

Congress of the United States

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Docket No. 02N-0209 - Request for Comments on First Amendment Issues

Introduction and Summary

The undersigned Members of Congress strongly object to the Administration's apparent intention to curtail FDA's ability to regulate promotional claims for drugs and other health-related products. Each of us has a long-standing commitment to advancing the public health and to ensuring that products on which our citizens rely to protect their health are safe for their intended uses, are adequately tested to demonstrate that they are effective, and are not deceptively promoted.

The Federal Food, Drug, and Cosmetic Act (FDCA) was enacted to protect consumers from injurious and fraudulent foods and drugs, and it has been amended several times over the past 75 years to expand its protections over drugs, medical devices, and foods. The FDCA's restrictions on misleading and unsubstantiated promotional claims are central to its goal of preventing injury from dangerous and deceptive products. The Administration, putting corporate interests ahead of consumer safety and cloaking itself in the First Amendment, now appears ready to undermine the core protections of the FDCA and to allow manufacturers to make questionable and potentially dangerous claims about products that intimately affect the health of all Americans.

Referring to recent court decisions giving protection to "commercial speech" under the First Amendment, a notice issued by FDA, dated May 16, 2002, states that these decisions may be in conflict with the FDA's long-standing implementation of the FDCA, and even with the Act itself. Despite the absence of any current lawsuit challenging these requirements, the leadership of the agency has taken it upon itself to suggest that much of FDA's regulation of the

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promotional activities of food and drug manufacturers is unconstitutional. The questions posed at the end of the notice challenge the validity of one of the cornerstones of the FDCA: the requirement that before marketing a new product or a new use of a product intended to treat disease, a manufacturer must demonstrate to FDA that the product is safe and effective for its intended use. The notice appears to doubt that promotion of unapproved medical products or unapproved uses causes sufficient harm to justify its current level of regulation.

The notice goes on to ask whether, under the First Amendment, the promotional requirements now applicable to dietary supplements might not be more appropriate for drugs. Using dietary supplement regulation as a model would dramatically deregulate the marketing of prescription drugs. The authors of the notice apparently believe that consumers can be adequately protected from harm when manufacturers are free to promote drugs for any use, whether substantiated or not. Under a dietary supplement model, neither the safety nor the effectiveness of these products would be subject to government review before marketing. Manufacturers would instead be trusted to provide truthful, non-misleading information about whatever evidence they have on the medical benefits and risks of their products. And if a manufacturer should fail in this responsibility, the market or FDA would somehow clean up the mess after the claims were made and the product was in wide use.

The Administration is contemplating action that flies in the face of almost a century of documented harm to the lives and health of Americans from unrestricted promotional claims about health-related products. Over the last 75 years, Congress has held numerous hearings documenting a long and sometimes shameful legacy of deceptive and dangerous claims made by manufacturers of products intended to improve health. As shown in a wealth of Congressional documents, the history of the FDCA demonstrates beyond question that without pre-market safety and effectiveness requirements, deceptive, unsubstantiated claims about health-related products proliferate, at a tremendous cost in human lives. It also demonstrates that post-market actions against misleading claims are incapable of protecting consumers from unsafe and ineffective products.

Recognizing this history, and the critical importance of drugs, medical devices, and foods to every American, the FDCA establishes requirements to assure that medical products (drugs, biological products, medical devices) are safe and effective. With the exception of the least risky types of medical devices (e.g., tongue depressors), the FDCA permits manufacturers to promote only those uses of their products that have been first reviewed for safety and effectiveness by FDA. It also requires that FDA review health claims for foods and determine that they are supported by significant scientific agreement. These requirements were enacted to serve the highest governmental interest: protecting the lives and health of Americans.

A restriction on commercial speech satisfies the First Amendment if it directly advances a substantial government interest, *Central Hudson Gas & Elec. v. Public Serv. Comm'n.*, 447 U.S. 557 (1980), is based on evidence of real harm and alleviates the harm to a material degree, *Edenfield v. Fane*, 507 U.S. 761 (1993), and is narrowly tailored to meet the desired ends, *Board*

of *Trustees v. Fox*, 492 U.S. 469, 480 (1989). As described in detail in the body of this comment, the evidence on which the promotional restrictions of the FDCA are based more than satisfies the requirements of the Constitution.

- *Evidence supporting premarket approval of safety.* Before drug and device companies were required to demonstrate the safety of their products before approval, Congress had evidence that dangerous, sometimes deadly, products abounded:
 - Widely promoted weight loss products containing toxic ingredients caused severe side effects, including blindness and death in young women;
 - An antibiotic produced by a reputable drug company, containing an untested solvent, killed 107 Americans within a few weeks, most of them children. The solvent was diethylene glycol, a component of anti-freeze, and the company was unaware of its toxicity. Neither full disclosure - e.g., “we know of no evidence of harm from this product” - nor post-market vigilance - FDA immediately sent out warnings and rounded up all remaining stores of the product within days of the first reports of deaths - would have saved the 107 victims; and
 - The Dalkon Shield, an IUD, caused life-threatening infections and robbed thousands of women of their fertility.
- *Evidence supporting premarket approval of effectiveness.* Before drug companies were required to demonstrate the effectiveness of their products before approval, they were subject to a regime much like that suggested by the Administration. They could make any promotional claims about their products, as long as they were truthful and not misleading. In practice, this regime led to unnecessary injuries and deaths. Several years of hearings preceding the enactment of the effectiveness requirement showed that:
 - The pharmaceutical marketplace was filled with misleading promotional claims;
 - The use of ineffective drugs subjected patients to serious side effects without any corresponding benefit and delayed or prevented effective treatment for serious and life-threatening conditions;
 - Drugs with serious side effects, such as potent tranquilizers and toxic antibiotics, were being widely promoted for minor conditions and for vulnerable populations, such as pregnant women, resulting in many injuries and deaths; and
 - After the effectiveness requirement was imposed, the agency reviewed the effectiveness of drugs already on the market. This review established that **80 %** of the uses for which drugs were promoted lacked adequate evidence to show their effectiveness. One third of all marketed drugs were ultimately removed from the

market because they were not effective for a single one of their promoted indications;

- Enforcement actions against these claims were futile because they took months and sometimes years, while the products continued to be promoted and to cause harm;
- Intense promotion caused physicians to switch from older, cheaper, and more effective drugs to newer, untested and sometimes ineffective drugs;
- Drugs were being promoted for indications far beyond the evidence of their effectiveness and even for indications for which they had been shown to be ineffective; drugs with serious side effects were widely promoted for mild conditions;
- It was impossible for physicians to ascertain which drugs were effective and which were not. In the absence of an effectiveness requirement, manufacturers rarely carried out adequate effectiveness tests. Such evidence as existed was generally unpublished or scattered through hundreds of medical journals of varying quality;

Such evidence provided Congress with a more than adequate justification for its conclusion that, in the absence of a requirement that manufacturers demonstrate safety and effectiveness for each promoted use before approval, Americans suffer great harm from the promotion of ineffective and unsafe health-related products. There was also abundant evidence to support the conclusion that alternatives, such as disclaimers disclosing the state of the evidence supporting a claim, and post-market enforcement actions, were inadequate to stop deceptive and dangerous products. The record revealed that when there is no requirement to conduct the tests necessary to establish safety and effectiveness, such tests are rarely conducted. Disclaimers cannot in any way address the grave harm to patients caused by a marketplace in which no one is sure which products work and which do not: many patients are denied effective treatment while others risk serious side effects without any benefit that would justify the risk. Post-market enforcement actions are cumbersome and time-consuming and leave consumers unprotected from dangerous products for months and even years. This evidence is equally relevant to the regulation of drugs, biological products, medical devices, and foods promoted to treat diseases. There is thus more than adequate evidence to sustain the constitutionality of the promotional restrictions currently in place under the FDCA.

