* value | <.001 | .01 | .36 | <.001 | <.001 | .008 | <.001 |
| Expected length of treatment | | | | | | | |
| Acute (n = 36) | | | | | | | |
| Intermediate (n = 57) | | | | | | | |
| Chronic (n = 108) | | | | | | | |
| *P* value | | | | | | | |
| Agent type | | | | | | | |
| Pharmacologic (n = 164) | | | | | | | |
| Biologic (n = 37) | [29.1-62.8] | [26.5-60.0] | [0.0-13.0] | [7.7-35.5] | [58.0-88.0] | [5.7-32.2] | [26.5-60.0] |
| *P* value | .02 | .18 | .46 | .01 | .06 | .01 | <.001 |

**Drugs indicated for treatment of cancer and CV/DM/Lipids frequently approved exclusively on basis of pivotal trials using surrogate endpoints**

Source: Downing et. al., JAMA 2014;311:368-377.

# “Special” FDA Regulatory Pathways

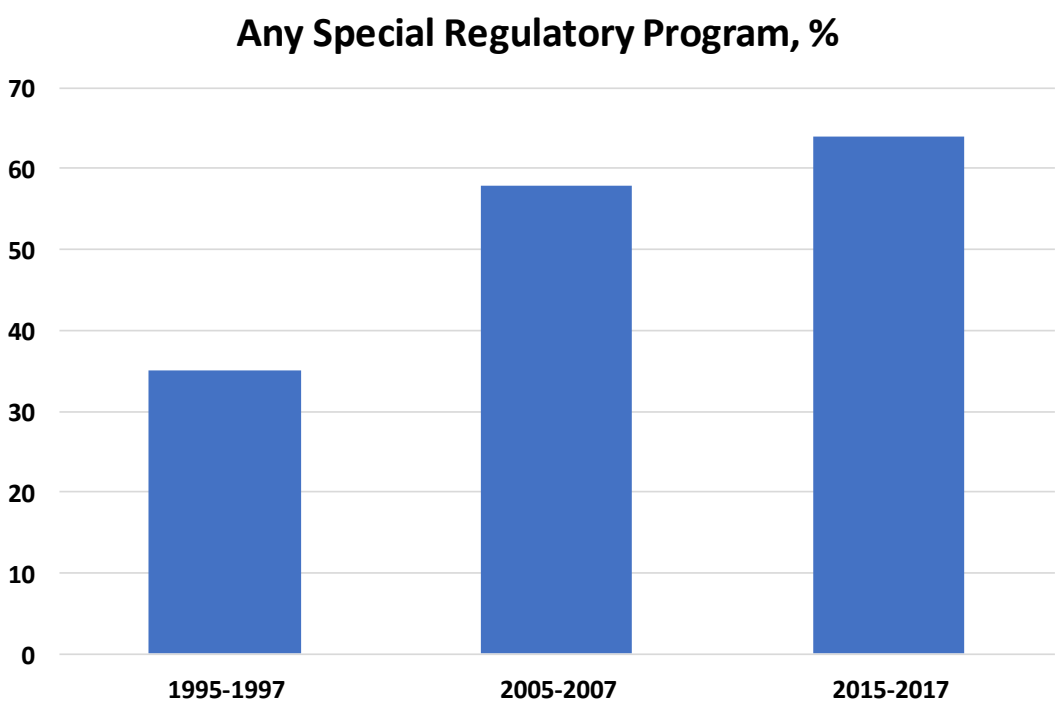
| Regulatory Pathway | Eligible Indications | Designation Period | Established | Benefits |
|---|---|---|---|---|
| Accelerated Approval | Serious conditions with an unmet medical need | Clinical development | 1992 | Allows approval on basis of surrogate endpoints |
| Priority Review | Offers significant improvement over existing treatments | Regulatory submission | 1992 | More rapid regulatory review (goal of 6 months) |
| Fast Track | Serious conditions with an unmet medical need | Pre-clinical development | 1997 | More frequent interactions w/ FDA |
| Breakthrough Therapy | Serious conditions where preliminary clinical evidence demonstrates potential for real improvement over standard of care | Early clinical development | 2013 | More frequent interactions w/ FDA & guidance during development |

