The FDA misleads patients, physicians, and Congress – a trio of shorts (attached)

1. **"The FDA's New Clothes"** (*BMJ* Sept 23, 2015). Ragged, torn, and missing evidence that new drugs are "safe and effective." A jacket with a missing sleeve, torn pocket, frayed edges, made of cheap cloth (for which a fortune has been paid).

    a. Accelerated approvals put the seriously ill at even greater risk than full reviews, with less evidence of benefit but at huge cost.

    b. Supplemental approvals made on thin evidence and put children especially at risk.

    c. Based on two new studies from Harvard.

2. **"Why do Cancer drugs get such an easy ride?"** (*BMJ* Apr 23, 2015) Why does the FDA approve most cancer drugs using trials they agree to that are unscientific and biased by design? No one can tell from these faster, cheaper trials whether the drugs have clinical advantages. When they do, they are usually small, while risks of serious side effects are high.

3. **"Serious Risks and Few New Benefits from FDA-Approved Drugs"** (*Health Affairs Blog* July 6, 2015). The FDA encourages companies to devote most research to developing scores of new drugs that are clinically minor but with substantial risks of hospitalization or death that testing hides.

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EDITORIALS

The FDA's new clothes

The FDA does not protect patients from harmful or ineffective drugs, but approves both

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The Vioxx disaster in the early 2000s triggered a crisis of mistrust in the US Food and Drug Administration (FDA), as evidence emerged that it had downplayed or ignored evidence of serious cardiovascular harm associated with Vioxx (rofecoxib), a cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drug.

The result was a renewed emphasis on drug safety throughout a product's lifecycle. At the same time, drug companies, which provide most of the funds for the FDA's review of their drugs, kept pushing for faster approvals and new uses for old drugs, supposedly so that more patients could benefit. Any possible risks in getting new drugs to market more quickly would be offset by more intensive monitoring once they were being prescribed.

Two linked papers (doi:10.1136/bmj.h4633, 10.1136/bmj.h4679) provide valuable accounts of how the FDA is using faster reviews for what it deems to be important new drugs and using supplemental approvals for existing drugs more widely.[1 2] This is just what patients and their doctors are said to want—more patients benefiting from taking more new drugs sooner, generating revenue for the companies to fund more breakthrough research.

Put in the context of the FDA's larger record, however, these studies give cause for concern about whether most new drugs are any more effective than existing products or whether their safety has been adequately assessed. The term "safe and effective" misleads patients and prescribers. Although the US Congress and the FDA require "substantial evidence of effectiveness" to approve new drugs, they require no evidence of substantial effectiveness.[3] Companies provide substantial evidence of effectiveness through trials that in most cases prove only that the product being tested has a non-zero level of effectiveness. The result is that independent reviews find that 85-90% of new drugs provide few or no advantages for patients.[4] The FDA's flexible criteria and low threshold for approval do not reward more research for breakthroughs but instead reward more research for minor variations that can clear this low threshold.

The growing number and widening application of expedited review programs are accompanied by evidence that many of the clinical trials accepted by an industry compliant FDA have features that contribute to biased results and compromised science (see box).[5 6] As a consequence, these trials are incapable of providing patients or doctors with valid information on what new clinical benefits a drug provides. The result is an ever larger number of drugs approved on the basis of weaker evidence and in shorter time periods. We documented this for cancer drugs,[5] and a much more comprehensive review comes to similar conclusions across many areas of medicine overseen by the FDA.[6] Yet both of the linked studies point out that Congress is poised to advocate for still more accelerated reviews based on even less evidence.

Do patients and doctors really want medicines for cancer and other life threatening conditions approved this way—quickly, with marginal evidence of real benefit? Do they know that faster reviews are associated with a significant increase in serious safety problems[7] and the risk of patients being admitted to hospital with or dying from adverse reactions?[8] Canadian data show that faster review increases the chances of harm serious enough to warrant a severe warning or market withdrawal from one in five to one in three.[9]

In most drug research, harm is called "safety" or "safety events," a fig leaf of pharmaceutical English covering up the real thing. The "risk-benefit ratio" can also obscure the real chance of serious harm. When the possibility of benefit declines, the chance of being harmed stays the same, so the ratio of harms to benefits increases.[10] Prescription drugs are the fourth leading cause of death in the United States and the third leading cause in Europe, according to one authority.[11 12]