Although the May 16 notice calls into question the constitutionality of several important statutory requirements, the notice also states that “FDA intends to defend the act against any constitutional challenges . . .” We will be watching closely to be sure that the agency lives up to its promise. We believe that defending and enforcing its governing statute is the only appropriate course for FDA. We are deeply concerned at the suggestion that FDA will cease enforcing key

regulations, or even statutory requirements, because the agency's current leadership believes they violate the First Amendment. Our concern is heightened because the agency has chosen to take the broadest possible interpretation of court decisions limiting restrictions on commercial speech (see FDA letter to Senator Reed, attached), when narrower interpretations that would preserve FDA's authority are legally sound. Insisting on such a broad interpretation suggests a deliberate intention to undermine FDA's critical public health activities.

The attempt to restrict FDA's authority over promotional claims is particularly offensive when the agency is operating without a Congressionally confirmed Commissioner. The Administration apparently contemplates stripping a vital public health agency of crucial powers while it is without a leader who has met the requirements of Congressional confirmation. It is unacceptable for the Administration to implement far-reaching, anti-consumer policies through an appointee whose qualifications to make decisions directly affecting the health of our citizens have never been subjected to Congressional scrutiny.

We demand that no further action be taken pursuant to this notice until FDA has a confirmed Commissioner.

II. A History of Harm from Unsubstantiated and Deceptive Claims

The questions posed at the end of the May 16 notice question the validity of one of the cornerstones of the FDCA: the requirement that before marketing a new drug or a new use of a drug, a manufacturer must obtain FDA approval by showing that the drug is safe and effective for its intended use. (Although not stated, the safety and effectiveness requirements for biological products and medical devices are implicitly questioned as well.) The notice suggests that there is inadequate support for the conclusion that promotion of unapproved drugs or unapproved uses is inherently misleading or that it causes sufficient harm to justify its strict regulation. It suggests further that consumers can be adequately protected from dangerous and deceptive products through (1) court actions to stop false or misleading claims, after they have been made; and (2) disclaimers.

The history of the FDCA is unfortunately replete with evidence that the regulatory scheme envisioned by the authors of the notice is inadequate to protect consumers from harm and carries a huge cost in human lives. In fact, at different times in history, the FDCA has looked much like the scheme envisioned by the Administration. Before 1938, drugs could be marketed without pre-market approval for safety or effectiveness. After many Americans died from inadequately tested drugs, Congress required in 1938 that drugs be approved for safety, but not effectiveness. Manufacturers could promote their products for any use and were trusted to make promotional claims that were truthful and not misleading. If FDA concluded that the claims were false or misleading, it was required to undertake an enforcement action to stop the claims. When experience revealed that manufacturers were promoting drugs for uses for which they were ineffective and even dangerous, Congress required in 1962 that drugs be approved for safety and effectiveness before marketing. This history has provided to Congress a revealing study of the

behavior of the marketplace when there are no or limited premarket approval requirements for drugs and other medical products and of the public health consequences of this behavior. Congressional oversight of the FDCA has demonstrated beyond question that without premarket safety and effectiveness requirements, deceptive and unsubstantiated claims about medical products proliferate, at tremendous cost to the public health. It has also amply demonstrated that promotion of unapproved uses is inherently misleading and that alternatives such as post-market enforcement actions cannot protect consumers from the harm caused by false and misleading promotional claims.

A. The Evidence Supporting Premarket Approval of Safety

The 1906 Pure Food and Drug Act contained no premarket approval requirements. It permitted FDA to take action against already-marketed drugs that it could prove were adulterated in certain ways. Congress first required that drugs be approved for safety in 1938, after five years of Congressional hearings showing that, under the limited post-market authority of the 1906 Act, consumers were being widely exposed to dangerous and fraudulent drugs. Congressional hearings into drugs being widely promoted for treatment of obesity showed that many of these drugs were hazardous when used for weight loss and that many people had been hurt.¹ One such agent, promoted as exceptionally effective, was Dinitrophenol, a compound used in the manufacture of explosives. This compound has more recently been used as an herbicide and insecticide and is now known to be extremely toxic to humans and animals. Over 100,000 Americans responded to the promotional claims for Dinitrophenol, and suffered skin rashes, cataracts, blindness, and in some cases, death.² Hearings showed that many other extremely dangerous drugs were widely promoted for various diseases.³

Congress' decision to require pre-market approval for safety was finally prompted by the Elixir Sulfanilamide disaster in 1937. Over 100 people, most of them children, died after taking an antibiotic being marketed by a S. E. Massengill, Inc., a reputable drug company. At the time,

¹ *Food, Drugs, and Cosmetics*, Hearings on S. 1944 before a Subcommittee of the Senate Committee on Commerce, 73rd Cong., 2d Sess 16 (1933) (Statement of Walter Campbell); *Food, Drugs, and Cosmetics*, Hearings on S. 2800 before a Subcommittee of the Senate Committee on Commerce, 73rd Cong., 2d Sess. 516 (1933)(Testimony of Walter Campbell); *Foods, Drugs, and Cosmetics*, Hearing on H.R. 6906, H.R. 8805, H.R. 8941, and S.5, Before a Subcommittee of the Committee on Interstate and Foreign Commerce, House of Representatives, 74th Cong. 1st Sess. 105 (1935). (Statement of Dr. A. T. McCormack, State Health Commissioner of Kentucky).

²*Foods, Drugs, and Cosmetics*, Hearing on H.R. 6906, H.R. 8805, H.R. 8941, and S.5, Before a Subcommittee of the Committee on Interstate and Foreign Commerce, *supra*, at 55-6.

