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Pharmaceuticals: The Battle for Control in the 21st Century

Rachel F. Ochs

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PHARMACEUTICALS: THE BATTLE FOR CONTROL IN THE 21ST CENTURY

RACHEL F. OCHS¹

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I. INTRODUCTION

The Japanese government has targeted the pharmaceutical industry for expansion and world domination within the next twenty years.² Although the United States (US) still enjoys world leadership in this \$130-160 billion dollar industry,³ commentators warn that we should not become complacent.⁴ The US, seemingly an unbeatable giant in the electronics and automotive industries, lost a significant share of these markets to the Japanese; Japanese manufacturers warn that the pharmaceutical market is next.⁵

The Japanese have already started their entry into the pharmaceutical market. They have implemented stricter controls so that their new drugs will meet Food and Drug Administration (FDA) requirements for marketing in the US, and most importantly the Japanese government, unlike the US, is supporting substantial funding for research to produce effective new drugs.⁶

The focus on the pharmaceutical market makes financial sense. While the US accounts for forty percent of the world pharmaceutical market,⁷ Japan is the second largest user of prescription drugs.⁸ In Japan, profits from pharmaceuticals continue to grow on an annual basis. Additionally, both US and Japanese pharmaceutical companies are expanding abroad.⁹ Mergers and

²Quote from Tomonori Miki, Executive director of Anyo Co.: "we may be heading toward a pharmaceutical war;" the author predicts that Japan will be a world class player in 15 years: "the way the industry is gearing up its R&D [Research and Development] engine and looking hungrily at overseas markets is faintly reminiscent of the auto industry 40 years ago." Takayuki Yamamoto, *Japan's Drug Makers - Tomorrow's Trade Warriors*, TOKYO BUS. TODAY, July 1994, at 35.

³Kathleen LaFrancis Popper & Robert Nason, *The Drug Lag: A 20 Year Analysis of Six Country Markets*, 13 J. PUB. POLY & MARKETING 290 (1994) (The global pharmaceutical industry had an estimated worth of \$130-160 billion in 1988). See also EC, U.S. and Japan Sign Commitment to Standardize Pharmaceutical Tests, 8 INT'L TRADE REP. (BNA) 1702 (Nov. 20, 1991) (The United States, (US), European Community (EC), and Japan account for seventy-five percent of the world's pharmaceutical market and ninety percent of all pharmaceutical research. The total market is estimated to be worth \$110 billion.)

⁴Irving Mason; *Looking Ahead: Japanese Firms' U.S. Dilemma*, L.A. TIMES, Oct. 24, 1990, at 3.

⁵Teruhisa Noguchi, vice-President of Yamanouchi warns that Japan has already caused trade friction in the car industry. Next, he asserts, they will start a trade war in biomedical products. Yamamoto, *supra* note 2, at 34.

⁶See *infra* § II.B.

⁷FIN. POST, Aug. 23, 1995, at 53.

⁸The US, Japan and the EC account for 75% of the world's pharmaceutical market and generate 90% of all pharmaceutical research. Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations among the United States, the European Economic Community and Japan*, 16 HOUS. J. INT'L L. 665, 667 (1994).

⁹Yamamoto, *supra* note 2, at 35. As of 1993, forty-one of the sixty-six members of the Japanese Pharmaceutical Manufacturers Association (JPMA) member companies

joint ventures are common in both countries¹⁰ as the industry becomes more streamlined in an attempt to maintain high profits in the face of expanding health care costs.¹¹

US actions may either help or hinder Japanese domination of the pharmaceutical market. Although the US has failed to adequately anticipate and defend against Japanese market offenses in the past, the Japanese government has clearly stated its objective to control the pharmaceutical market within the next twenty years. The US government may play a crucial role in maintaining US leadership in the pharmaceutical market in two key areas. First, the US must support the FDA to maintain and enforce a strong pharmaceutical regulatory system. Historically, the US government has both protected the public and contributed to the growth of the pharmaceutical industry by requiring manufacturers to produce safe and effective drugs under the strict regulation of the FDA. Given the unique character of prescription drugs, a recent proposal to deregulate the FDA is misplaced. Neither market forces nor the legal system can effectively protect the public from unsafe or ineffective drugs under deregulation.¹²

