

## 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.<sup>1 2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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).<sup>5 6</sup> 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,<sup>5</sup> and a much more comprehensive review comes to similar conclusions across many areas of medicine overseen by the FDA.<sup>6</sup> 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<sup>7</sup> and the risk of patients being admitted to hospital with or dying from adverse reactions?<sup>8</sup> 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.<sup>9</sup>

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.<sup>10</sup> Prescription drugs are the fourth leading cause of death in the United States and the third leading cause in Europe, according to one authority.<sup>11 12</sup>

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

**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.”<sup>13</sup>

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.<sup>14</sup> 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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