Creating a Mandate *for* Drug Safety, Lacking a Mandate *for* Drug Efficacy

In 1933, with the election of Franklin Roosevelt and the emergence of the New Deal, FDA and the Department of Agriculture worked with Congress to introduce new, comprehensive legislation to replace the 1906 Food and Drugs Act. But the bills stagnated under heavy resistance. Change came soon after the Elixir Sulfanilamide disaster of 1937, in which an untested drug preparation used for systemic infections killed over 100 Americans. Outrage over this calamity spurred passage of the 1938 Food, Drug, and Cosmetic Act, which among other provisions required companies to provide FDA with evidence of a new drug's safety before marketing.

In addition to requiring evidence of safety under the new 1938 law, FDA sometimes required manufacturers to show that their drugs actually worked. FDA did this, for example, for new drugs that claimed to treat a deadly condition such as cancer – when effective treatments already existed for it. In those instances, FDA expected the manufacturer to prove that the new drug worked, on the grounds that it was unsafe to use a worthless drug when a proven treatment was already available. Nevertheless, when experts later examined medicines introduced between 1938 and 1962, they found that about 40 percent of the drugs on the market were not effective.

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Senator Estes Kefauver and the Investigation *of* Pharmaceutical Industry Practices

As Chair of the Senate Subcommittee on Antitrust and Monopoly, Senator Estes Kefauver of Tennessee launched hearings in 1959 into the costs of pharmaceuticals. His investigation began with a focus on such issues as the length of patent protections for drugs and high prices of pharmaceuticals in relation to their research and development costs. However, additional issues arose during the hearings that exposed other concerns with pharmaceuticals and their distribution and regulation, which drastically affected the bill Kefauver soon introduced.

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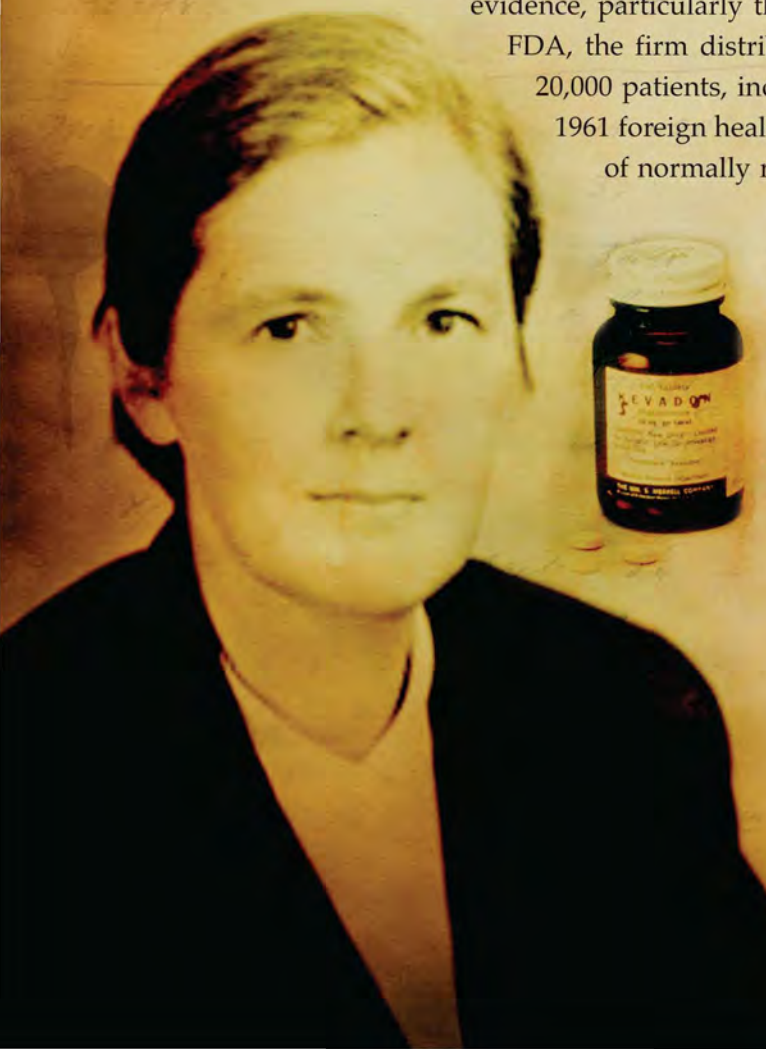
1960-61