JAMA Network Open

Original Investigation | Health Policy

# Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017

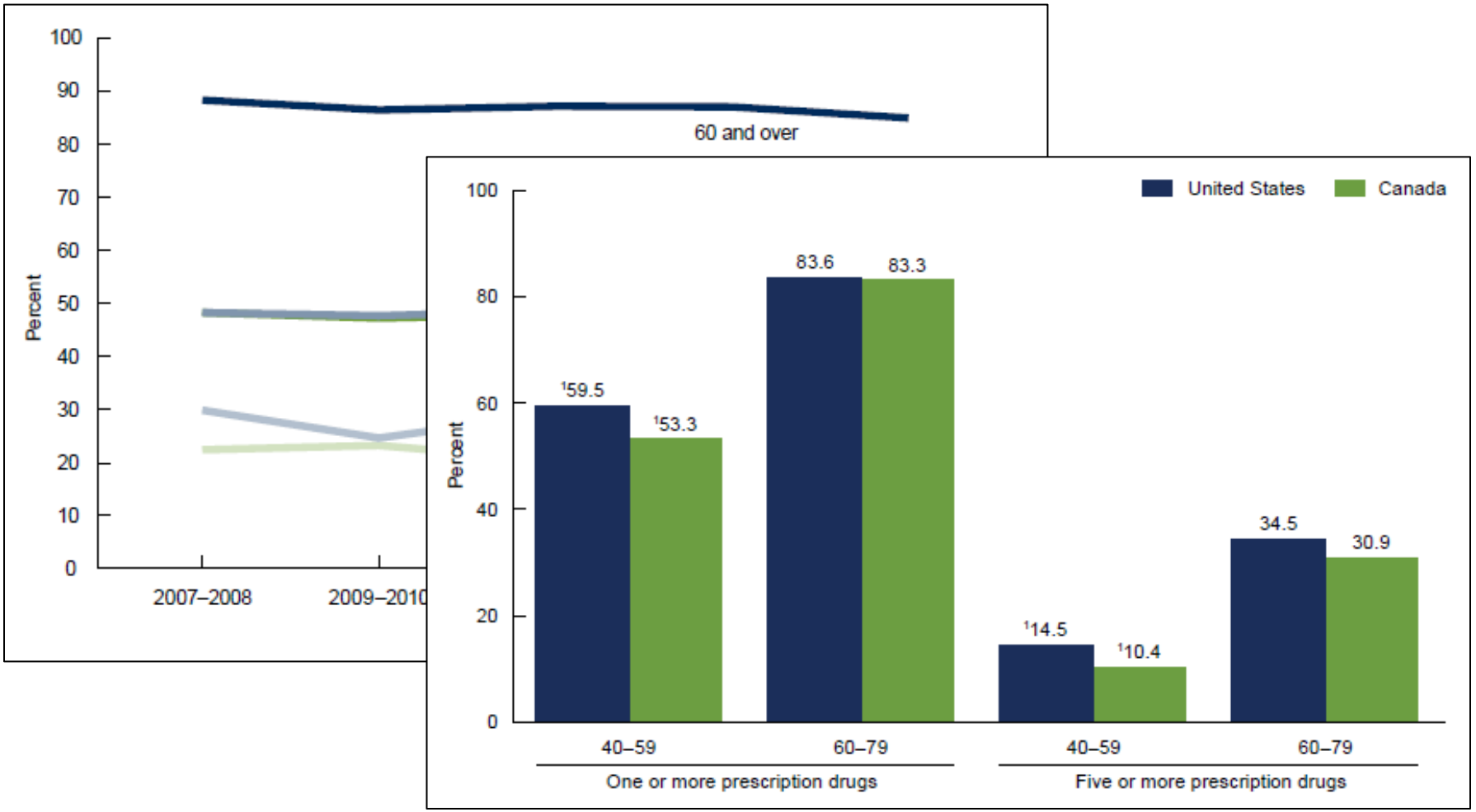
Audrey D. Zhang, AB; Jeremy Puthumana, MS; Nicholas S. Downing, MD; Nilay D. Shah, PhD; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS




- **Approvals based on a single pivotal trial increased, from 25% to 62%**
- **% that were randomized, double-blind, and used a comparator declined**
- **Study size stayed about the same, duration a bit longer**
- **% that exclusively focused on surrogate markers increased**