These twin studies are part of a series drawing on impressive datasets assembled under Kesselheim's direction at Harvard University. However, these data are hard to abstract and collate and require searches through multiple FDA databases, along with Freedom of Information Act requests. Wang and Kesselheim could not locate the FDA medical reviews containing the clinical evidence for the basis of approval for 80% of the supplemental applications. Just one medical review was available among the 66 approvals in 2013-14. Only slightly

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Some features of trials that make drugs look safer and more effective than they are

Random samples from biased populations that exclude people more likely to have adverse reactions or less likely to generate positive outcomes; prescribing to patients in actual clinical practice often produces weaker, less consistent outcomes and more adverse reactions
Non-randomized trials in unrepresentative populations
Benefits often measured with surrogate endpoints rather than real clinical outcomes that matter to patients
Trials primarily designed to measure benefits, not harms
Trials lacking a comparator or control arm (single arm)
Trials not blinded or easily unblinded
High doses used to generate evidence of benefit for the drug under evaluation
Trials too short to pick up adverse reactions to high doses but long enough to pick up the benefits
Poor measurement and reporting of the number needed to treat and number needed to harm
Trials stopped early because results look beneficial at that point in time; this prevents full evaluation and reporting of harms and benefits

more than 30% of supplemental approvals were supported by trials against active comparators, and more than 70% of approvals were based on trials using surrogate endpoints. Effectively, the FDA has been granting most supplemental approvals without evidence of meaningful clinical benefit.

FDA data on drug withdrawals are equally lacking. A recent review of safety warnings finally concludes that, "Remarkably, no comprehensive source of information on black-box warnings and withdrawals is available."[13]

The United States and other countries need an alternative paradigm—one in which research focuses on better medicines for patients rather than for profits, where clinical trials with low risk of bias look for real benefits and faithfully report harms. Such a paradigm of ethical, open, not for profit research already exists at research institutes such as the Mario Negri Institute for Pharmacological Research.[14] Although this institute accepts funding from drug companies, it operates under rules and practices for keeping drug research independent, transparent, and accountable. The institute's leaders have long advocated for publicly funded regulators whose deliberations are transparent and accountable. With so much misdirected investment, biased science, and harm resulting from industry directed research, with little offsetting benefit, perhaps it is time to consider the Mario Negri public health model for developing better medicines for patients.

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EDITORIALS

Why do cancer drugs get such an easy ride?

Rushed approvals result in a poor deal for both patients and cancer research

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Unlike most other diseases, cancer instils a special fear and "is treated as an evil, invincible predator, not just a disease."[1] The ability of drug companies to charge very high prices, even when most approved cancer drugs provide little gain for patients, drives much of the research, as desperate patients lead some governments and private insurers to pay whatever companies charge. Officials within the US Food and Drug Administration are enthusiastic about new cancer drugs. Richard Pazdur, who oversees oncology activities for the FDA says that new cancer drugs are so effective that "We don't have a lot of questions on [these] drugs because they're slam dunks. It's not if we're going to approve them. It's how fast we're going to approve them."[2]

The methodological weaknesses in oncology trials do not support such enthusiasm. Researchers compared 8942 oncology clinical trials conducted between 2007 and 2010 with trials for other diseases.[3] Trials for cancer drugs were 2.8 times more likely not to be randomised, 2.6 times more likely not to use a comparator (single arm), and 1.8 times more likely not to be blinded. Each undermines the validity of outcomes but reflects what regulators will allow.

Less valid trials reflect an easy ride from regulators for drugs that usually offer few significant benefits for patients. A review of drugs for solid cancers approved by the European Medicines Agency (EMA) in its first 10 years found that, overall, new oncology drugs improved survival by a mean and median of 1.5 and 1.2 months, respectively.[4] The 71 drugs approved by the FDA from 2002 to 2014 for solid tumours have resulted in median gains in progression-free and overall survival of only 2.5 and 2.1 months, respectively.[5] Further, only 42% met criteria set by the American Society of Clinical Oncology Cancer Research Committee for meaningful results for patients.[6]

