The price of pills:

A brief history of the Kefauver-Harris Amendment

Reid Wilkening, MD, PhD

Dr. Wilkening is a 2019 graduate of the University of Illinois at Chicago College of Medicine, Chicago, IL. His essay received first place in the Alpha Omega Alpha Honor Medical Society 2019 Helen H. Glaser Student Essay Award.

The Kefauver-Harris Amendment to the 1932 Federal Food Drug and Cosmetics Act is best remembered for creating the Food and Drug Administration (FDA) as the United States' regulatory agency. For the celebration of the 50th anniversary of the bill in 2012, the FDA wrote, "Fifty years ago, landmark legislation was signed into law by President John F. Kennedy that established the scientific safeguards used today by the FDA to ensure that consumers will not be the victims of unsafe and ineffective medications."[1]

The Kefauver-Harris Amendment diverged significantly from the intent of its namesake Sen. Estes Kefauver (D-TN). Kefauver made his name as a crusader for consumer rights, taking on monopolies in the steel, automotive and banking industries before turning his attention to what he felt was the astronomical cost of pharmaceutical products in the U.S.

Post-World War II

The availability of an advanced arsenal of pharmaceutical products was a novel feature of the post-World War II era. Discovered in 1928 by Alexander Fleming, MD (ΑΩΑ, University of Oklahoma College of Medicine, 1954, Faculty), penicillin was not widely available in the U.S. until the late 1940s.[4] The first broad spectrum antibiotic, chloramphenicol, was isolated in 1947, and received FDA approval in 1949.[5] This era also saw the rapid discovery and adaptation of additional antibiotics, oral anti-diabetics, and the corticosteroids. At the same time, health care spending also increased. Though driven by many factors, spending on prescription medications (ethical drugs in the parlance of the era) was a major contributor.

Drug prices were becoming a source of economic stress for Americans.[2] Even before Kefauver's hearings, the Federal Trade Commission (FTC) in 1958 published *Economic Report on Antibiotic Manufacture,* investigating the economic impact of antibiotic manufacture and pricing. The report, though narrowly focused on antibiotics, assessed similar issues as later studied by the Kefauver hearings, including marketing, research, the production process, pricing, patents, and sales data.[6] The report

makes note of the importance of the antibiotic trade to the pharmaceutical industry, and the significant consolidation in the industry, noting that by 1956 three manufacturers were producing 47.4 percent of all antibiotics.

The report also references the massive amount spent on marketing, stating that somewhere between one-third and one-half of the price of antibiotics was devoted to marketing.[6] It states, "...certain patents have been handled in ways that may represent a conflict with the antitrust laws...unusual rigidity of prices were observed, and the provisions of some term purchase contracts appeared to warrant further study with respect to differences in prices charged different buyers...."[6]

Though no legal action was taken at the time in response to this study, it set the stage for Kefauver's investigation into the pharmaceutical industry pricing schemes.

Drug pricing, monopolies, and patents

Kefauver chose to focus his efforts on four aspects of the ethical drug industry: mechanisms of drug pricing; unreasonably high prices; monopolistic behavior by the manufacturers; and shortcomings of the U.S. patent system. Kefauver argued that manufacturers priced drugs not relative to their manufacturing or development cost, but based on other products they were meant to compete against. When Upjohn began selling Orinase, an oral antidiabetic, patients were sold the drug at 14 cents per tablet when the cost of production was only one cent per tablet. When Upjohn's president testified before Congress he revealed that the price for Orinase "was arrived at on the basis of competition...diabetic patients can be treated by diet or by insulin."[2] At the time, insulin cost 14 cents per dose to manufacture, far greater than Orinase, but as the two products were seen as equivalent, they were priced to maximize profit and avoid undercutting the price of insulin.