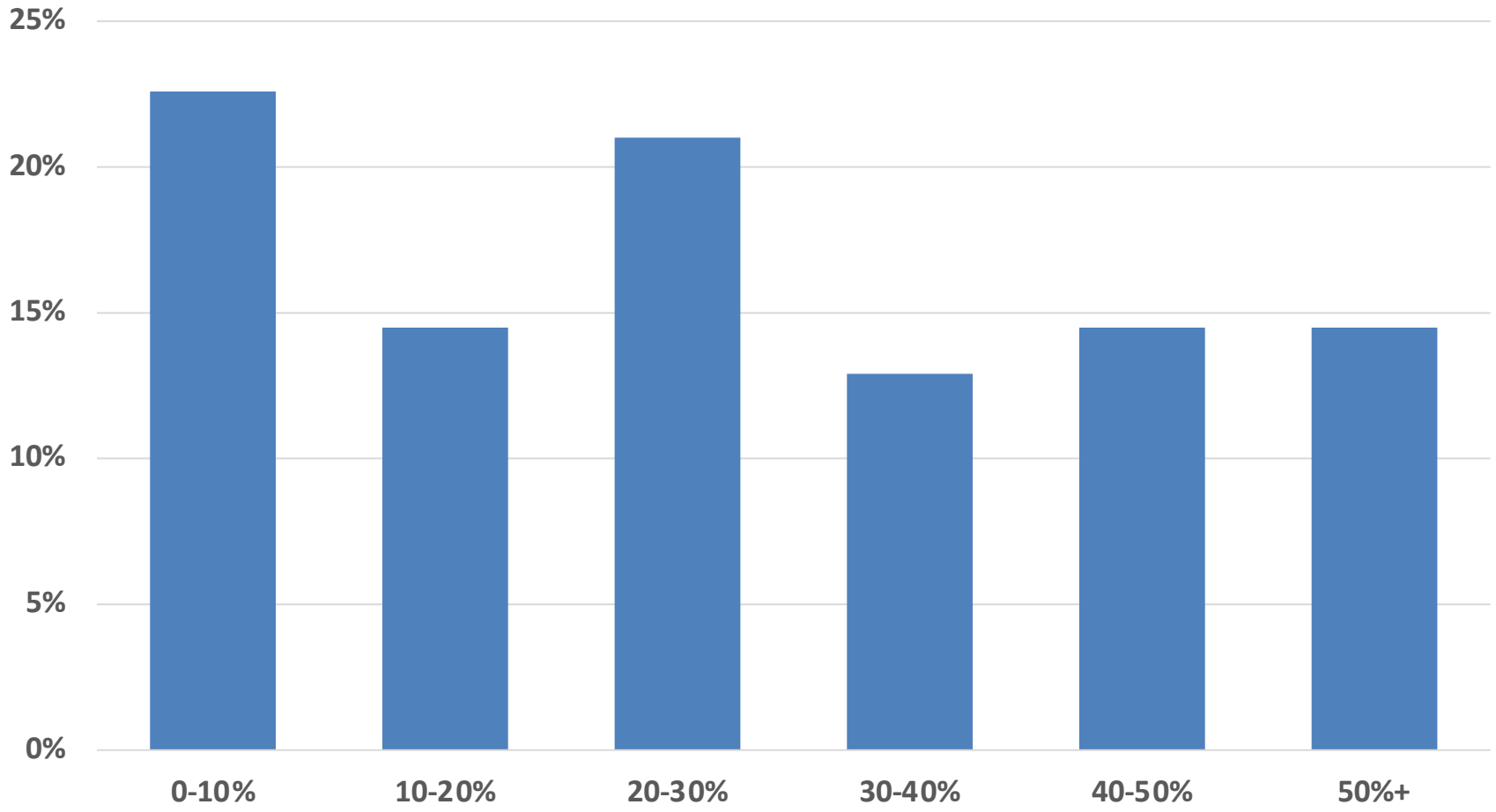
Source: Zhang et. al., JAMA Network Open 2020;3:e203284.

# Prescription Drug Use, 2007-2016




Source: CDC, NCHS Data Briefs No. 334 and 347, 2019

# Enrollment of Patients Aged 65 and Older in Pivotal Trials, 2011-2013 Approvals (n=61)*




* Age stratification only available for 61 of 92 (66.1%) approvals

Source: Downing et. al., Trials 2016;17:199.