³ *Foods, Drugs, and Cosmetics*, Hearing on H.R. 6906, H.R. 8805, H.R. 8941, and S.5, Before a Subcommittee of the Committee on Interstate and Foreign commerce, *supra*, at 523-30.

the FDCA did not require that drug ingredients be studied for safety before marketing and the company had added an untested solvent to create a liquid version of the drug for children. The solvent was diethylene glycol, a component of anti-freeze, and parents watched their children die slow and painful deaths. Massengill denied responsibility for the deaths and FDA was able to charge the company only with a minor labeling infraction.⁴

Congress concluded that pre-market approval for safety was essential to prevent future incidents like these. It would be irresponsible to claim that a pre-market safety requirement for drugs is an unnecessary burden on First Amendment rights, in the face of this history. The accumulated evidence was more than sufficient to conclude that lesser restrictions, such as full disclosure or strong post-marketing enforcement, would not have prevented another Elixir Sulfanilamide disaster. Because it was not required to test for safety, Massengill did not know of the toxicity of diethylene glycol. Therefore, a requirement that the company provide a true statement of the information available about the product –e.g., “we know of no evidence of harm from this product”-- would have protected no one. Nor could prompt action by FDA, once the toxicity was known, have saved the victims. In the actual event, as soon as physicians began to report the deaths from Elixir Sulfanilamide, FDA investigators, together with State and local officials, immediately conducted a massive search for all remaining stocks of the drug, quickly recovering all but a small amount of the finished product. During this short period of time, 107 people died.

B. The Evidence Supporting Premarket Approval for Effectiveness

The 1906 Pure Food and Drug Act allowed FDA to take action against false labeling claims made about products, but only if the agency could prove intentional fraud. If the manufacturer showed an honest belief in his product, FDA could take no action. In hearings leading up to the passage of the 1938 Act, Congress heard testimony from FDA that Banbar, a product widely promoted for diabetes, was ineffective, and that many diabetic patients were taking it instead of insulin, the only effective treatment for diabetes. FDA had tracked down many of the patients taking Banbar and learned that a large number had died after abandoning their insulin. FDA brought an enforcement action against the maker of Banbar but lost the case, because the agency couldn't prove deliberate fraud.⁵

In response to evidence of cases like this, Congress in 1938 modified the law to permit FDA to bring cases against products promoted with false and misleading claims, regardless of whether the manufacturer committed deliberate fraud. Congress did not require that drugs be shown to be effective in 1938; it took the lesser step of requiring that claims be truthful and not

⁴ *Elixir Sulfanilamide*, S. Doc. 124, 75th Cong., 2d Sess. (1937).

⁵ Hearings on H.R. 6906, H.R. 8805, H.R. 8941, and S.5, before a Subcommittee of the Committee on Interstate and Foreign Commerce, supra at 89 (Testimony of Walter Campbell).

misleading. Pub. L. No. 75-717, 52 Stat.1040, §502. For the next 24 years, the U.S. pharmaceutical marketplace operated under a system much like that suggested in the FDA notice. Manufacturers could promote their products for any uses as long as their claims were not false or misleading. If FDA believed that claims were false or misleading, it had the burden of demonstrating this to a court, while the product was already on the market.

1. Evidence from House and Senate Hearings in the 1950's and 1960's

Beginning in the 1950's and extending into the early 1960's, both the House and Senate held extensive hearings on the drug industry. A large part of these hearings focused on the false and misleading promotion of drugs by the pharmaceutical industry. *False and Misleading Advertising (Weight Reducing Preparations)*, Hearings Before a Subcommittee of the Committee on Government Operations, House of Representatives, 85th Cong. 1st Sess. (1957); *False and Misleading Advertising (Prescription Tranquilizing Drugs)*, Hearings Before a Subcommittee of the Committee on Government Operations, House of Representatives, 85th Cong. 2d Sess. (1958); *Administered Prices, Drugs*, S. Rep. No. 448, 87th Cong., 1st Sess. 171 (1961); *The Drug Industry Antitrust Act*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, 87th Cong. 2d Sess (1962); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, 87th Cong. 2d Sess. (1962).

The evidence developed from these hearings demonstrated that a regulatory scheme that depended on post-market enforcement against false and misleading promotion was grossly inadequate to protect Americans from serious harm. The hearings showed that the pharmaceutical marketplace was filled with misleading promotional material on which physicians relied, that there was no reliable source of evidence from which physicians could tell effective drugs from ineffective drugs, and that many Americans were being unnecessarily subjected to toxic drugs whose benefits had been greatly exaggerated or were non-existent. Public health experts, physicians, and experts in drug pharmacology testified that:

- Hundreds of new drugs were being introduced each year, many of them minor modifications of existing products or combinations of existing drugs, but promoted as significant breakthroughs;⁶

⁶*Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 60-62 (Statement of Sen. Kefauver, quoting Senate testimony of medical experts); *id.*, at 211-212 (testimony of Dr. Martin Cherkasky, Dir. Montefiore Hosp.); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 170, 175-6, 179-180 (proliferation of fixed combinations of antibiotics clouds diagnosis, encourages inadequate dosing, inadequate treatment, and antibiotic resistance, and exposes patients to unnecessary toxicity); *id.* at 203 (testimony of Dr. Louis Lasagna concerning introduction of new steroids with minor chemical differences from older ones); *id.* at 206-207.

- Drugs were being promoted for indications far beyond any responsible evidence of their effectiveness and even for indications for which they were known to be ineffective;⁷
- Intense promotion of these drugs caused physicians to switch from older, cheaper, and more effective drugs to new, but untested drugs; a considerable period usually elapsed before it became widely known that a highly advertised new drug fell short of its claims;⁸
- When an ineffective drug was prescribed, it usually replaced an older but effective drug, subjecting patients to side effects without benefits and to lack of effective treatment for serious and even life-threatening conditions;⁹

⁷ S. Rep. 1744, 87th Cong. 2d Sess. 37 (1962); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 85-6 (list prepared by FDA of drugs with questionable indications); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 66-68 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); *id.*, at 173 (statement of Abraham Ribicoff, Secretary of HEW: drug being widely promoted for heart disease despite AMA statement that it lacked evidence of effectiveness); *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at 183.

⁸ S. Rep. 1744, *supra* at 37; *False and Misleading advertising (Prescription Tranquilizing Drugs)*, Hearing Before a Subcommittee of the Committee on Government Operations, *supra*, at 116 (Statement of Dr. Ian Stevenson, Chairman, Department of Neurology and Psychiatry, U. VA); *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at 202 (testimony of Dr. Russell L. Cecil)(new steroids promoted to replace older ones, without adequate evidence of either effectiveness or side effects).

⁹ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, (1962), at 62 (Statement of Sen. Kefauver, *supra*); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 632 (Statement of James B. Carey, Industrial Union Dept. AFL-CIO)(MER/29 widely promoted for lowering cholesterol even after shown to cause cataracts; Decadron widely promoted for arthritis after shown to cause severe mental disturbances and other injuries); *id.* at 213 (testimony of Dr. Cherkasky, *supra*) (drug for serious staphylococci infection shown to be ineffective after marketing); *id.* at 222, 235 (citing article on Deprol, a tranquilizer promoted for use in depressed patients for whom it had been shown to be ineffective, with serious side effects, including addiction, and risk of suicide); *id.*, at 460 (Statement of Andrew J. Biemiller, director, Dept of Legislation, AFL-CIO and former Congressman, “This is an essential measure to protect the user of medicines against wasting his money and delaying adequate treatment of his illness. Ineffective drugs are worse than useless; they are actually dangerous.”

