Through the FDA Looking Glass, And What Can Be Found There

Johns Hopkins Bloomberg School of Public Health CDSE Seminar
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Center for Outcomes Research and Evaluation, Yale-New Haven Hospital
Potential Conflicts of Interest

• Research grant funding through Yale from:
  – FDA: Center of Excellence in Regulatory Science
  – FDA and Medtronic: post-market surveillance
  – Blue Cross Blue Shield Association: medical technology evidence generation
  – Johnson & Johnson: clinical trial data sharing
  – CMS: performance measure development
  – Laura & John Arnold Foundation: CRIT
As clinicians and investigators, most of our focus is on use of medications, and their safety and effectiveness, once available on the market; as opposed to the FDA’s role in this process.
1862 – President Lincoln appointed a chemist, Charles M. Wetherill, to serve in the new Department of Agriculture – beginning the Bureau of Chemistry, which became the FDA. Efforts focused on monitoring for toxic chemical adulteration of food and agriculture, such as alum, clay used to cut wheat.
1938 – Passage of the Food, Drug and Cosmetic Act, spurred by scandals, ‘muck-racking’ journalists. Required pre-market safety proof for drugs, quality and identity standards for foods, prohibition of false therapeutic claims for drugs, coverage of cosmetics and medical devices, and clarification of the FDA's right to conduct factory inspections and control of product advertising.
1960s – Passage of the Kefauver-Harris Drug Amendments in wake of thalidomide tragedy in Europe. Required pre-market efficacy proof for drugs. Afterwards, FDA contracted with National Academy of Science to evaluate effectiveness of drugs approved on basis of safety alone from 1938 to 1962.
1988 – Passage of the Food and Drug Administration Act, officially establishing FDA as an agency of the Department of Health and Human Services with a Commissioner appointed by the President and with the advice and consent of the Senate. Responsibilities span research, enforcement, education, and information generation.
Many Roles & Broad Responsibilities

• 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
- ~$4,500,000,000 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
We’ve heard that laughter is the best medicine, so beginning Monday we’ll be regulating it.
FDA PROCESS FOR APPROVING NEW DRUGS...
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 consumers, industry, and FDA - drug approvals taking too long
- Companies wanted to recoup R&D costs; every delay of 1 month cost $10 million
- 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
NOW NO ONE IS SAFE FROM AIDS

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 the approval of new drugs charged fees (~$2M) to supplement, but not replace, direct appropriations from Congress.

Prescription Drug User Fee Act

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PDUFA: Review Times 27→14 months

FY 2015 ~2,500 actions
• Priority NDA/BLA (92%)
• Standard NDA/BLA (100%)
• Class 1 resubs (100%)
• Class 2 resubs (97%)
• NDA/BLA manufacturing supp rq approval (93%)
• NDA/BLA manufacturing supp not rq approval (96%)

Met 11 of 12 Goals
• Priority NME/BLA (100%)
• Standard NME/BLA (95%)
• Priority efficacy supp (94%)
• Standard efficacy supp (95%)
• Class 1 resub efficacy supp (n/a)
• Class 2 resub efficacy supp (64%)
<table>
<thead>
<tr>
<th>Event</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety-based withdrawal</td>
<td>1.28</td>
<td>5.48</td>
</tr>
<tr>
<td>Black-box warning</td>
<td>1.19</td>
<td>4.44</td>
</tr>
<tr>
<td>Withdrawal or black-box warning</td>
<td>1.56</td>
<td>4.42</td>
</tr>
<tr>
<td>At least one dosage-form discontinuation</td>
<td>1.46</td>
<td>7.53</td>
</tr>
</tbody>
</table>

**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 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.
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.
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Agency Approvals, 2001-2010

- FDA (n=225)
- EMA (n=186)
- Health Canada (n=99)