# What do these evidentiary standards mean for patients and clinicians?

VIEWPOINT

ONLINE FIRST

# A Lifecycle Approach to the Evaluation of FDA Approval Methods and Regulatory Actions

## Opportunities Provided by a New IOM Report

Bruce M. Psaty, MD, PhD
Eric M. Meslin, PhD
Alasdair Breckenridge, MD, FRCP

VIEWPOINT

# Advances in Regulatory Science at the Food and Drug Administration

Bruce M. Psaty, MD, PhD
Steven N. Goodman, MD, MHS, PhD
Alasdair Breckenridge, MD

Source: Psaty et. al., JAMA 2012;307:2491-2492 and JAMA 2013;309:2103-2014.

# Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review

Alison M Pease,[1] Harlan M Krumholz,[2,3,4,5] Nicholas S Downing,[6] Jenerius A Aminawung,[7] Nilay D Shah,[8] Joseph S Ross[3,4,5,7]

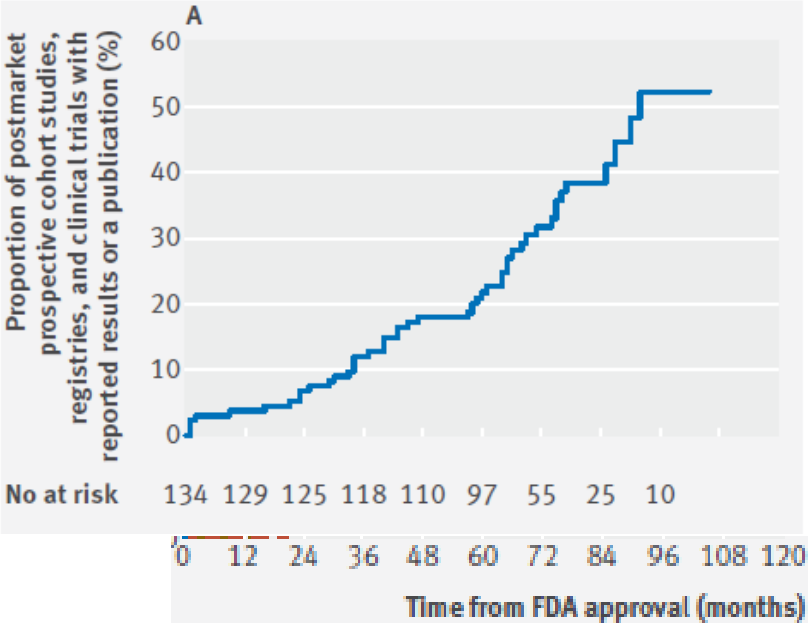
- **From 2005 to 2012, 117 novel drugs approved for 123 indications on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease, or both**
- **35% had 0 controlled trials postapproval**
- **Median no. of studies / patients enrolled**
  - **Single pivotal trials: 1 (IQR, 0-2) / 90 (IQR, 0-509)**
  - **Surrogate marker focused pivotal trials: 3 (IQR, 1-8) / 533 (IQR, 122-3633)**
- **Only 8% had ≥ 1 randomized, double-blind, controlled trial postapproval focused on clinical outcome that demonstrated superior efficacy**

Source: Pease et. al., BMJ 2017;357:j1680.

# Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross sectional analysis

Joshua D Wallach,[1,2] Alexander C Egilman,[1,2] Sanket S Dhruva,[3,4] Margaret E McCarthy,[2] Jennifer E Miller,[5] Steven Woloshin,[6] Lisa M Schwartz,[6] Joseph S Ross[1,3,7,8]

- **437 postmarketing requirements associated with 106 approvals**
- **134 (30%) were clinical studies**
- **Only 65 (49%) completed [68% late]**
- **Of these, 72% published or reported results**




Source: Wallach et. al., BMJ 2018;361:k2031.