S. Rep. No. 1744, 87th Cong., 2d Sess. Pt. 1, at 37 (views of Sens. Kefauver, Carroll, Dodd,

- Drugs with serious side effects, such as potent tranquilizers and anti-psychotic drugs, were being widely promoted for minor conditions and for vulnerable populations, such as pregnant women;¹⁰
- Physicians were being inundated with promotional material from drug companies that was misleading and unreliable, often in subtle ways;¹¹
- Post-market enforcement actions against misleading claims were almost always futile because they took “months or even years,” while the drugs stayed on the market causing harm. An FTC report showed that actions against misleading advertising completed between 1955 and 1957 took from several months up to 9 years. By the time the misleading claim was finally eliminated, the company had switched to a new, often

Hart, and Long)(1962); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 170; Hearings on Administered Prices in the Drug Industry before the Antitrust and Monopoly Subcommittee to the Senate Judiciary Committee, 86th Cong. pt. 14 at 8139 (testimony of Dr. Louis Lasagna)(newer steroids have more side effects than older ones, including growth suppression in children);

¹⁰ *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, supra, (1962), at 215 (testimony of Dr. Martin Cherkasky)(drug marketed to pregnant women even after it was shown to produce birth defects); *id.* at 504-05 (Statement of Miles Robinson, MD)(three powerful anti-psychotics with severe side effects, Librium, Mellaril, and Thorazine, promoted for minor tension and anxiety and for pregnant women);

¹¹ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 66-68, 72 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); *id.*, at 113 (statement of Dr. Harold Book, Dir. Of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Grad. School of Med., U. Penn.); *False and Misleading advertising (Prescription Tranquilizing Drugs)*, Hearing Before a Subcommittee of the Committee on Government Operations, supra, at 117 (Statement of Dr. Ian Stevenson, Chairman, Department of Neurology and Psychiatry, U. VA)(study of drug ads showed consistent, but subtle deceptions: inflating the quality of cited data, exclusive reliance on unpublished data, use of findings taken out of context, failure to report negative data, emotional appeals through use of images); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 165-187 (studies of drug ads showed variety of misleading techniques, including use of testimonials, understatement or omission of unfavorable evidence, use of false associations and irrelevant facts, and publication of studies written by drug companies under the name of an independent physician).

equally misleading claim.¹²

- “Educational” efforts by detailmen, widely used by the pharmaceutical companies to promote products out of sight of regulatory scrutiny, and relied on more heavily by physicians than any other source of drug information, were misleading physicians about the true merits of prescription drugs;¹³
- In the absence of an effectiveness requirement, manufacturers rarely carried out adequate effectiveness tests of their products;¹⁴

¹²*Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, supra, at 63 (statement of Abraham Ribicoff, Secretary of HEW); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 171 (statement of Abraham Ribicoff, Secretary of HEW); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, supra, at 463-64 (statement of Andrew J. Biemiller, Director, Dept of Legislation, AFL-CIO, and former Congressman)(FTC’s attempts to correct false advertising of Doan’s pills took several years); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 66-68, 71 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 102-103 (statement of Dr. Harold Book, Director of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Graduate School of Medicine, University of Pennsylvania); *False and Misleading advertising (Weight Reducing Preparations)*, Hearing Before a Subcommittee of the Committee on Government Operations, supra, at 42 (Statement of Maye Russ, National Better Business Bureau); *id.* at 197-212 (FTC table showing lengthy period of time between initiation of investigation of deceptive claims and final cease and desist orders).

¹³*Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, supra, at 211-212 (testimony of Dr. Martin Cherkasky); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 80(statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health, citing AMA opinion survey of physicians); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 190-198 (drug company promoted chloramphenicol through detailmen for broad uses despite risk of aplastic anemia, misrepresenting official FDA/NRC warnings).

¹⁴ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 105-106 (statement of Dr. Harold Book, Dir. Of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Grad. School of Med., U. Penn.); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 203, quoting Dr. Louis Lasagna,

“Adequately controlled comparisons of these drugs are almost impossible to find”;

- It was impossible for physicians to ascertain which drugs were effective for their claimed uses because of the large number of drugs being introduced, misleading advertising, the absence of adequate effectiveness testing, the fact that the evidence, if there was any, was either unpublished or scattered through hundreds of medical journals, and the lack of time and training most physicians have to devote to the study of detailed clinical reports;¹⁵
- There was no reliable source of information to which physicians could turn when trying to assess the effectiveness of a drug;¹⁶ and
- Huge expenditures on promotion and on development of minor modifications of existing drugs left little room for development of new drugs for significant health problems.¹⁷

id., at 187, quoting Dr. Dowling,

“a number of drugs have been put on the market with efficacy claims based on extremely meager and unobjective observations”;

id. at 176-7, quoting Dr. Frederick Meyers,

“Much of what passes as clinical investigation . . . is really an effort to get the drug used in a medical center before general release, to get a physician of some influence to use the drug as part of a clinical trial...”

¹⁵S. Rep. No. 1744, *supra*, Pt. 1, at 37; *Administered Prices, Drugs*, S. Rep. No. 448, 87th Cong., 1st Sess., *supra*, at 171; 108 Cong. Rec. 19,925-19,926 (1962); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 222-23 (testimony of Dr. Martin Cherkasky); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 76 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at 204 (“as was repeatedly emphasized during the hearings, detailed clinical reports tend to be perused carefully only by the specialists in the field.”)

¹⁶*Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 73 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); Committee on the Judiciary, *supra*, at 173 (statement of Abraham Ribicoff, Secretary of HEW, quoting from JAMA article by Dr. Isaac Starr); *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at 187.

¹⁷ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 60-62 (Statement of Sen. Kefauver, quoting Senate testimony of Dr. Henry Dowling:

“Under the present system, a successful pharmaceutical company works at a frenetic pace to produce slight modifications of existing drugs to keep abreast of its competitors. . . the money spent on discovering, developing, and promoting these drugs is largely wasted. This money could be better spent in looking for truly new drugs.”);

A later review by the National Academy of Sciences of drugs on the market before 1962 showed that Congress's concerns about widespread promotion of ineffective drugs were more than justified. Over 80 % of the uses for which drugs were promoted before 1962 were found to lack adequate evidence of effectiveness. One third of all drugs (1,099 of 3,443) on the market in 1962 could not be shown to be effective for a single indication and were taken off the market. These included widely promoted drugs that were among the top 200 in sales.¹⁸ A large percentage of the remaining drugs lost one or more of the indications for which they had been previously marketed.