Thalidomide and Dr. Frances Kelsey

German pharmaceutical firm Chemie Grünenthal introduced thalidomide in 1956 as a sedative, far safer than the old standby, phenobarbital, and found to be useful for morning sickness among pregnant women. It was soon on the market in over 40 countries under various brand names. On September 12, 1960, American licensee William S. Merrell Company filed with FDA a new drug application for Kevadon, its brand of thalidomide, as a sedative, which the agency assigned to a newly hired medical officer, Frances Kelsey, a pharmacologist and physician.

Despite the firm's intense pressure on both herself and her superiors, Kelsey refused to approve the application based on the small amount of clinical evidence, particularly the lack of chronic toxicity data. Unknown to FDA, the firm distributed Kevadon widely in the U. S. to nearly 20,000 patients, including some pregnant women. By the fall of 1961 foreign health officials linked the drug to growing clusters of normally rare severe birth defects known as phocomelia (hands extending directly from the shoulders, and feet from the hips). Eventually thousands of such cases developed around the world. Though thalidomide was never approved here, FDA identified 17 cases of thalidomide-linked birth defects in the U.S., and the agency launched a nationwide program to recover all supplies of the drug.



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The Kefauver Hearings Continue

Senator Kefauver's hearings continued, and though they focused on economic issues, a number of unanticipated problems came to light. For example, witnesses testified to the many misleading advertising practices used in the industry, and even more significantly, the public learned that many drugs on the market simply didn't work. Over the next few years the hearings generated thousands of pages of testimony and exhibits.

Kefauver introduced a bill in 1961 that would, among other elements, address some of the pricing issues through patent modifications, require evidence of effectiveness before a drug could be approved, strengthen FDA's oversight of clinical investigations, and enhance the agency's authority to inspect manufacturing facilities. However, the bill met strong opposition from industry, the American Medical Association, many clinical researchers, and many members of the Senate, where his colleagues weakened the bill without Kefauver's approval. The legislation appeared headed nowhere until America's close call with thalidomide came to light.

News outlets had not shown much interest in the early reports about thalidomide's effects, but Estes Kefauver's staff discovered Kelsey's role and passed the information along to Morton Mintz of the Washington Post. His front-page story of the nation averting the thalidomide nightmare gave rise to broader calls for drug controls, President Kennedy among them.

The Washington Post
Times Herald
SUNDAY, JULY 15, 1962

Linked to Malformed Babies

'Heroine' of FDA Keeps Bad Drug Off Market

By Morton Mintz
Staff Reporter

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.

The story of Dr. Frances Oldham Kelsey, a Food and Drug Administration medical officer, is not one of inspired prophesies nor of dramatic research breakthroughs.

She saw her duty in sternly simple terms, and she carried it out, living the while with insinuations that she was a bureaucratic nitpicker, unreasonable — even, she said, stupid. That such attributes would have been ascribed to

standards and her belief that the drug was "peculiar" against these facts:

The drug had come into widespread use in other countries. In West Germany, where it was used primarily as a sedative, huge quantities of it were sold over the counter before it was put on a prescription basis. It gave a prompt, deep, natural sleep that was not followed by a hangover. It was cheap. It failed to kill even the would-be suicides who swallowed massive doses.

And there were the reports on experiments with animals. Only a few weeks ago the American licensee told of giving the drug to rats in doses 6 to 60 times greater than the comparable human dosage. Of 1510 offspring, none was delivered with "evidence of malformation."

In a separate study, one rat in 4 delivered a malformed offspring when given a dosage

The Washington Post
FRANCES O. KELSEY
...on FRANCES O. KELSEY wins

U.S. Captain Is Killed in Red Attack

Viet Cong Also Slay 23 Others In Road Battle

By Peter Arnett

SAIGON, South Viet-Nam, July 14 (AP).—Nearly 500 Communist guerrillas ambushed a government convoy 40 miles north of Saigon this morning and killed a U. S. Army captain and at least 23 Vietnamese soldiers in a fierce but short battle.