Promote Timely Drug Approval
Assure Drug Safety & Efficacy
Encourage Innovation

Research

JAMA | Original Investigation

# Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD; Nilay D. Shah, PhD; Jenerius A. Aminawung, MD, MPH; Alison M. Pease, BS; Jean-David Zeitoun, MD, MHPM; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

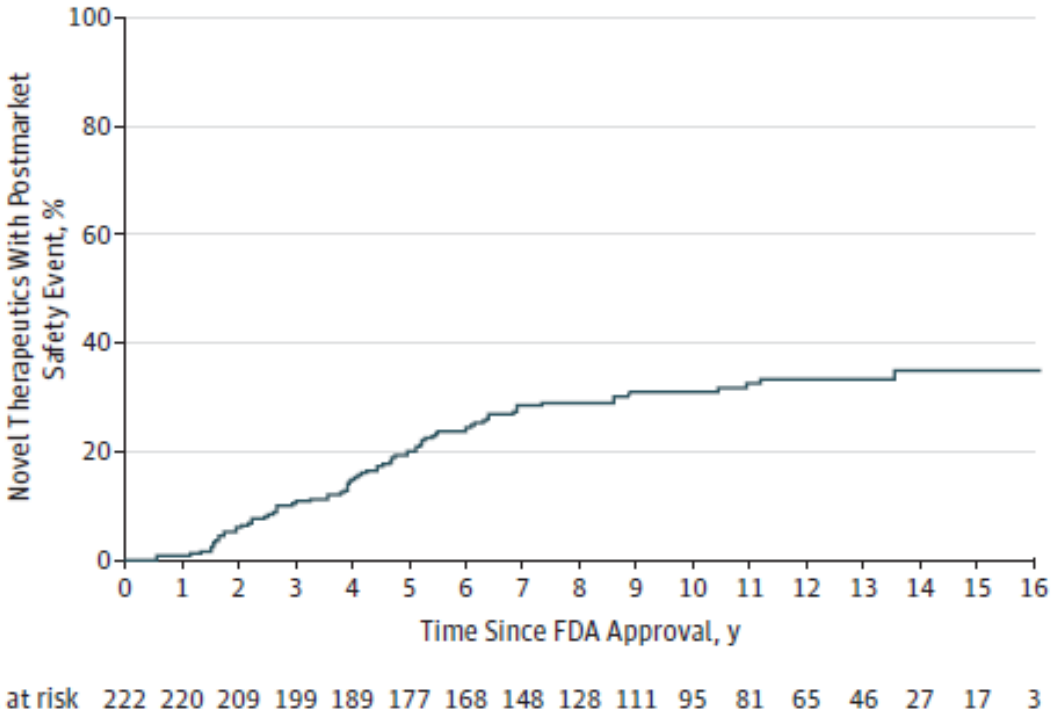
Source: Downing et. al., JAMA 2017;317:1854-1863.

# Postmarket Safety Actions

- **Withdrawals due to safety concerns**
  - **Public index of FDA's postmarket announcements**
- **FDA issuance of new black box warning**
  - **Side by side comparison of first and last label**
- **FDA issuance of safety communication**

**FDA Drug Safety Communication: FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended dose**
**Safety Announcement**
**[5-15-2014]** The U.S. Food and Drug Administration (FDA) is warning that the insomnia drug Lunesta (eszopiclone) can cause next-day impairment of driving and other activities that require alertness. As a result, we have decreased the recommended starting dose of Lunesta to 1 mg at bedtime. Health care professionals should follow the new dosing recommendations ... Patients should continue …

Figure 2. Proportion of Novel Therapeutics Approved by the US Food and Drug Administration (FDA) From 2001 Through 2010 Affected by Any Postmarket Safety Event as of February 2017




- **Overall, 123 safety actions affecting 71 (32.0%) of the 222 novel therapeutics**
  - **3 withdrawals, 61 boxed warnings, 59 letters**
- **Median time from approval to 1st action: 4.2 years (IQR, 2.5 – 6.0 years)**

Source: Downing et. al., JAMA 2017;317:1854-1863.