2. Specific Examples of Harm

The hearings leading up to the enactment of an effectiveness requirement identified several specific types of harm to which Americans were being daily subjected from this tide of ineffective and over-promoted drugs. One was promotion of toxic drugs for uses for which the drugs' benefits did not outweigh their risks. For example, the antibiotic chloramphenicol (Chloromycetin) was widely promoted for a wide range of uses, from life-threatening to minor infections. When cases of aplastic anemia, a serious, sometimes fatal blood disorder, were shown to be caused by chloramphenicol, FDA required the company to include warnings in the drug's label and both FDA and the AMA recommended that the drug's uses be restricted. These warnings about serious and even fatal adverse reactions failed to slow demand, however. Documents provided in Congressional hearings showed that detailmen continued to promote the drug as effective for a wide range of uses and to downplay the warnings, resulting in widespread use of the drug for minor infections, and an unnecessary toll of serious adverse reactions and deaths.¹⁹

Congress heard testimony that drug companies promoted tranquilizers for every type of psychological distress from serious depression to mild anxiety, and added them to a variety of other drugs, from heart disease medications to gastrointestinal drugs.²⁰ Even mild tranquilizers can be addictive, while many others cause serious, often irreversible side effects. Tranquilizers were later shown to be ineffective in all of the combination products and unsafe or ineffective for most of the remaining uses for which they were promoted. Thus, consumers were subjected to serious injuries that outweighed any possible benefit.

S. Rep. No. 1744, Drug Industry Act of 1962, 87th Cong. 2d Sess. 48 (1962).

¹⁸FDA Talk Paper, "DESI Drug Review for Effectiveness is Concluding," Sept. 17, 1984.

¹⁹ *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at 192-98.

²⁰ *False and Misleading Advertising (Prescription Tranquilizing Drugs)*, Hearings Before a Subcommittee of the Committee on Government Operations, House of Representatives, 85th Cong. 2d Sess. (1958).

Some of the widely promoted tranquilizers were in fact powerful anti-psychotic drugs with side effects so severe they are now used only for the treatment of serious mental illnesses like schizophrenia and manic-depression. Librium, a drug now reserved for manic-depression, was advertised for the pregnant woman "who imagines that she is having birth pains 6 months ahead of her time," and for the "surgical patient who sees doom in the frown of a nurse."²¹ An ad for Thorazine, now reserved for schizophrenia, in the Maryland State Medical Journal for July 1962 showed "a beautiful picture of a happy family, with the caption-

'Emotional control regained*** a family restored *** thanks to a doctor and Thorazine *** Experience in over 14 million Americans *** A fundamental drug in both office and hospital practice.'"²²

Thorazine was already known to cause agranulocytosis, a depletion of white blood cells that is frequently fatal. One expert testified that he had personally seen 11 cases of agranulocytosis and 4 deaths from over-prescription of Thorazine.²³

Mellaril, now a drug of last resort for schizophrenia because of its severe side effects, including sudden death, was widely promoted to general practitioners for pregnant women with emotional symptoms in connection with childbirth, and "tense, nervous patients seen in everyday practice * * * for chronic fatigue, insomnia, anxiety, and apprehension, vague digestive disorders, etc."²⁴ An expert testified that he was "impressed with that 'etc.' It just tapers off into the wide, blue yonder where tranquilizers are claimed to be good for everything."²⁵ Both Thorazine and Mellaril also cause tardive dyskinesia, a serious and sometimes irreversible movement disorder, in which the patient suffers from involuntary and disfiguring movements of the face, tongue, and neck. The severe risks associated with these drugs could never justify their use for such minor conditions as everyday tension or insomnia, and yet that is exactly what they were promoted for in a setting where there was no effectiveness requirement for each promoted use.

²¹ *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 504 (Statement of Miles Robinson, MD).

²² *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 505 (Statement of Miles Robinson, MD).

²³ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 105 (Statement of Dr. Harold Book, Dir. Of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Grad. School of Med.)

²⁴ *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 505 (Statement of Miles Robinson, MD).

²⁵ *Id.*

These examples illustrate the public health damage that results from a system that approves medical products for safety but not effectiveness, or that permits promotional claims about uses for which the product has not been demonstrated to be effective to regulators. Because drugs have potentially serious risks, a drug can be considered safe only when its risks are outweighed by its benefits for particular uses. A drug with significant side effects may be considered safe if it is known to be effective in the treatment of a serious condition, but may be unacceptably harmful for a minor condition or even for another serious condition when the drug's benefits for that condition have not been established. Because safety and effectiveness are inextricably related, it is meaningless to say that a drug is "safe" except in relation to a specific demonstrated benefit. Almost no drug can be considered safe for uses for which it has no demonstrated benefits.²⁶

There were also examples of ineffective drugs promoted for serious conditions, where other treatments were available. Deprol, a tranquilizer was promoted to general practitioners for all types of depression, including serious depression. A psychiatric expert testified that there was no evidence that Deprol was effective for depression, and that the vigorous promotion of Deprol caused him deep concern about the fate of depressed patients seen by general practitioners.²⁷ The Secretary of Health, Education, and Welfare testified about the widespread promotion of Clarin for heart disease, despite an AMA determination that the drug lacked effectiveness.²⁸

A final example illustrates the grave harm that can befall patients when drugs do not have to be shown to be effective before marketing. In the 1940's and 50's, diethylstilbestrol (DES) was widely promoted to prevent threatened spontaneous abortion (miscarriage). Because DES was considered safe and effective, it was also prescribed for normal pregnancies. It has been estimated that between 5 and 10 million American women received DES before FDA issued a warning against its use in pregnant women in 1971.²⁹ In 1970, evidence began to accumulate that exposure to DES *in utero* caused a high rate of reproductive abnormalities in the daughters and sons of women given DES, including hundreds of cases in girls and young women of a rare

²⁶ *Administered Prices, Drugs*, S. Rep. No. 448, 87th Cong., 1st Sess., supra, at 189-90 (testimony of Dr. Barbara Moulton).

²⁷ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 62 (Statement of Dr. Freyhan).

²⁸ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 173 (Statement of Abraham Ribicoff, Secretary of HEW).

²⁹ Guiusti RM, Iwamoto K, Hatch EE. Diethylstilbestrol revisited: A review of the long-term health effects. *Ann Intern Med* 122:778-788, 1995.

form of vaginal cancer previously found only in elderly women.³⁰ Among the reproductive injuries caused by DES, daughters of women who took DES have an increased rate of premature births, casting the shadow of DES toxicity over the next generation.³¹ Perhaps the greatest tragedy of DES is that years after it was first marketed, an independent study showed that it was completely ineffective for preventing miscarriages.³² Even after this study was published, the drug continued to be prescribed for pregnant women.³³

Had there been an effectiveness requirement in place when DES was introduced, thousands of men and women would have been spared the serious, sometimes fatal injuries caused by the drug. Of course the terrible side effects of the drug were not known at the time the drug was prescribed. But that is the nature of drugs: as countless examples demonstrate, their true toxicity is often not known until many thousands or millions of people have been exposed. Knowing this to be true, it is unconscionable to expose patients to drugs without a well-established benefit for each promoted use.

3. Unsubstantiated Promotional Claims Shown to be Inherently Misleading

The evidence accumulated by Congress before passage of the 1962 Amendments to the FDCA demonstrated that, without benefit of pre-market review of a drug's effectiveness by an objective body, it was simply not possible for most physicians to discern which products were effective and which were not. Three features of the pre-1962 scheme caused promotional claims about unproven uses to be considered inherently misleading: (1) physicians relied heavily on promotional information from manufacturers, much of which was misleading; (2) what reliable, objective evidence existed was difficult or impossible for average physicians to find because they were too busy to track down scattered, often unpublished data on hundreds of new drugs; and (3) in the absence of required testing, few, if any, companies conducted the kind of studies that would provide reliable evidence of their products' effectiveness.³⁴ In this setting, only academic

³⁰ *Id.*; Hatch EE, Palmer, JR, Titus-Ernstoff L, Noller KL, et al. Cancer risk in women exposed to diethylstilbestrol *in utero*. *JAMA* 280:630-634, 1998.