Accelerated approval and surrogate outcomes

A second easy ride comes from regulators creating more ways to shorten review times.[7] In Europe between 1999 and 2009, oncology drugs were the class that was most likely to be approved through an accelerated pathway.[8] Priority approval shortens the FDA review time from the standard 300 days to 180 days, but the two processes are supposed to be equivalent. In practice, postmarketing label changes are substantially more common for oncology drugs approved by priority review than for those subject to standard reviews, suggesting possible deficiencies in the priority review evaluation.[9] Cancer drugs approved using early stage evidence had "a 72% greater odds of serious adverse events occurring in their pivotal trials than did cancer drugs that were approved with more rigorous studies."[7] Once drugs are available, even if they subsequently prove to be ineffective, withdrawing them can be a lengthy process and generates substantial opposition, as the case of bevacizumab for metastatic breast cancer demonstrates.[7]

A third easy ride comes from European and US regulators allowing companies to test cancer drugs using surrogate measures instead of survival and other patient centred measures. The three most commonly used surrogate endpoints all use radiological measurement of tumour size as evidence of benefit, even though the exact date of tumour progression can never be precisely known from these measurements.[10]

Surrogate endpoints are highly variable in their ability to predict overall survival.[11-13] A review by the German Institute for Quality and Efficiency in Health Care concluded that the validity of tumour response measures as surrogates for patient relevant endpoints in colon and breast cancer remains unclear.[14] Despite these limitations drug companies are eager to use surrogate endpoints because the trials require fewer patients and can be completed faster and more cheaply than trials that test for survival. The FDA and EMA find them acceptable and base most of their approvals on them. The FDA used surrogate endpoints to approve 68% (39/57) of oncology drugs processed through the standard approval pathway and for all 14 applications granted accelerated approval from January 1990 to November 2002.[15] In Europe, from January 1995 to December 2004, most cancer medicines were approved on the basis of surrogate endpoints such as "tumour shrinkage [that] did not translate most of the time into significant survival benefit."[4]

In 2013, over 100 oncologists protested against the high prices charged for cancer drugs, when 11 out of 12 approved in 2012 provided only small benefits to patients.[16 17] The easy ride syndrome and lowering the efficacy bar encourage "the pursuit of marginal outcomes and a me-too mentality evidenced by the

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duplication of effort and redundant pharmaceutical pipelines."[5 18] Beyond cancer drugs, low bars for approval are why 90% of new drugs that companies develop are judged to add few or no clinical advantages over existing ones and yet have substantial risks of serious adverse events.[19 20] Easy ride regulators serve both patients and research badly.

A few changes could greatly improve the quality of cancer drugs and research. Leaders of Italy's Mario Negri Institute have long advocated a coherent model for the development, regulation, and use of better medicines.[21] They see no reason why regulators cannot insist on randomisation, improved overall survival, and phase III trials since good results in phase II are often not persuasive.[4] Patients and their doctors need to insist that regulators, established to protect the public, should require clear evidence that new drugs are clinically effective, based whenever possible on trials that compare them to current effective therapy using designs that are methodologically rigorous.

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- Health Affairs Blog - http://healthaffairs.org/blog -

Serious Risks And Few New Benefits From FDA-Approved Drugs

Posted By Donald W. Light On July 6, 2015 @ 12:24 pm In Costs and Spending,Drugs and Medical Technology,Equity and Disparities,Health Policy Lab,Public Health | 3 Comments

Over the past year, the U.S. Senate and *The New York Times* have been investigating the failure of the nation's auto safety regulators to protect citizens from cars with occasionally dangerous faulty devices.

But neither august institution has paid attention to the Food and Drug Administration's (FDA) failure to protect the 170 million Americans who take prescription drugs from adverse reactions that are killing more than 2,400 [1] people every week. Annually, prescription drugs cause over 81 million adverse reactions and result in 2.7 million hospitalizations.

This epidemic [2] of harm from medications makes our prescription drugs the fourth leading cause of death in the United States. Including hospitalizations and deaths from prescribing errors, overdosing, and self-medication, drugs move up to third place.