STANTIS
FDA APPROVED DRUG
WARNING: CONTAINS FDA APPROVED DRUG

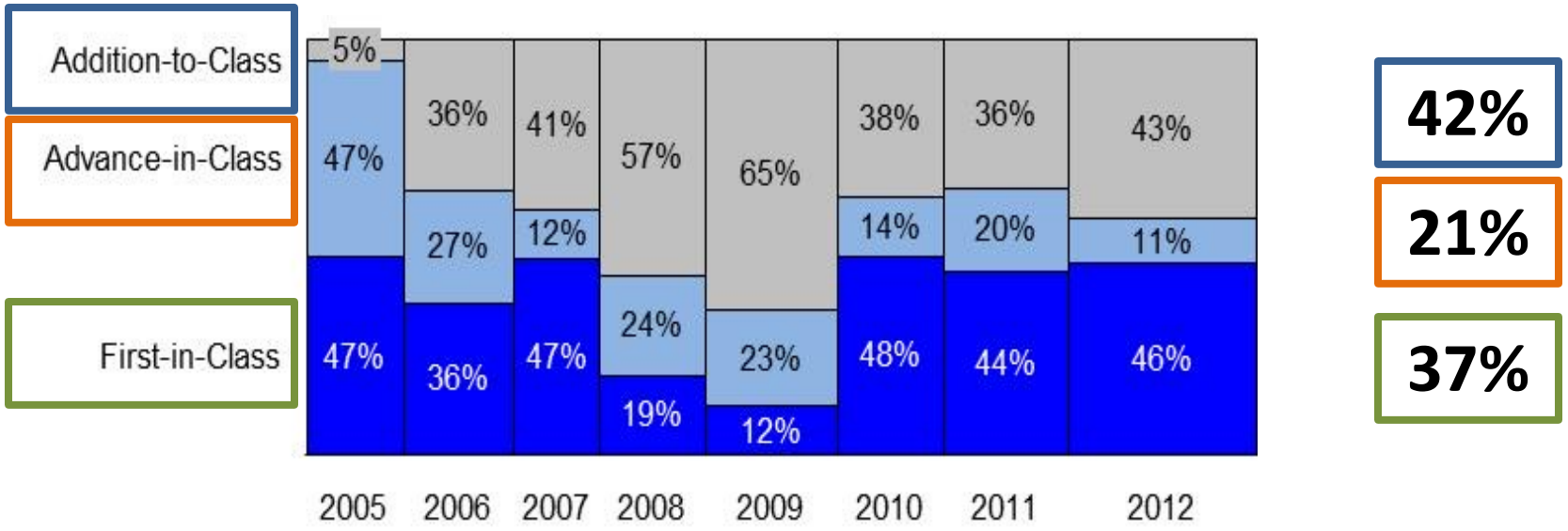

Promote Timely Drug Approval
Assure Drug Safety & Efficacy
Encourage Innovation

REGULATORY WATCH

# Characterizing the US FDA's approach to promoting transformative innovation


*"The F.D.A. is nuts about it."*

# Novelty of Approved Therapeutics

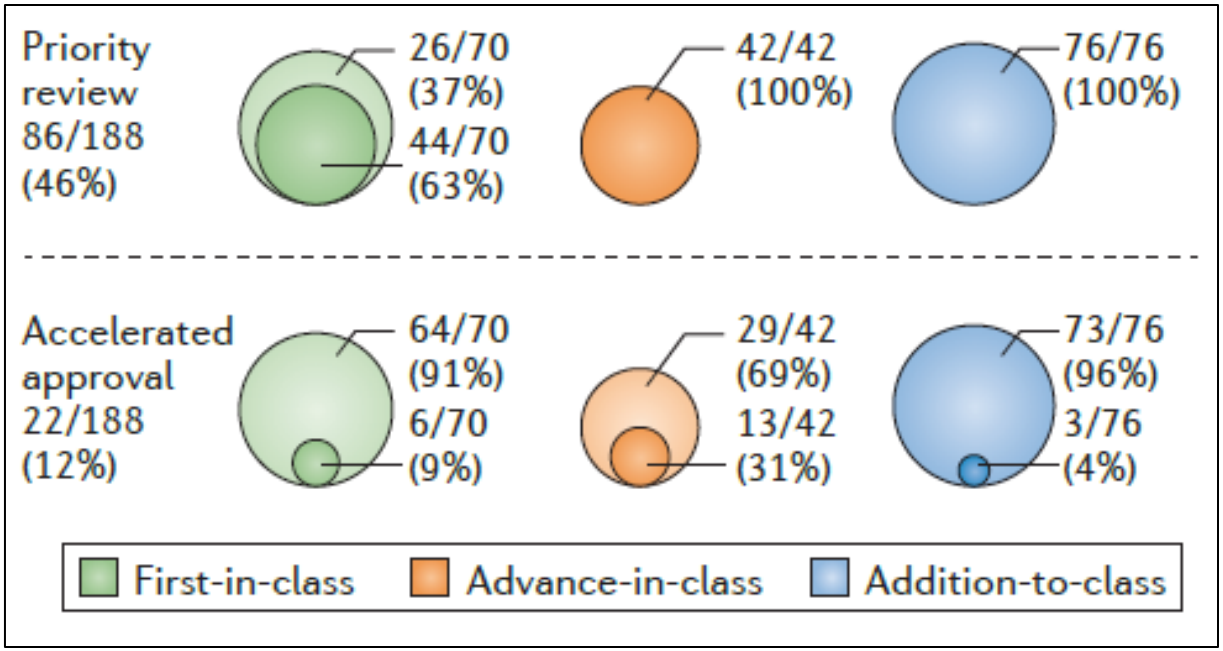



**First-in-Class: Novel mechanism for treating a medical condition**

**Advance-in-Class: Not mechanistically novel, but provides important clinical benefit over existing therapies**

**Addition-to-Class: Neither mechanistically novel nor clinically superior**

Methods Source: Lanthier et. al., Health Affairs 2013;32:1433-1439.