³¹National Cancer Institute, NIH, DES Research Update 1999: Current Knowledge, Future Directions, Meeting Summary. July 19-20, 1999.

³²Dieckmann WJ, Davis ME, Rynkiwicz LM, Pottinger RE, Does the administration of diethylstilbestrol during pregnancy have therapeutic value? *Am J Obstet Gynecol* 66: 1062-1081, 1953.

³³ National Cancer Institute, NIH, DES Research Update 1999: Current Knowledge, Future Directions, Meeting Summary. July 19-20, 1999.

³⁴S. Rep. No. 1744, supra, Pt. 1, at 37, 39 (Views of Senators Kefauver, Carroll, Dodd, Hart, and Long); *Administered Prices, Drugs*, S. Rep. No. 448, 87th Cong., 1st Sess., supra, at

specialists had the knowledge and time to ferret out the truth about drug products within their specialities.³⁵ Even then, there were few, if any, definitive studies on the effectiveness of marketed drugs, leaving the experts to guess which drugs were effective and which were not.³⁶

In the world envisioned by the May 16 notice, physicians are somehow able to make rational prescribing decisions based primarily on promotional material from manufacturers and in the absence of access to well-designed, objective studies of effectiveness. As the Secretary of HEW testified in 1962, however, it is meaningless to say that a physician should have the right to decide for himself whether a drug is effective, unless “truthful and complete information” about the effectiveness of a drug is available to any physician in the ordinary course of practice.³⁷ The marketplace as it existed before there was an effectiveness requirement provided neither. For most physicians, “truthful” information was impossible to separate from misleading information, and “complete information” was almost never available.

Truthful information was impossible to separate from misleading information because promotional material cited scientific evidence in ways that made harried physicians believe they had adequate information to make prescribing decisions. One expert testified about the “exceedingly subtle” methods employed in promotional material to convey the impression that claims were supported by scientific evidence, when, in fact, there was no little or no support for the claims. He provided a representative ad that cited seven references to demonstrate the

171; 108 Cong. Rec. 19,925-19,926 (1962); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, supra, at 222-23 (testimony of Dr. Martin Cherkasky); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 76 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); *False and Misleading advertising (Prescription Tranquilizing Drugs)*, Hearing Before a Subcommittee of the Committee on Government Operations, supra, at 123-24 (Statement of Dr. Ian Stevenson, Chairman, Department of Neurology and Psychiatry, U. VA)(physicians could not assess the effectiveness of a drug based on their own clinical practices or historical use).

³⁵ *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 204 (“as was repeatedly emphasized during the hearings, detailed clinical reports tend to be perused carefully only by the specialists in the field.”)

³⁶ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 105-106 (statement of Dr. Harold Book, Dir. Of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Grad. School of Med., U. Penn.); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 203, quoting Dr. Louis Lasagna; *id.*, at 187, quoting Dr. Dowling.

³⁷ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 173 (statement of Abraham Ribicoff, Secretary of HEW).

scientific support for the advertised claims. When the expert took the time to look into these references, not one could be shown to support the claims in the ad. The first and third cited studies were "in press" and unavailable for review, the second study was uncontrolled and its results had been distorted in the ad, the fourth study was clearly misrepresented, and the fifth, sixth, and seventh references were "personal communications" with the company and unavailable for review.³⁸ The expert also presented data on a larger review of prescription drug advertising which showed that the problems seen in his example were commonplace. In addition, he found that (1) negative studies (studies that failed to show that the drug worked) were never reported in promotional material; (2) data were presented as if they were of high scientific quality when in fact they were not; (3) studies cited were frequently from low quality or foreign publications; and (4) statements and findings in studies were taken out of context.³⁹ Many other experts testified that promotional material appeared to provide scientific support that was in fact lacking, but in ways that would be difficult for the average physician to detect.⁴⁰

Hearings on advertising of over-the-counter drugs showed that promotion to consumers was at least as misleading as that to physicians.⁴¹

Where the evidence showed that physicians and consumers had no access to objective information about the effectiveness of drugs and neither the time nor the knowledge to pin down the truthfulness of promotional material, it was entirely appropriate for Congress to consider such material inherently misleading.

4. Other Restrictions Shown to Be Inadequate to Prevent Harm

The notice suggests that rules against false and misleading claims and/or disclaimers

³⁸ *False and Misleading advertising (Prescription Tranquilizing Drugs)*, Hearing Before a Subcommittee of the Committee on Government Operations, *supra*, at 117 (Statement of Dr. Ian Stevenson, Chairman, Department of Neurology and Psychiatry, U. VA).

³⁹ *Id.*

⁴⁰ *Administered Prices, Drugs*, S. Rep. No. 448, *supra*, at 165-187 (studies of drug ads showed variety of misleading techniques, including use of testimonials, understatement or omission of unfavorable evidence, use of false associations and irrelevant facts, and publication of studies written by drug companies under the name of an independent physician).

⁴¹ *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at p. 461 (Statement of Andrew J. Biemiller, Director, Dept of Legislation, AFL-CIO, and former Congressman); *False and Misleading advertising (Prescription Tranquilizing Drugs)*, Hearing Before a Subcommittee of the Committee on Government Operations, *supra*, at 37-41 (Statement of Maye Russ, National Better Business Bureau).

could provide adequate protection to consumers from dangerous and deceptive products, and that prohibiting promotion of unapproved uses is therefore unconstitutional. To the contrary, Congress had more than enough evidence to find that neither of these methods could protect consumers.

When Congress imposed effectiveness requirements on drugs and devices, it had abundant evidence that a rule against false and misleading advertising coupled with post-market enforcement actions was ineffective in protecting consumers from harm. As described above, the major thrust of five years of hearings was a demonstration that this very regulatory regime failed to stop the promotion of deceptive and dangerous products.⁴² As one public health expert testified:

“It is not sufficient to say that some law in some book presently forbids some of these practices. Long before governmental authorities are in a position to prove the illegality of these practices and get the cumbersome legal machinery into motion and remove the drug from the market, grave harm has been done.

"This evil can only be remedied, we believe, in a fair and practical way by putting the burden where it belongs, on the manufacturers of these potent drugs, by requiring them to demonstrate the efficacy and safety of their products.”⁴³

⁴² *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 63 (statement of Abraham Ribicoff, Secretary of HEW); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 171 (statement of Abraham Ribicoff, Secretary of HEW); *Drug Industry Act of 1962*, Hearings before the House Committee on Interstate and Foreign Commerce, *supra*, at 463-64 (statement of Andrew J. Biemiller, Director, Dept of Legislation, AFL-CIO, and former Congressman)(FTC’s attempts to correct false advertising of Doan’s pills took several years); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 66-68, 71 (statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 102-103 (statement of Dr. Harold Book, Director of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Graduate School of Medicine, University of Pennsylvania); *False and Misleading advertising (Weight Reducing Preparations)*, Hearing Before a Subcommittee of the Committee on Government Operations, *supra*, at 42 (Statement of Maye Russ, National Better Business Bureau); *id.* at 197-212 (FTC table showing lengthy period of time between initiation of investigation of deceptive claims and final cease and desist orders).