Neither time nor competition affected the pricing of the broad-spectrum antibiotic market. Hearings revealed that many agents from different manufacturers cost $5.10 for sixteen 250 milligram tablets for almost a decade. These prices dropped for the first time after the Kefauver hearings, and by the mid 1960s the manufacturers were formally found to be guilty of price fixing.[3,7]

Kefauver also charged that the pharmaceutical industry was engaged in behaviors designed to shut smaller, potentially disruptive manufacturers out of the market in order to attain functional monopolies. Though there were approximately 1,300 drug makers with FDA approval in the U.S. in the 1950s, the industry was dominated by 22 companies. Representatives from smaller manufacturers testified that they avoided direct competition with larger firms due to the cost of marketing. One manufacturer stated that it would cost between $2 million and $3 million to compete directly against Parke-Davis or Pfizer. Attempts at price competition were often quashed with litigation.[3]

Kefauver also looked at profit margins in the pharmaceutical industry. Profits were driven by the monopolies and market manipulations, and the unique aspects of patent protection in the U.S. As Kefauver stated, "the man who orders does not pay, and the man who pays does not order."[2] These features generated an inelastic market for pharmaceuticals where supply was no longer linked to demand.

The hearings revealed that the majority of manufacturers saw margins greater than 70 percent, with the lowest reported margin at 58.6 percent. These profits were driven by huge markups over cost, such as 1,891 percent for prednisone, 6,270 percent for reserpine, 1,557 percent for tetracycline, and 927 percent for meprobamate.[3]

Kefauver also took issue with the cost of drugs in the U.S. as opposed to those abroad, pointing out that Penicillin V cost $18.00 per dose in Indianapolis, the city where it was manufactured, and only $10.75 per dose in Australia. However, the manufacturers did not operate at a loss outside of the U.S., even at these lower margins.[2] Kefauver hypothesized that the patent model in the U.S. was responsible for these differences.

Much of the financial success of the pharmaceutical industry in U.S. was built on unique patent laws. While many countries only allow patents for a novel process, the U.S. patent system granted protections for specific molecules. Unique patents could be granted for subtle and functionally meaningless molecular modifications of a new compound, and for new combinations of existing compounds.[3,8]

When considering prices of drugs in the U.S., firms were granted much more open-ended patent protection than overseas. Kefauver found that drug prices were between 1.8 and three times greater in the U.S. than elsewhere, concluding that this difference was secondary to patent law.[3]

The drug manufacturers were able to further fortify their profits via the successful expansion of state-specific anti-substitution laws. Originally written to protect consumers from poorly compounded bootleg or counterfeit therapeutics, these laws required that pharmacists dispense medications exactly as prescriptions were written.[9] This meant that a prescription calling for an antibiotic by brand name could not be replaced by a generic equivalent or another branded variant.

Recognizing the monetary value of such laws, the National Pharmaceutical Council aggressively lobbied for their expansion. In 1953, there were only four states with anti-substitution laws, but by 1959 that number had expanded to 44 states.[8,9] This created an environment in which firms were incentivized to market their branded variant of products directly to physicians. In 1959, drug manufacturers spent $750 million on advertising.[10]

Advertising pharmaceuticals

The FDA was not responsible for regulating advertising, a responsibility which fell to the Federal Trade Commission (FTC).[10] The FTC gave extreme deference to these advertising claims, stating "[n]o advertisement of a drug shall be deemed to be false if it disseminated only to members of the medical profession, contains no false representation of material fact, and includes or is accompanied in each instance by truthful disclosure of, the formula showing quantitatively each ingredient of such drug."[10]

The lack of advertising regulation coupled with the rapid development of prescription medications led to a therapeutic jungle whereby physicians were educated about new products via promotions and advertising veiled as scholarly manuscripts. Print advertisements ran concurrently with studies disproving the claims made by the advertisements.[10]

Senate Bill 1552

After 17 months of Congressional hearings, and more than 10,000 pages of testimony transcripts, Kefauver introduced Senate Bill 1552, intended to remedy the troubling behaviors of the drug manufacturers, and reduce prices for consumers. The bill would also alter patent architecture in the U.S. by requiring compulsory cross-licensure of compounds after a three-year period of exclusivity. Companies would be forced to negotiate licenses with a fixed fee of eight percent, with the goal of ensuring generic competition. New compounds could only be marketed if they had proven efficacy over older compounds, thus limiting molecular modifications and combination therapies. This change would prevent fixed-dose antibiotic combinations from obtaining unique patents with old compounds.