| | 2007 – 2016 New Drug Approvals by FDA | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Priority Review** | | **Accelerated Approval** | | **Fast Track** | | **Breakthrough Designation** | |
| | **YES** | **NO** | **YES** | **NO** | **YES** | **NO** | **YES** | **NO** |
| **"High" Rating** | **49%** | **13%** | **50%** | **28%** | **56%** | **20%** | **65%** | **27%** |
| | < 0.001 | | 0.02 | | < 0.001 | | < 0.001 | |

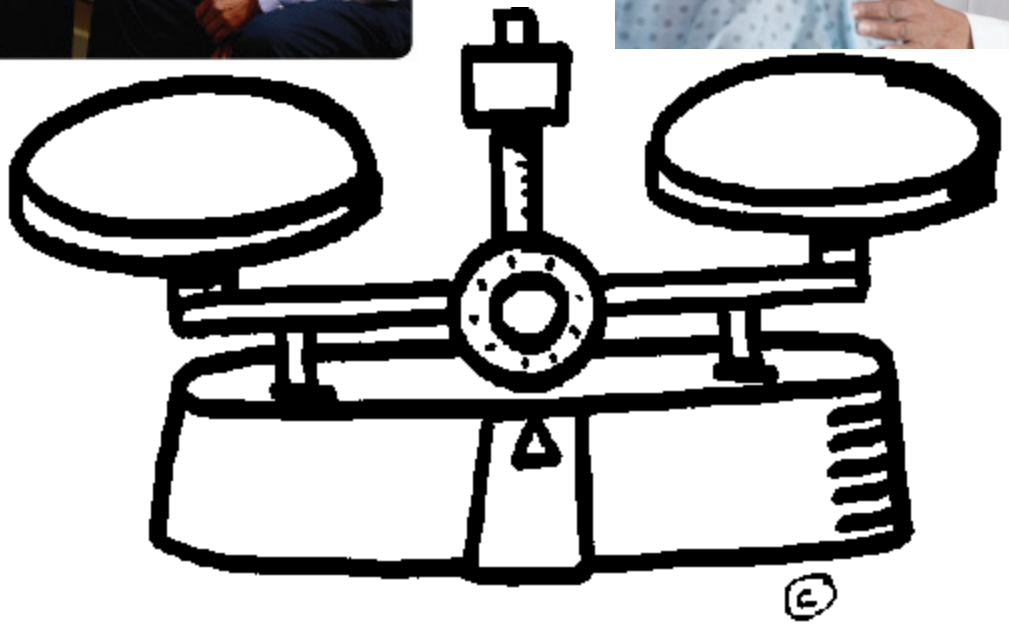
Source: Downing et. al., Nature Reviews Drug Discovery 2015;14:740-741. Hwang et. al., BMJ 2020;371:m3434.