⁴³ *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, *supra*, at 66-8 (Statement of Dr. Leona Baumgartner, Commissioner, New York City Department of Health).

The Secretary of HEW, too, testified that the absence of an effectiveness requirement left consumers unprotected from harmful products and that reliance on post-market actions against misleading advertising had proven itself to be “indefensible”:

"Even if the FDA has reason to believe that [a] new drug is not effective for the purposes claimed, it must approve the new drug application once the requirements of safety have been met. Then the manufacturer is at liberty to promote his product. If claims for effectiveness are made which the FDA believes are groundless, a proceeding must then be brought to take the drug off the market as a misbranded product. At that point the burden of proof is on the FDA to establish that the drug is not effective. And throughout the period of time it takes for the FDA to prepare its case and secure relief in the courts, the manufacturer will have foisted his product upon an unsuspecting public.

". . . . We believe that where public health is involved it is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse game where a manufacturer can fool the public until the Food and Drug Administration finally catches up with him."⁴⁴

The May 16 notice also suggests that disclaimers might be adequate replacements for a demonstration of safety or effectiveness. The record before Congress is more than sufficient to demonstrate the fallacy that disclaimers can broadly protect consumers from unsafe and ineffective products to improve health. A disclaimer could take many forms, but the two most obvious forms are (1) a required statement that the government has not reviewed the claim; and (2) a statement created by the manufacturer ostensibly providing adequate information for a consumer to assess the weight of the evidence supporting a claim, e.g., “some studies suggest that this product is effective while others are inconclusive.” In a variation of the second type of disclaimer, FDA might issue a regulation specifying types of information that must be in a disclaimer or specifying other details of presentation. The drafting of specific disclaimers would still be the responsibility of the manufacturer, and, in absence of pre-market review of claims, FDA would still be required to initiate an enforcement action if it believed the disclaimer violated the regulation or was otherwise misleading.

The first type of disclaimer would provide precisely the information known to every physician before 1962: at that time, as everyone knew, the government did not review the effectiveness of drugs. This knowledge, however, did not in any way assist physicians in determining which products would help their patients and which would not, because that information was generally unavailable. Thus, a disclaimer stating that a claim had not been reviewed by FDA would provide no useful information to a physician about whether to prescribe the drug and would offer her patients no protection from unsafe or ineffective products, or from

⁴⁴ *Drug Industry Antitrust Act of 1962*, Hearings Before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 173 (Statement of Abraham Ribicoff).

the harm that can flow from such products (described in detail above).

The second type of disclaimer relies on the manufacturer to disclose the true state of the scientific evidence supporting a claim. As the record before Congress amply demonstrated, in the absence of pre-market safety and effectiveness requirements, many companies fail to conduct adequate tests of their products' safety or effectiveness.⁴⁵ Once again, when there is little or no reliable evidence to support a claim, a disclaimer, no matter how truthful, cannot help physicians determine which products will provide treatment for their patients and which will not. The harm that flows from a marketplace in which there is no reliable evidence on the effectiveness of the products physicians must prescribe for their patients was described in great detail in the Congressional hearings preceding the 1962 Amendments to the FDCA.

Moreover, both those hearings and subsequent hearings on drug advertising repeatedly showed that, in the absence of government review, many companies fail to provide, in promotional material, an objective presentation of the evidence supporting their products.⁴⁶ There is ample evidence that information provided to doctors by pharmaceutical companies continues to lack objectivity.⁴⁷ There is no more reason to expect these companies to provide a truthful, non-misleading disclaimer than there is to expect that the promotional claims themselves will be truthful and non-misleading.

⁴⁵ *Elixir Sulfanilamide*, S. Doc. 124, 75th Cong., 2d Sess. (1937); *Drug Industry Antitrust Act of 1962*, Hearings before the Antitrust Subcommittee of the Committee on the Judiciary, supra, at 105-106 (Statement of Dr. Harold Book, Director of Laboratories at Norristown State Hosp., and Assistant Professor of Neuropathology in the Graduate School of Medicine, U. Penn.); *Administered Prices, Drugs*, S. Rep. No. 448, supra, at 203, quoting Dr. Louis Lasagna; *id.*, at 187, quoting Dr. Dowling; *id.* at 176-7, quoting Dr. Frederick Meyers.

⁴⁶ *Competitive Problems in the Drug Industry*, Summary and Analysis of Hearings Before the Select Committee on Small Business, Subcommittee on Monopoly, United States Senate, 92d Cong. 2d Sess. (1972).

⁴⁷See, e.g., Dr. Gutknecht, *Evidence-Based Advertising? A Survey of Four Major Journals*, *Journal of the American Board of Family Practice*, 197-200 (May-June 2001) ("Descriptions of research in pharmaceutical advertisements were brief and incomplete, and they inconsistently provided the basic design and statistical information needed to judge the results reported."); M. Wilkes, B. Doblin, M. Shapiro, *Pharmaceutical Advertisements in Leading Medical Journals: Experts' Assessments*, *Annals of Internal Medicine*, 912-9 (June 1, 1992) ("In 44% of the cases, reviewers felt that the advertisement would lead to improper prescribing if a physician had no other information about the drug other than that contained in the advertisement.").

5. Permitting Promotion of Unapproved Uses Eliminates the Incentive to Establish Effectiveness

One possible interpretation of the May 16 notice is that the current FDA leadership believes that there is a sufficient basis to require manufacturers to establish the safety and effectiveness of the first use of a new product, but that, after the first approval, manufacturers should be free to promote additional uses of their products without FDA approval. The legislative history of the 1962 Amendments to the FDCA and the statute itself could not be clearer that Congress intended manufacturers of drugs to establish the effectiveness of each new use before marketing.⁴⁸ Nevertheless, the May 16 notice questions this statutory requirement and asks for evidence that permitting manufacturers to promote unapproved uses would undermine the requirement that they obtain approval for these uses. Not only is it abundantly clear that permitting promotion of unapproved uses would undermine the requirement that these uses be approved, but the legislative history recited above provides ample evidence of the harm that flows from unrestricted promotion of products for new unapproved uses.

First, the legislative history shows that when products can be promoted for unapproved uses, manufacturers frequently advertise them for uses that are unsubstantiated, for uses that do not justify the risks posed by the drugs, and for uses for which older drugs are more effective. Promotion of unapproved uses has been shown to subject patients to serious side effects without corresponding benefits and to denial or delay of effective treatment. See sections II.B.1 and 2, above. The evidence adequately demonstrates that neither post-market enforcement actions nor disclaimers can protect patients from these consequences of promotion of unapproved uses. See section II.B.4. For these reasons alone, Congress had adequate evidence to conclude that a prohibition on promotion of unapproved new uses was necessary to alleviate real harm, and that lesser restrictions were inadequate to address the harm.