FDA: 80
EMA: 53
ALL: 72
FDA+Canada: 16
EMA+Canada: 4
FDA+EMA: 57
Canada: 7

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

<table>
<thead>
<tr>
<th>Approved by all 3 agencies (n=72)</th>
<th>FIRST REVIEW TIME</th>
<th></th>
<th>TOTAL REVIEW TIME</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>P value</td>
<td>Median</td>
</tr>
<tr>
<td>FDA</td>
<td>254</td>
<td>182-307</td>
<td>0.001</td>
<td>268</td>
</tr>
<tr>
<td>EMA</td>
<td>356</td>
<td>302-410</td>
<td></td>
<td>356</td>
</tr>
<tr>
<td>Health Canada</td>
<td>346</td>
<td>228-424</td>
<td></td>
<td>266</td>
</tr>
</tbody>
</table>

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.
Promote Timely Drug Approval

Assure Drug Safety & Efficacy

Encourage Innovation
10 x 40,000 Units/mL Single Use Vials

EPOGEN®
EPOETIN ALFA
recombinant

40,000 Units/mL

Single Use Vials (containing 1 mL)
For Intravenous or Subcutaneous Use Only
Sterile Solution - No Preservative
Store at 2° to 8°C (36° to 46°F). Do Not Freeze or Shake.

Manufactured by Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A.
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Rx Only
Assure Drug Safety and Efficacy

• At approval, must balance innovation and regulatory requirements
  – Speed versus safety
  – Tight pre- versus loose post-approval regulation
  – Active versus passive data collection
• Focus on clinical efficacy data

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".
Communicating Uncertainties About Prescription Drugs to the Public

- 39% believe FDA only approves “extremely effective” drugs, 25% believe FDA only approves drugs without serious side effects

U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey†

- Physicians aware of 55% FDA-approved indications and believe FDA-approval implies stronger supporting efficacy evidence

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

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

<table>
<thead>
<tr>
<th>Trial Design Features</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, %</td>
<td>89%</td>
</tr>
<tr>
<td>Double-blinded, %</td>
<td>80%</td>
</tr>
<tr>
<td>Comparator, %</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>32%</td>
</tr>
<tr>
<td>Placebo</td>
<td>55%</td>
</tr>
<tr>
<td>None</td>
<td>13%</td>
</tr>
<tr>
<td>End Point, %</td>
<td></td>
</tr>
<tr>
<td>Surrogate Outcome</td>
<td>49%</td>
</tr>
<tr>
<td>Clinical Outcome or Scale</td>
<td>51%</td>
</tr>
<tr>
<td>Overall Patients, Median (IQR)</td>
<td>446 (205-678)</td>
</tr>
<tr>
<td>Intervention Patients, Median (IQR)</td>
<td>271 (133-426)</td>
</tr>
<tr>
<td>Duration, Median (IQR)</td>
<td>14.0 (6.0-26.0)</td>
</tr>
</tbody>
</table>

Source: Downing et. al., JAMA 2014;311:368-377.
Aggregated Trials by Indication (n=201)