The bill would expand the purview of the FDA to also regulate efficacy, assess truthful claims in advertising, and require that all branded drugs be accompanied by simple generic names.[11,12] This would limit the value of minor molecular modifications to drugs, alter the regulation of advertising, and boost the recognizability of generic competitors.

SB1552 did not involve anti-substitution laws, which were written at the state level. However, the simplification of nomenclature may have been a way around this issue.

The drug industry was less than enthusiastic about SB1552. William Graham, chairman of the Pharmaceutical Manufacturers Association (PMA), stated that the bill challenged "...the continued success, in fact the very existence of our industry in its present form...."[11]

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Industry rebuttal

The industry took a three-pronged approach in rebutting the bill, via testimony in the Senate combined with a public relations campaign to solidify the support of practicing physicians and the general public. The industry framed the issue as a referendum on socialized medicine, claiming that the hearings and SB1552 were a communist attack on free enterprise. They argued that the patent changes would quash competitive development, and that the molecular modifications to corticosteroids that led to the development of dexamethasone and prednisolone would not have been viable under the new rules. They cited free market competition as the explanation for their success as compared to that of the Soviet Union.

Graham stated "[P]robably through no other industry can the superiority of our American competitive system be demonstrated so impressively."[11]

Though the pharmaceutical industry in the U.S. was far more productive than their Soviet rivals, the biomedical work force in the USSR was far larger, and the Soviet's proved adept at leveraging this work force for international influence. This gave the U.S. pharmaceutical industry leverage explaining that they needed to be free of constraints to best ensure capitalism.[11]

The industry attempted to sway public opinion on SB1552 via direct outreach with advertisements appearing

in *Reader's Digest*, *The Saturday Evening Post* and *Look*. These ads highlighted decreases in morbidity and mortality that the industry attributed to their products. They illustrated the process by which new products were discovered and emphasized the financial risk born by the manufacturer in the development of new products. They ran ads describing the success of the American industry versus that of the Russian industry saying it was due to "a competitive American drug industry and medical center research. And by a patent system that encourages new inventions and discoveries."[11]

Though the result of the campaign remains challenging to quantify, the Senators debating the bill were affected by it. One Michigan senator reportedly received numerous, almost identical, letters from constituents in Detroit, where Parke-Davis was headquartered. The letters were in response to a request published in the *Parke-Davis Review*, an internal publication for employees and stockholders of the firm.[11]

The industry also took advantage of their unique relationship with the American Medical Association (AMA). The AMA had run into financial troubles in the 1950s, and the drug manufacturers became one of the primary funders of the AMA through advertising in the *Journal of the American Medical Association* (*JAMA*).

The AMA lobbied against SB1552 on the platform that only practicing physicians should be in the position of dictating whether drugs were efficacious or not. Said one AMA member during the hearings, "[T]he 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 community."[12]

The *New England Journal of Medicine* (*NEJM*) took a more measured approach. Its editorial board ran a series of articles in 1961: *Ethical Drugs—The Proposed Legislation, Ethical Drugs—To Assure Efficacy* and *Safety, and Ethical Drugs—Reflections on the Inquiry*.[13-15] The series was supportive of the legislation concluding, "[M]ost of the basic principles embodied in the bill seem well designed to serve the primary purpose of protecting the health of the public."[15]

The *NEJM* did take issue with the alterations to patent protection, questioning why drug makers should be subject to patent rules different from other industries. The journal also questioned the wisdom of requiring that new drugs have proven superiority over older products in order to obtain patent protection. The objection of the *NEJM* was based on questioning whether this was necessary, rather than framing it as an attack on physician independence. The latter approach was taken by the AMA's representative, Dr. Hugh H. Hussey (ΑΩΑ, Georgetown University, 1955).[14]

Lacking support

Despite the evidence gathered and presented during the hearings, SB1552 failed to gain sufficient support for its passage. Drug manufacturers and the AMA successfully convinced a majority of senators that SB1552 was overly broad and discriminatory against the pharmaceutical manufacturers, specifically citing the unique patent limitations.