Market forces lack the systematic structure and motivation to identify and correct for infrequent adverse events from pharmaceutical drugs. Identifying adverse events requires extensive data collection and analysis because of the difficulty in determining whether infrequent life threatening situations that occur after patients take a pharmaceutical drug result from a chance association between an event and a drug, or occur because the drug caused the adverse event.¹³ The FDA, through extensive regulation, is in the best position to monitor adverse events and to protect the public.¹⁴

Similarly, the legal system cannot protect the public from dangerous pharmaceutical drugs.¹⁵ Instead, courts have contributed to escalating legal costs by inappropriately applying strict liability to pharmaceutical drugs.¹⁶ Excessive liability costs have financially drained the pharmaceutical industry,

had established 245 bases (fifty-four for production) with overseas investments of 310 billion yen. The majority of investments (63%) are in North America; 28% in Europe. *Id.*

¹⁰Milt Freudenheim, *Keeping the Pipeline Filled at Merck*, N.Y. TIMES, Feb. 16, 1992 § 3, at 1 (Merck formed a joint venture Banyu in Japan; 1991 sales were \$800 million or 10% of Merck's worldwide revenue). *Id.* § 3, at 6.

¹¹Health care spending one of the fastest-growing sectors of the federal budget. In 1991 health care was 13.2% of the US budget and 6.6% of the Japanese budget. See Tom Hamburger & Eric Black, *Seeking a Cure*, STAR TRIB., Oct. 25, 1993 (MINN. ST. PAUL).

¹²See *infra* §§ III.B.2 and III.B.3.

¹³See *infra* §§ III.B.2.a and III.B.2.b.

¹⁴See *infra* § III.B.1.

¹⁵See *infra* § III.B.3.

¹⁶See *infra* § III.B.3.a.

forcing companies to remove valuable drugs from the market, and has chilled research by impairing the discovery of innovative new drugs.¹⁷

Stringent FDA standards are also critical to preserve the US public policy to protect the individual in an evolving worldwide market.¹⁸ Japan, the US and the European Community (EC) are attempting to harmonize the regulatory and approval processes for pharmaceutical drugs to provide uniformity in the approval process between their countries. Of these countries, US public policy, through strict FDA regulation, has shown the greatest concern for protection of its citizens from unsafe drugs.¹⁹ The US must support a strong FDA to continue this policy of concern for the safety and welfare of our citizens in a global market. Additionally, the US must promote research to develop innovative new drugs to compete effectively with other countries and to maintain its dominant position as the leader in world pharmaceutical markets.²⁰

To explore these concepts, this paper focuses on the Japanese motivation for taking control in the pharmaceutical industry and efforts that the US can take to ensure its role as a leader in the pharmaceutical industry. First, the paper discusses how Japan is poised to invade the US pharmaceutical market, reasons for Japanese entry into the market, the Japanese focus on research, recent examples of Japanese expansion and how US policy may affect Japanese expansion into the pharmaceutical market. The next section describes the need for the FDA to protect consumer interests in the US since market forces and/or the legal system cannot protect consumers against unsafe or ineffective drugs. The third section discusses both the fallacy of a proposal to deregulate the FDA and the effects of the proposed deregulation on the Japanese penetration of the pharmaceutical industry. Additionally, the need for FDA protection in a global market is stressed. The fourth section deals with the critical role of research to maintain US leadership in the pharmaceutical market. Finally, the fifth section discusses Japanese approaches that the US may adopt to help maintain its leadership position in the world pharmaceutical market.²¹

II. JAPAN IS POISED TO INVADE US PHARMACEUTICAL MARKET

A. Reasons for Japan to Enter the Pharmaceutical Market

The aging world population and the heavy consumption of pharmaceutical drugs make the pharmaceutical market lucrative. Many look to innovative

¹⁷See *infra* § III.B.3.b.

¹⁸See *infra* § III.B.6.

¹⁹See *infra* § III.B.6.d.

²⁰See *infra* § IV.