Second, it is clear that permitting products to be promoted for unapproved uses would undermine the requirement that new uses be approved. We believe that it is self-evident that many, if not most, manufacturers of new medical products permitted to promote freely their products for unapproved uses would decide, on economic grounds, not to undertake the considerable and unnecessary expense of obtaining FDA approval for new uses. Gaining the right to promote new uses is the only substantial incentive manufacturers have to obtain FDA approval.

Even if it were not self-evident, the pre-1962 marketplace provides a sufficiently revealing model of whether, when permitted to promote freely their products for any use, manufacturer undergo the expense of conducting adequate and well-controlled studies (the standard for FDA approval) of their products' effectiveness. Many, if not most, do not. See

⁴⁸S. Rep. No. 1744, *supra*, Pt. 1, at 17; Conf. Rep. No. 2526, 87th Cong. 2d, at 22-23 (1962); 21 U.S.C. 321(p) and 355(d).

section II.B.1. As the post-1962 NAS/NRC review of the effectiveness of marketed drugs showed, 80% (4 out of 5) of the uses for which drugs were promoted were not supported by reliable evidence of effectiveness. Thus, the long-standing prohibition against promotion of unapproved new uses is an adequately justified restriction on commercial speech.

6. Biological products, medical devices, and foods promoted to treat disease.

The evidence of harm from unrestricted promotion of drugs applies equally to other medical products and to foods promoted for treatment of disease. The pre-1962 hearings showed how manufacturers of prescription drugs behave where there is no requirement that they establish the effectiveness of each use of their products: many of them engage in deceptive promotion of products whose effectiveness has not been established and whose risks outweigh their benefits. Manufacturers of medical devices and biological products market products with identical purposes and market them to precisely the same audiences as drug manufacturers. Their incentives to promote truthfully or deceptively are the same as those of drug manufacturers.⁴⁹ Food manufacturers who seek to promote their products to prevent or treat diseases have similar incentives. The only significant difference between food manufacturers who promote their products to prevent or treat disease and drug manufacturers is that food manufacturers promote primarily to consumers, an audience with less ability than physicians to weigh the scientific evidence supporting claims.

The evidence from the prescription drug marketplace that Americans are harmed by promotion of products that have not been approved for effectiveness is therefore applicable to biological products, medical devices, and foods. The evidence that post-market enforcement actions and disclaimers cannot protect consumers from harm is equally relevant.

III. Conclusion

Our country's long-standing requirements that medical products be shown to be safe and effective before marketing are well-justified. They are supported by decades of experience and thousands of pages of Congressional documents showing the grave harm to the public health that follows unrestricted promotion of health-related products.

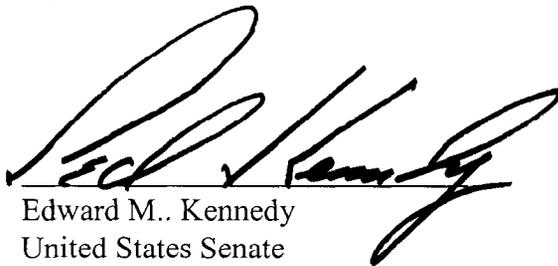
The May 16 notice suggests that FDA would like to cease enforcing many of the

⁴⁹ The evidence before Congress when it enacted safety and effectiveness requirements for devices under the Medical Device Amendments of 1976 confirmed that without restrictions on promotion of unapproved products and uses, the medical device marketplace is filled with ineffective products, products that have been inadequately tested, and products whose risks outweighed any demonstrated benefits. *Medical Devices*, Hearings Before the Subcommittee on Public Health and Environment of the House Committee on Interstate and Foreign Commerce 93rd Cong., 1st sess. (1973).

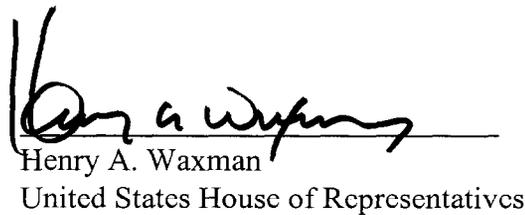
promotional restrictions of the FDCA. The agency is apparently contemplating this action because its current leadership believes that under the First Amendment, the only way that the agency may protect the public health is to trust the pharmaceutical industry not to make deceptive or dangerous promotional claims about its products. This conclusion is unsound as a matter of law, and disastrous as a matter of public policy. If there has been any lesson that we have learned in the last year from the accumulation of corporate accounting scandals, it is that even some of the largest and most successful corporations in America are capable of abusing the public trust. When corporate wrongdoers placed short-term profits ahead of the truth in accounting, millions of Americans lost their jobs and their savings. If we remove some of our most important requirements on promotion of products to improve health, and corporations do not live up to their obligation to promote them objectively and truthfully, many Americans could lose their lives.

In conclusion, the detailed record of past abuses by those marketing products to improve health is more than sufficient to justify the constitutionality of the current protections. These restrictions were enacted to prevent repetition of real harm to American lives and were based on evidence that lesser restrictions had failed to prevent these harms. FDA has no basis under the First Amendment for failing to enforce the current limitations on promotion of health-related claims. No further action on the May 16 notice should be taken until FDA has a Congressionally confirmed Commissioner with adequate qualifications to make decisions of this importance to the public health.

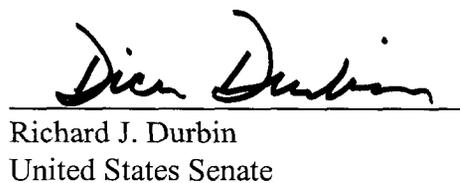
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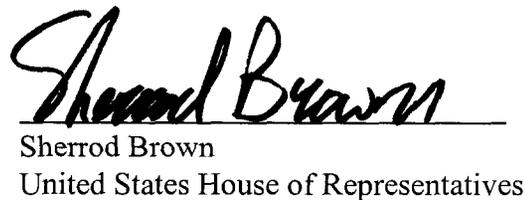
Edward M. Kennedy
United States Senate



Henry A. Waxman
United States House of Representatives



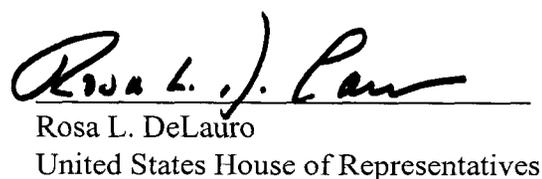
Richard J. Durbin
United States Senate



Sherrod Brown
United States House of Representatives



Charles Schumer
United States Senate



Rosa L. DeLauro
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Louise M. Slaughter

Louise Slaughter
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Marcy Kaptur

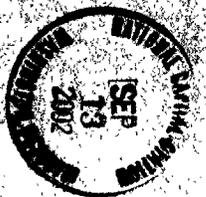
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