The ever-escalating Cold War tensions gave critics of the bill a crucial lever as pharmaceutical regulation and manufacture was transformed into a issue of capitalism versus communism. In addition, Kefauver staunchly refused to remove any provisions from SB1552, leading to a loss of support from the Kennedy Administration. After a narrow electoral victory in 1960, Kennedy was no longer willing to expend political capital on the controversial bill.

The final chapter of the report issued by Kefauver and the Senate Subcommittee on Antitrust and Monopoly represents the personal views of minority members of the committee, including Sen. Alexander Wiley (R-WI), who begins his critique with the title of part I of the report, "The reasonableness of price." Wiley argues that reasonableness is not a legal term, and therefore not subject to antitrust laws. He contends that without their profits the drug industry would not have attained its level of productivity writing, "It is the drug industry's success story that provided the necessary capital for the industry's growth."[16]

Wiley concludes that the risks associated with drug discovery justify the rates of return. He refutes concerns over monopolistic behavior and patent abuse on a philosophical level asking, "Is it a crime to be successful in an economy that believes in free enterprise? After all, one of the major aims of our economy is to encourage success."[16]

He also notes that trademark use was expanding in what had recently become Communist China, once again revisiting the Cold War as a foil. Wiley writes that prescription by generic name would "...Deny the physician the right to prescribe a brand-named product manufactured by a pharmaceutical house known and trusted by him," and this "...may well be destructive to the traditional doctor-patient relationship."[16] He closes his argument with a quote from John Adams, "Consumption is the sole end and purpose of all production."[16]

The Kefauver-Harris Amendment

It was not until 1962 and the thalidomide scandal in Europe that a Kefauver-Harris Amendment was passed.

The full effects of the thalidomide catastrophe in the U.S. was mitigated by the decision of FDA Medical Officer Frances Kelsey to block thalidomide's new drug application on the basis of insufficient, anecdotal data. Though Kelsey was operating under the older FDA regulations, the scare was sufficient to catalyze the passage of the modified Kefauver-Harris Amendment with the support of the Kennedy Administration.[1,17] However, much of the original bill's content was removed, including changes to patent law and price regulation.

The FDA was granted the power to ensure that all new drugs were not just safe, but also efficacious, as found by "adequate and well controlled investigations."[12] These investigations gave rise to randomized clinical trials.

The amendment also allowed for retrospective review of previously approved compounds which led to the removal of the vast majority of fixed-dose combination antibiotics (several antibiotics in one tablet, or a combination of an antibiotic with other cold remedies) from the market.

The amendment transferred advertising control of pharmaceuticals to the FDA requiring accurate information on side effects to be included, and ensuring that generic drugs could not be sold under brand names.[1]

Though the amendment significantly diverged from what was originally proposed by Kefauver, it has had, and continues to exert, a significant influence on the practice of medicine. The randomized controlled trial remains the gold standard for biomedical investigation, and the FDA still utilizes the phases of drug development that derived from the amendment. Its efficacy requirements had the unintended consequence of increasing the time necessary to develop new compounds.

In 1984, the Drug Price Competition and Patent Term Restoration Act was passed, and extended patent protection for new compounds during the approval stages.

While Kefauver's goal of expanding FDA powers to protect consumers was realized, the Kefauver-Harris Amendment indirectly led to the expansion of patent protection for pharmaceuticals, in direct opposition to Kefauver's original goals.

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The author's E-mail address is Reid.wilkening@cuanschutz.edu.