²¹Although many issues may be relevant to other countries than Japan, the scope of this paper is limited to discussion of US and Japanese pharmaceutical companies and the impact of regulation and underlying public policy.

pharmaceutical drugs as a way to treat and or prevent disease in an effort to contain exploding health care costs. As a result, the world pharmaceutical industry, an estimated \$ 110 billion dollar market in 1991,²² has continued to grow. In 1993, US shipments alone accounted for \$69 billion in sales,²³ while in 1995 the Japanese market accounted for \$50 billion in sales.²⁴ The US, EC, and Japan account for seventy-five percent of the world's pharmaceutical market and ninety percent of all pharmaceutical research.²⁵

Japan has the world's highest per capita consumption of drugs; more than double that of the US or Western Europe.²⁶ In 1988, one commentator hypothesized that the market would grow at a rate of seven percent per year.²⁷ In 1963, Japan spent three percent of its national income for health care; commentators have predicted that that figure will be ten percent by the year 2000.²⁸

Although Japan has the second largest market for pharmaceuticals,²⁹ in the past Japan did not need to export its pharmaceuticals because its government protected their local market. The Japanese government regulated the prices of prescription drugs while the national health service created a stable demand for local pharmaceutical drugs at artificially high prices.³⁰ As a result, Japanese pharmaceutical companies had a poor record in research and development and were slow to exploit lower overseas production costs.³¹ Also, instead of developing new drugs, the Japanese merely copied drugs from other countries.³²

Additionally, until 1984 the Japanese government prohibited foreign companies from operating independently in Japan, further assuring a captive

²²EC, *U.S. and Japan Sign Commitment to Standardize Pharmaceutical Tests*, 8 INT'L TRADE REP. (BNA) 1702, 1702 (Nov. 20, 1991).

²³Melissa Harrington, *Drugs*, U.S. INDUSTRIAL OUTLOOK, 43-1 (1994).

²⁴Roberta Gerry, *An Asia-Pacific market prescription: succeeding in pharmaceuticals in Asia is not easy*, CHEMICAL MARKETING REP., May 22, 1995, at 21.

²⁵EC, *U.S. and Japan Sign Commitment to Standardize Pharmaceutical Tests*, 8 INT'L TRADE REP. (BNA) 1702, 1702 (Nov. 20, 1991).

²⁶Peter Lee, *Today the Friendly Offer, Tomorrow the Hostile Bid*, EUROMONEY, Aug. 1989, at 54.

²⁷Elizabeth Rubinfiel, *Foreign Drug Companies Go It Alone in Japan as Old Partners Become Rivals*, WALL ST. J., Sept. 9, 1988, at 26.

²⁸Lee *supra* note 26.

²⁹*Id.*; Freudenheim *supra* note 10.

³⁰Lee, *supra* note 26.

³¹*Id.* at 9; See also Yamamoto *supra* note 2. Even Japan's largest firm, Takeda Chemical Industries, Ltd, does not rank among the top fifteen companies in the world.

³²Yamamoto, *supra* note 2; (in fact, pharmaceutical products represented one of the few areas where Japan runs a persistent trade deficit).

local market. However, in the early 1980s, the Japanese government faced criticism for the Japanese trade imbalance. In 1984, in an effort to cooperate with the international free trade system in an emerging world economy, the Japanese government allowed foreign companies to go directly to the *Konseisho*³³ for drug approval.³⁴

By 1989, the Japanese government had begun to reduce prices of pharmaceutical drugs and to ease the restrictions for listing new drugs.³⁵ These changes further benefitted foreign firms with more research and development expertise than Japanese firms. With the easing of local restrictions, US and European companies infiltrated the Japanese market, forcing Japanese companies to compete for local markets. Thus, to become a world leader, it is imperative that the Japanese not only deal with competition within Japan, but they must also expand their companies in external markets.

B. Japanese Focus on Research

Japanese firms recognize the need to develop world-class drugs to survive in a global market and are now focusing on both research and development (R&D) and on expansion outside of Japan.³⁶ Japanese pharmaceutical companies recognize that business prosperity depends on the development of breakthrough new drugs and refuse to curtail research to conserve revenues or to capture short term profits at the expense of long term gains.³⁷ Instead, the Japanese are investing heavily in R&D, not only in Japan but in the US and Europe,³⁸ and have increased research expenditures from 11.7 percent in 1980 to 16.8 percent in 1990.³⁹ In fact, two companies, Yamanouchi and Eisai, have developed research institutes dedicated to creating novel drugs.⁴⁰ Efforts directed toward innovative research have paid off; Japanese drugs are now ranked among the world's top ten best selling medications.⁴¹

³³The Japanese equivalent of the U.S. Food and Drug Administration (FDA).

³⁴Mason, *supra* note 4, at 1.

³⁵Lee, *supra* note 26, at 10.

