A scientific basis for safety

Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation

by Philip J Hilts

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The US Food and Drug Administration (FDA) is the granddaddy of government agencies mandated to protect the health of the public. It is respected globally. Polls indicate that most Americans regard its role in assuring safe foods, drugs and medical devices as necessary and positive. Progressive business leaders value its regulations, inspections and sleuthing as a credible basis for competition (while still complaining about compliance costs.) It exercises huge responsibilities, covering one-fourth of the economy, with a budget of just \$4 per year per person.

Crises involving contaminated foods and hazardous or ineffective drugs have periodically thrust the agency into the spotlight. Absent a crisis, however, the agency gets slim budgets for its scientific and regulatory work. Case histories vividly described by Philip Hilts, a veteran journalist, show how the pendulum of public opinion and political ideology has swung hard against the FDA approximately every 20 years, generally when Republican advocates for the autonomy and profit imperative of business wrest control of the federal government from Democratic advocates for governmental intervention in the marketplace.

The FDA has been shaped most by four legislative acts in 1906, 1938, 1962 and 1992—each followed by long struggles to gain the resources and expertise to carry out new missions. Each political tale is a juicy combination of scandals about foods or drugs gone amok, compelling new science, bills already pending in Congress, and finally a 'deal'. The story of the first pendulum swing begins in the 1880s, with Harvey Wiley heading the Department of Agriculture's Bureau of Chemistry. Intense media coverage of Wiley's 'poison squad experiment' with controlled exposures to food preservatives was followed by Upton Sinclair's provocative 1905 book about the meat industry, *The Jungle*. Unfortunately, the Pure Food and Drug act of 1906 laid the burden on the FDA to prove and prosecute misdeeds, despite negligible enforcement funds and unsympathetic judges. The most effective provision introduced the "government-inspected" stamp on foods, required for interstate shipping.

After total dominance of government by business in the Roaring

Twenties came the Great Depression and a turn toward more interventionist government. Women's clubs, consumer advocates, public health officials, muckrakers and scientists mobilized. Secret-formula drug-makers still blocked legislation, however, until over 100 patients died in 1937 from elixir of sulfanilamide, an untested syrup containing toxic ethylene glycol. The 1938 act required companies to submit evidence of safety before drugs could be sold. Ironically, this crucial provision was inserted only at the last minute when a previous opponent of the legislation, now converted, asked what could have prevented the elixir tragedy.

In 1962 came the requirement that drugs meet a new standard: "substantial evidence [of safety and efficacy] from adequate and well-controlled scientific experiments." This act launched requirements for randomized clinical trials. Despite hearings about ineffective drugs, confusing brand names and price-fixing, crusading Senator Estes Kefauver made no headway with his colleagues or President Kennedy until the thalidomide story broke. Meanwhile, one US company rushed tablets of this drug to 20,000 patients via 1,200 doctors without record-keeping, under an 'experimental loophole' the FDA felt powerless to contest.

By the early 1950s, 90% of prescriptions were for drugs that had not existed in 1938; advertising shifted from being aimed 95% to the public in 1930 to 90% to doctors by 1972. But the FDA still had negligible resources for toxicity reviews. Eventually the agency called on the National Academy of Sciences to exhaustively evaluate 4,000 drugs.

Last, in 1992, after decades of companies and patients attacking the FDA as risk averse, delaying drug approval and "killing thousands with red tape," Congress created a user-fee system that allowed the hiring of more medical reviewers, with faster processing and earlier drug approvals. Companies and the FDA also learned to plan clinical trials together, raising standards and preparing the reviewers for data submissions—a scheme that seems to be working pretty well. Hilts also emphasizes the remarkably constructive relationship the FDA developed with HIV/AIDS activists desperate to get new drugs, yet determined to obtain information about toxicities and evidence for good choices—resulting in the parallel tracks of early treatment and active recruitment to clinical trials.

In every generation, FDA inspectors and medical reviewers have been crucial to resolving nasty incidents: botulism from olives, polio from inadequately inactivated vaccine, fatal aplastic anemia from chloramphenicol, defective Shiley heart valves, cataracts from cholesterol-lowering MER-29, liver damage from Panalba, Reye syndrome from aspirin, infections from unpasteurized milk, sudden deaths from heart rhythm drugs—too many problems to just be brushed off as tolerable risks. Sometimes the FDA has taken the initiative, as in declaring cyclamate and saccharin carcinogenic, requiring patient package inserts for drugs and labeling for processed foods, and attacking cigarettes as nicotine-delivery devices. And sometimes the US Congress has slapped the FDA down, as with the 1994 law removing the agency's authority over health claims for dietary supplements.

Hilts is clearly pro-regulation. He struggles to understand why the business community at large tolerates the most extreme anti-government rhetoric or dangerous products. He concludes, appropriately, that the stepwise introduction of requirements for credible scientific evidence of safety and efficacy have brought progress over the self-interested claims of manufacturers and casual assertions by physicians.

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