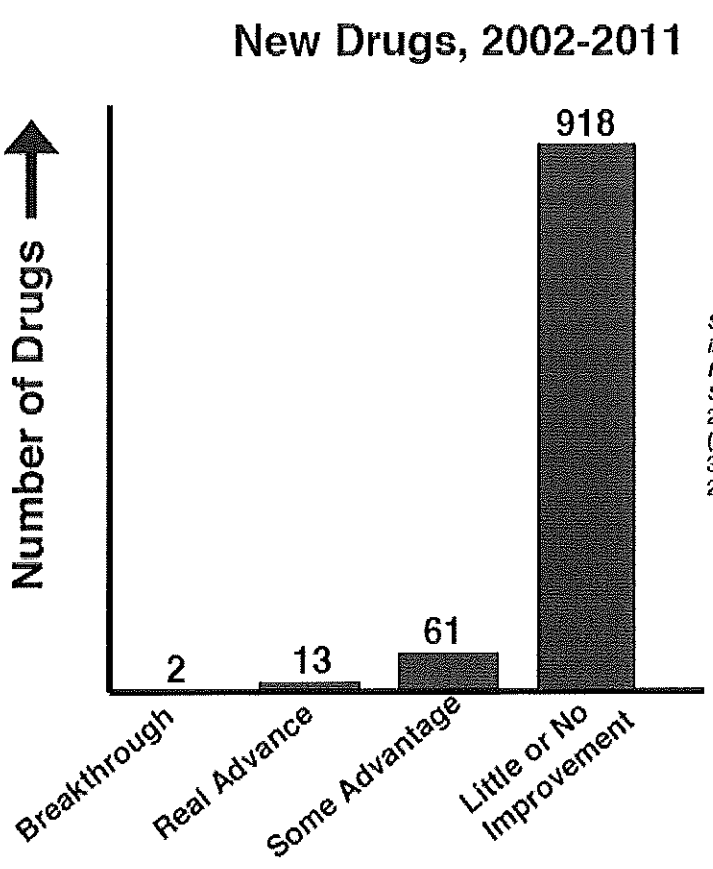
Below I describe the biases that appear throughout the drug development process, from initial research to FDA review and approval. I conclude with recommendations that would reduce drug development costs and ensure that drugs are only approved if they are safe and significantly more effective than already existing medications.

A Me-Too Business Model

Every drug has risks, so any drug considered for FDA approval should demonstrate clinical advantages that justify those risks. Yet public, independent advisory teams of physicians and pharmacists in several countries found over 90 percent of new drugs approved by the FDA and the European Medicines Agency (EMA) offer few or no advantages over existing drugs to offset their risks of serious harm.

Figure 1 shows the scorecard for 979 newly approved drugs over a 10-year span, based on detailed assessment of clinical benefits and risks by Prescrire, one of the world's most distinguished, independent review bodies of physicians and pharmacists. (The exhibit focuses on France, a country whose consumer-oriented drug market features an array of products similar to the U.S.)

Figure 1. Few Clinical Advances in a Decade and Hundreds of Other Drugs Approved for Promotion



SOURCE: New Drugs and Indications in 2011: France Is Better Focused on Patients Interests After the Mediator Scandal, But Stagnation Elsewhere, 21(126) La Revue Prescrire 106, 107 (Apr. 2012) (table) (translated from 32(340) La Revue Prescrire 134 (Feb. 2012) (in French))

[3]

Only two were breakthrough advances and fewer than 10 percent offered substantial clinical advantages over existing drugs. Yet approved drugs have a 20 percent risk of producing enough harm for regulators to add a serious warning or have them withdrawn.

Flooding the market with hundreds of minor variations on existing drugs and technically innovative but clinically inconsequential new drugs, appears to be the de facto hidden business model [4] of drug companies. In spite of its primary charge to protect the public, the FDA criteria for approval encourage that business model. The main products of pharmaceutical research are scores of clinically minor drugs that win patent protection for high prices, with only a few clinically important advances like Sovaldi or Gleevec.

This business model works. Despite producing drugs with few clinical advantages and significant health risks, industry sales and profits have grown substantially, at public expense. Companies spend 2-3 times less on research than on marketing to convince physicians to prescribe these minor variations.

Industry figures show the public pays companies about six times R&D costs through high prices on drugs. According to a study by Consumer Reports [5], high costs to patients lead them to postpone visits to physicians, avoid medical tests, and be able unable to afford other, effective drugs. For society as a whole, a leading health economist [6] found that 80 percent of all new expenditures for drugs was spent on the minor variations, not the major advances.