<table>
<thead>
<tr>
<th>Agent/Indication Characteristic (Indications)</th>
<th>Pivotal Efficacy Trials</th>
<th>Patients in Aggregated Pivotal Efficacy Trials</th>
<th>Total Safety Populationb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR), No.</td>
<td>Overall</td>
<td>Intervention Group</td>
</tr>
<tr>
<td>All indications (N = 201)</td>
<td>2.0 (1.0-2.5)</td>
<td>760 (270-1550)</td>
<td>445 (169-936)</td>
</tr>
<tr>
<td>Therapeutic area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer (n = 41)</td>
<td>1.0 (1.0-1.0)</td>
<td>397 (180-634)</td>
<td>277 (159-414)</td>
</tr>
<tr>
<td>Infectious disease (n = 27)</td>
<td>2.0 (2.0-2.0)</td>
<td>1171 (763-1408)</td>
<td>605 (462-817)</td>
</tr>
<tr>
<td>Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 23)</td>
<td>3.0 (1.0-5.0)</td>
<td>3645 (1446-5942)</td>
<td>2291 (832-3947)</td>
</tr>
<tr>
<td>Neurology (n = 17)</td>
<td>2.0 (2.0-3.0)</td>
<td>1088 (448-1394)</td>
<td>661 (279-877)</td>
</tr>
<tr>
<td>Dermatology (n = 15)</td>
<td>2.0 (1.0-2.0)</td>
<td>374 (233-1005)</td>
<td>187 (127-376)</td>
</tr>
<tr>
<td>Autoimmune/musculoskeletal (n = 13)</td>
<td>2.0 (2.0-3.0)</td>
<td>1209 (289-2893)</td>
<td>804 (223-1906)</td>
</tr>
<tr>
<td>Psychiatry (n = 10)</td>
<td>4.0 (2.0-5.5)</td>
<td>1492 (947-3000)</td>
<td>878 (417-1812)</td>
</tr>
<tr>
<td>Other (n = 55)</td>
<td>2.0 (1.0-2.0)</td>
<td>418 (105-1608)</td>
<td>238 (78-968)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Expected length of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (n = 36)</td>
<td>2.0 (2.0-2.0)</td>
<td>586 (305-1194)</td>
<td>349 (155-613)</td>
</tr>
<tr>
<td>Intermediate (n = 57)</td>
<td>1.0 (1.0-2.0)</td>
<td>435 (192-787)</td>
<td>290 (159-507)</td>
</tr>
<tr>
<td>Chronic (n = 108)</td>
<td>2.0 (1.0-3.0)</td>
<td>1203 (361-2062)</td>
<td>694 (234-1407)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Agent type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacologic (n = 164)</td>
<td>2.0 (1.0-3.0)</td>
<td>825 (322-1607)</td>
<td>503 (209-956)</td>
</tr>
<tr>
<td>Biologic (n = 37)</td>
<td>1.0 (1.0-2.0)</td>
<td>374 (105-1213)</td>
<td>229 (70-683)</td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.009</td>
<td>.003</td>
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Source: Downing et. al., JAMA 2014;311:368-377.
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<tr>
<td>P value</td>
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Source: Downing et. al., JAMA 2014;311:368-377.

~37% approved on basis of a single pivotal trial
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.
~33% approved on basis of at least one pivotal trial of 6 months or longer

Source: Downing et. al., JAMA 2014;311:368-377.
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
~39% approved on basis of at least one pivotal trial using an active comparator.
~45% approved exclusively on basis of pivotal trials using surrogate endpoints
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.
Summary of Findings

• Quality of clinical trial evidence varied widely across new drug indications

• Clear limitations for purpose of demonstrating safety (many small, short duration)

• Questionable whether trials provide “substantial evidence” to support claims of efficacy
  – Most randomized, double-blinded, used placebo or active comparator
  – But, one-third not replicated, few lasted a year or longer, half focused on surrogates, fewer than half used active comparator
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
Promote Timely Drug Approval

Assure Drug Safety & Efficacy

Encourage Innovation
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 …
Overall, 123 safety actions affecting 71 (32.0%) of the 222 novel therapeutics
At 10 years, 30.8% (95% CI, 25.1% – 37.5%) had 1 or more safety action
Median time from approval to 1\textsuperscript{st} action: 4.2 years (IQR, 2.5 – 6.0 years)

Source: Downing et. al., JAMA 2017;317:1854-1863.
Promote Timely Drug Approval

Assure Drug Safety & Efficacy

Encourage Innovation
Characterizing the US FDA's approach to promoting transformative innovation

"The F.D.A. is nuts about it."
Novelty of Approved Therapeutics

Methods Source: Lanthier et. al., Health Affairs 2013;32:1433-1439.
## “Special” FDA Approval Pathways

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

Encourage Innovation

Assure Drug Safety & Efficacy
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)
Newly Approved Does Not Always Mean New and Improved

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