Promote Timely Drug Approval
Assure Drug Safety & Efficacy
Encourage Innovation


- **FDA plays a key role in assuring drug safety, efficacy**
- **By several measures, FDA successfully promoting timely drug approval and is in some ways successfully encouraging innovation**
- **Consequences for public health and safety deserve careful scrutiny**
  - **Post-market withdrawals, safety communications**

- **Flexible approval standards have clear consequences for clinical evidence available at drug approval**
  - **Life-cycle approach needed for efficacy & safety**
- **Information needs to be conveyed to patients and physicians to inform decision making**

# Benefit vs. Risk
# Certainty vs. Uncertainty
# (Need to Communicate with Patients)



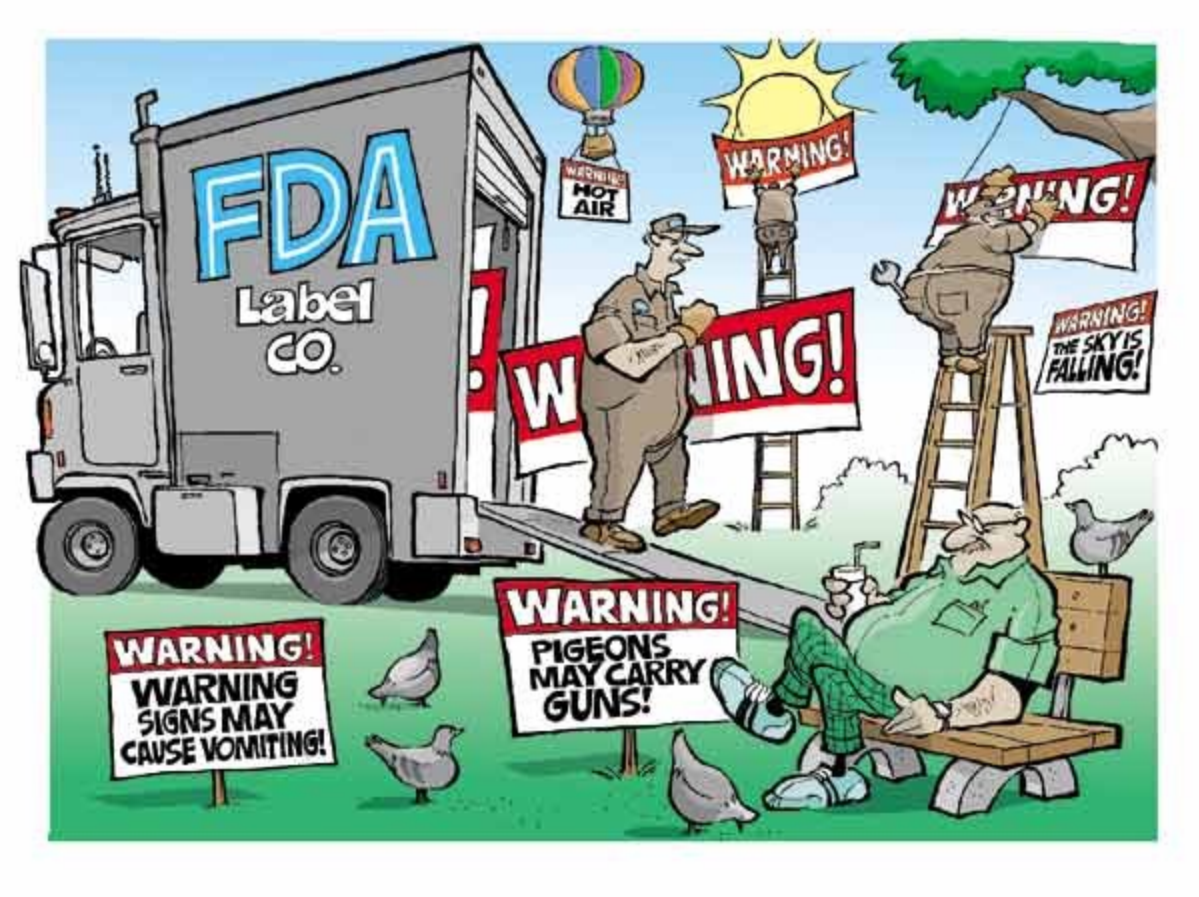
COMMENTARY

# Newly Approved Does Not Always Mean New and Improved

Geoffrey M. Anderson, MD, PhD
David Juurlink, MD, PhD
Allan S. Detsky, MD, PhD

Source: Anderson et. al., JAMA 2008;299:1598-1599.

# Questions?




@jsross119