Institutional Corruption

These startling results reflect studies from the Edmond J. Safra Center for Ethics at Harvard University, where research fellows have investigated [7] "institutional corruption" in the

pharmaceutical industry. "Institutional corruption" refers to systemic, legal ways that social institutions such as medical science, the medical profession, and the FDA become compromised by corporate and special-interest funding and influence.

Peer-reviewed studies already demonstrate how pharmaceutical companies manipulate FDA rules to generate evidence that their new drugs are more effective and less harmful than unbiased studies would show. The industry then recruits teams of medical writers, editors, and statisticians to select and repackage trial results into peer-reviewed articles that become accepted as reliable medical knowledge.

Based on his investigations, Marc Rodwin [8] concludes, "Scholarly studies have revealed that drug firms design trials that skew the results and that they distort the evidence by selective reporting or biased interpretation." This distorted evidence goes into clinical guidelines that become, Lisa Cosgrove and Emily Wheeler [9] note, "essentially marketing tools for drug companies."

Often Neither Safe Nor Effective

The Center for Drug Evaluation and Research (CDER – pronounced "C-DER") is the FDA division responsible for determining whether new drugs should be approved. Its funding, however, now largely comes not from taxpayers but from the companies submitting their drugs to CDER for review.

This clear conflict of interest and approving so many new drugs with few clinical benefits serve corporate interests more than public interests, especially given the large risks of serious harm. Direct and indirect costs to society far exceed the cost of funding the FDA as a public, independent review body.

New FDA policies to get more drugs reviewed faster so that they can reach patients sooner result ironically in even more drugs being approved with less evidence that they are either safer or more effective. Faster reviews mean the chance that a drug will generate an FDA warning of serious harm jumps from one in five to one in three.

A systematic study [10] of shortened reviews found that each 10-month reduction in review time produced an 18 percent increase of serious adverse reactions, an 11 percent increase of drug-related hospitalizations, and a 7.2 percent increase of drug-related deaths. Only 72 out of 1,300 CDER staff are charged with investigating drug safety [11], hard evidence that drug safety is a low priority at the FDA.

A recent review of FDA policies [12] in *Health Affairs* describes how the FDA creates initiatives that ostensibly demonstrate its concern for safety from faster approvals. But the authors then describe how these initiatives frequently fail or backfire. They report no evidence of reduced harm or improved benefit to patients receiving these expedited drugs.

People imagine the FDA has stringent standards that take months or sometimes years for companies to meet. To a degree, that's true. But the external independent evidence cited here of few new benefits and substantial risks of harm, calls into question what all this costly, lengthy review process is about.

An anthropologist might conclude it's an elaborate ritual to make the FDA look like a tough watchdog against unsafe and ineffective drugs while it's an industry-funded lapdog. Consider the easy ride [13] that the FDA gives cancer drugs, requiring little evidence of improved patient outcomes.

For example, approving that new drugs are better than placebo is a low standard when other effective drugs already exist. Placebo trials are also unethical in these situations because they deny subjects in the control arm the use of an effective drug.

Another FDA standard, to prove that approved drugs are "non-inferior," or not too much worse than an existing drug, does not allow patients to know if the new drug is better than the one they are taking. Using substitute measures for real benefits to patients makes approved drugs

look more effective than they are. Allowing randomized trials to be drawn from biased populations that exclude many people who are likely to take the drug and experience an adverse reaction makes new drugs appear safer than they are.

Why does the FDA allow paymasters to design such trials?

Failure To Warn

The FDA is charged with providing physicians and the public with objective, scientific evidence showing that new drugs are safe and effective. Conveniently for drug companies, it carries out this responsibility narrowly by focusing on the label and not on alerting physicians or the public about biased evidence from those trials in leading medical journals that go into guidelines.

The FDA could alert the profession and public about how end points and other details get switched by industry ghost-writing teams, about unpublished negative results, and about positive results published twice; but it does not. Ghost writing and the ghost management of medical knowledge thrive.

To protect the public from unsafe and ineffective drugs and earn public trust, the FDA and Congress must acknowledge the biases described here that result from pharmaceutical corporations financing the public regulator. They should also require two changes: that new drugs demonstrate patient-based clinical advantages through comparative trials, and that these trials be based on the population that will actually take a drug.

These changes would reduce the flood of minor variations shown in Exhibit 1 and the subsequent billions spent [14] on them.
