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Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50

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Fifty years ago this month, President John F. Kennedy signed into law the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act (see photo). With the stroke of a pen, a threadbare Food and Drug Administration (FDA) was given the authority to require proof of efficacy (rather than just safety) before approving a new drug — a move that laid the groundwork for the phased system of clinical trials that has since served as the infrastructure for the production of knowledge about therapeutics in this country. We often remember the Kefauver–Harris Amendments for the thalidomide scandal that drove their passage in 1962. But there is much we have collectively forgotten about Senator Estes Kefauver (D-TN) and his hearings on administered prices in the drug industry. Many parts of the bill left on Congress's cutting-room floor in 1962 — and left out of our memories since — have not disappeared, but continue to confront those who would ensure access to innovative, safe, efficacious, and affordable therapeutics.

By the time Kefauver began his investigation into the pharmaceutical industry in the late 1950s, the escalating expense of lifesaving prescription drugs was illustrating that the free-market approach to medical innovation had costs as well as benefits. From the development of insulin in the 1920s, through the “wonder drug” revolutions of sulfa drugs, steroids, antibiotics, tranquilizers, antipsychotics, and cardiovascular drugs in the ensuing decades, the American pharmaceutical industry had come to play a dominant role in the public understanding of medical science, the economics of patient care, and the rising politics of consumerism. For Kefauver, the “captivity” of the prescription-drug consumer in the face of price gouging and dubious claims of efficacy underscored the need for the state to ensure that innovative industries worked to the benefit of the average American.

After 17 months of hearings, in which pharmaceutical executives were openly berated for profiteering and doctors were portrayed as dupes of pharmaceutical companies' marketing departments, Kefauver presented his bill, S.1552. Perhaps its least controversial components were its calls for ensuring that the FDA review claims of efficacy prior to drug approval, monitor pharmaceutical advertising, and ensure that all drugs had readable generic names. More radically, Kefauver proposed completely overhauling the relationship between patents

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and therapeutic innovation. First, he proposed a compulsory licensing provision so that all important new drugs would generate competitive markets after 3 years. Second, and more controversial still, Kefauver wanted to eliminate “me-too drugs” and “molecular modifications” by insisting that a new drug be granted a patent only if it produced a therapeutic effect “significantly greater than that of the drug before modification.”[1] Proving that a drug worked, according to Kefauver, was not enough: he wanted proof that a drug worked better than its predecessors. In contemporary terms, he wanted to know its comparative effectiveness.

Kefauver's bill met strong resistance as it made its way through the Subcommittee on Antitrust and Monopoly.[2] The American Medical Asssociation firmly opposed the regulation of efficacy by a government agency, arguing that “the only possible final determination as to the efficacy and ultimate use of a drug is the extensive clinical use of that drug by large numbers of the medical profession over a long period of time.”[3] The editors of the *Journal*, on the other hand, supported the efficacy provision and the expansion of generic drug names but opposed the patent provisions (considering them an “arbitrary discrimination” against the pharmaceutical industry) and the comparative effectiveness provisions (considering “proof of superiority” necessary only if superiority was actually being “claimed by the manufacturer”).[4] The pharmaceutical industry echoed such concerns regarding comparative effectiveness, arguing that any *a priori* determination of which medicines were “me-too” and which were true innovations would be arbitrary. Efficacy was hard enough to prove, they suggested; proving *comparative* efficacy would be “completely impracticable.”[3]

Kefauver initially stuck to his guns on issues of compulsory licensing and patents, but his persistence ultimately cost him control of his own bill. In June of 1962, officials from the Kennedy administration and the pharmaceutical industry presented the subcommittee with an alternate bill — with no regulatory language about patents included. Kefauver cried foul, the Kennedy administration dropped its support, and S.1552 seemed to all observers to be a dead letter. It was only by chance timing that the summer of 1962 also produced a highly visible tragedy (thalidomide), a hero (Frances Kelsey), and enough ensuing public outcry to persuade Kefauver and Kennedy to embrace the gutted bill.

The amendments granted the FDA the power to demand proof of efficacy — in the form of “adequate and well-controlled investigations”— before approving a new drug for the U.S. market. They also led to a retrospective review of all drugs approved between 1938 and 1962 (the Drug Efficacy Study Implementation program), which by the early 1970s had categorized approximately 600 medicines as “ineffective” and forced their removal from the market. These market-making and -unmaking powers were also tied to a new structure of knowledge generation: the orderly sequence of phase 1, phase 2, and phase 3 trials now seen as a natural part of any pharmaceutical life cycle.

However, a well-circulated grievance pointed to one unanticipated consequence of the amendments: the new burden of proof appeared to make the process of drug development both more expensive and much longer, leading to increasing drug prices and a “drug lag” in which innovative compounds reached markets in Europe long before the U.S. market.

Industry agitation surrounding the “drug lag” finally led to modification of the drug patenting system in the Drug Price Competition and Patent Term Restoration Act of 1984 — through further extension of drug patents. Indirectly, then, Kefauver's amendments ultimately affected both pharmaceutical pricing and patenting — in a manner diametrically opposed to the one he intended.

Another unintended consequence of the amendments was that the new structures of proof changed not only the behavior of the pharmaceutical industry, but also the conceptual categories used by biomedical researchers around the world.[5] Pharmaceutical research came to be overwhelmingly organized around the placebo-controlled, randomized controlled trial. Although this system has greatly helped researchers gauge the efficacy of an individual drug, it has also rendered data on comparative efficacy much more difficult — and much more expensive — to find or produce.

Renewed attention to comparative effectiveness research in the 21st century illustrates the consequences of sidelining Kefauver's initial demand for comparative data for evaluating the promotion of novel therapeutics. By 2000, pharmaceutical expenditures had become one of the fastest-growing parts of the budget of many U.S. states and third-party insurers; but the kind of knowledge required for entry into the U.S. drug market offers consumers and payers little information relevant to choosing between classes of “me-too” drugs whose action may or may not be the same. Only in the past decade, through the action of the Reforming States Group, the Drug Effectiveness Research Program, and most recently funding of comparative effectiveness research through the American Recovery and Reinvestment Act, the Affordable Care Act, and now the Patient-Centered Outcomes Research Institute, have we begun to catch up on the vital project of comparing therapeutics so that American consumers and their physicians can make meaningful treatment decisions — the project that motivated Kefauver's original investigations a half-century ago.

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photo figure 1.
President John F. Kennedy Signing the Kefauver Amendments.