The Defense Department in Washington identified the U. S. officer killed as Capt. Dan F. York, of Asheville, N. C. He is survived by his wife, Joanna, a son, Michael, 7, and a daughter, Anne K., 4, and his parents, Mr. and Mrs. Arthur A. York of Asheville.

Capt. York was training a 24-vehicle convoy when

President K... Mayor of C... As Secreta...

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1962

Part I: 1962 Drug Amendments

Congress passed the Kefauver-Harris Drug Amendments on October 10, 1962; Oren Harris was the chief co-sponsor of the bill in the House. The price-control provisions in Kefauver's original bill did not survive, but many other elements did, including some new ones.

The new law required substantial evidence of both safety and effectiveness as demonstrated by adequate and well controlled clinical investigations conducted by qualified experts.

Also, establishments had to abide by current good manufacturing practices to ensure that drugs met the requirements of identity, strength, quality, and purity, and FDA was given enhanced access to a manufacturer's records.

FDA would monitor clinical investigations more closely, and—with some exceptions—experimental subjects had to give their informed consent to be involved in such studies.

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Part II: 1962 Drug Amendments

Regulatory authority over prescription drug advertising was transferred from the Federal Trade Commission to FDA. Previously, insistence by industry and others that FTC—and not FDA—regulate drug advertising had held up passage of the 1938 Food, Drug, and Cosmetic Act until FTC's authority was clarified.

The new law also required that manufacturers maintain records of adverse events associated with drugs and report these promptly to FDA.

Under the 1938 law, a drug application automatically became effective after 60 days unless FDA intervened. The 1962 amendments changed this by requiring an affirmative decision by the agency within 180 days, or a period as required for the agency's review.

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1966-69

Drug Efficacy Study Implementation (DESI)

The new law authorized a review for effectiveness of all new drugs approved on the basis of safety from 1938 to 1962, about 4000 of which remained on the market; 85 percent were prescription drugs. FDA contracted with the National Academy of Sciences in June 1966 to conduct a review of company-submitted effectiveness data, which ended in June 1969. Thirty panels, each consisting of six expert members, evaluated the evidence about the drugs and rated them as effective, ineffective, or somewhere in between.

Their evaluations covered submissions for about 3400 formulations representing 16,000 approved uses. Only 12 percent of the drugs were found to be effective for all their claims, and 40 percent of the indications were less than "effective." It was then FDA's responsibility to follow through on the recommendations, a challenging and often litigious process.

By 1984 FDA had completed 98 percent of the DESI program, having analyzed additional efficacy data, designed trials as necessary, and processed hearings and court actions with firms. Reducing the final judgments to either "effective" or "ineffective," FDA found that about one-third of the new drugs approved between 1938 and 1962 were ineffective.

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The Long-Term Effects *of* the 1962 Drug Amendments

In calling for substantial proof based on clinical trials conducted by experts, the new law established an evidence-based model for drug evaluation decisions that still stands as the gold-standard globally. FDA itself drew upon outside experts by instituting advisory committees to counsel agency reviewers in a formalized venue.

Over the next two decades, debate ensued over whether or not the law and FDA's oversight slowed down access to medicines compared to other nations, though that discussion dissipated with the passage of the first Prescription Drug User Fee Act in 1992, with industry paying fees to support FDA's review process and the agency's commitment to meet certain drug review goals.

Broad press and public attention to FDA's work, witnessed only intermittently before 1962, began to be more frequent from the mid-1960s forward. Finally, the aftermath of the 1962 law saw an elevation of public expectations for FDA, a heightened sense of confidence in the reliability of pharmaceuticals. And when that confidence was shaken by a safety or other issue, the reaction could be predictably quick and dramatic. Thus, the 1962 Drug Amendments and the circumstances that brought it about engaged the public in a way not seen before.

Moreover, these amendments helped usher in today's sophisticated, science-based biotech and pharmaceutical industry. For the very first time, many companies put in place rigorous research and development programs, including the design and implementation of controlled clinical trials.

At their core, the 1962 drug amendments —by demanding excellence and creating a culture of quality and innovation—laid the foundation for our current regulatory environment which is emulated around the world. It's an environment that has offered enormous progress for patients and consumers—while encouraging private sector innovation and economic growth.

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