³⁶*Id.*

³⁷*The Japanese Pharmaceutical Industry of Japan*, DAILY NEWS BIOTECHNOLOGY & MED. TECH., May 18, 1995.

³⁸Melissa Harrington, *Drugs*, U.S. INDUSTRIAL OUTLOOK, 43-1 (1994). *See also Japanese Firms should Deploy Own Sales Teams in World Markets*, BIOTECH & MED. TECH., Nov. 9, 1995.

³⁹Kathleen M. LaFrancis Popper & Robert W. Nason, *The Drug Lag: A 20 year analysis of six country markets* 13 J. PUB. POL. & MARKETING 290 (1994).

⁴⁰*Japanese Firms should Jump over 3 Hurdles: Mr. Tanaka of Arthur D. Little*, BIOTECH & MED. TECH., Oct. 30, 1995.

⁴¹Yamamoto, *supra* note 2; (Sanyo's antihyperlipedemic drug Mevalotin and Yamonouchi Pharmaceutical's antiulcer synthetic antibacterial Castar. Additionally, Fugisawa Pharmaceutical's immunosuppressant, Prograf, was used in the world's first

The Japanese government has also supported R&D by awarding substantial price premiums for innovative research so that companies can charge more for new drugs. This incentive has resulted in a significant improvement in research in the Japanese pharmaceutical industry over the past twenty years.⁴² In contrast to the US, where pharmaceutical companies have fewer new compounds than they did in the past, the number of new compounds launched by Japanese firms grew threefold from the late 1970s to the late 1980s.⁴³ Although Japan still lags behind the US in bringing new products to market, Japan now has new capabilities for drug development, including advances in biotechnology.⁴⁴

Recognizing the importance of R&D, the Pharmaceutical Affairs Bureau of Koseisho has also organized a working group for the promotion of new drug development.⁴⁵ According to one commentator, the "way the industry is gearing up its R&D engine and looking hungrily at overseas markets is faintly reminiscent of the auto industry 40 years ago."⁴⁶

C. Recent Examples of Japanese Expansion

Over the past few years, Japanese pharmaceutical companies have expanded into the world market. Between 1988 and 1990, Japanese pharmaceuticals acquired four US concerns.⁴⁷ One reporter in 1989 warned that the Japanese would move aggressively to capture the US pharmaceutical market in the same way that they dominated the US automotive and electronics industries. The author predicted that the Japanese would build hundreds of joint ventures which would then give way to full blown acquisitions.⁴⁸

In addition, Japanese middle managers have gained increasing experience and education in the US, which allows them to move aggressively into US (and European) markets.⁴⁹ The Japanese have steadily established overseas bases through acquisitions and capital participation. As of 1993, forty-one of the sixty-six members of the Japanese Pharmaceutical Manufacturers Association (JPMA) member companies had established 245 bases with overseas

baboon-kidney transplant operation at the request of the University of Pittsburgh).

⁴²*Future of the Japanese Pharma Industry*, MARKETLETTER, Sept. 11, 1995.

⁴³*Id.*

⁴⁴*Id.*

⁴⁵PAB to Form Working Group on New Drug Development Within Council, DAILY NEWS BIOTECHNOLOGY & MED. TECH., July 31, 1995.

⁴⁶Yamamoto, *supra* note 2.

⁴⁷Mason, *supra* note 4, at 1.

⁴⁸*Id.*

⁴⁹*Id.* at 2; See also Lee *supra* note 26, at 10; (Yamanouchi acquired an overseas production plant in Ireland to produce an ulcer compound in an "aggressive white knight" takeover).

investments of 310 billion yen, with the majority of investments in North America (63%) and in Europe (28%).⁵⁰

D. Changes in US Help the Japanese

The restructuring of US and European firms, with raiders breaking up large conglomerates, may open up new opportunities for Japanese firms to pick up the pieces.⁵¹ This would allow Japanese companies to assume their most advantageous position, by acquiring wholly owned US industries complete with manufacturing and sales forces. The Japanese have begun to move in that direction.⁵²

Additionally, changes in pharmaceutical marketing in the US may help the Japanese. Wholesalers now sell directly to Health Maintenance Organizations (HMOs) instead of to drugstores. The HMOs then distribute the drugs, thus decreasing the need for a large sales force in the US.⁵³ Without the impediment of providing an expensive sales force with technical expertise, it will be easier for the Japanese to infiltrate the US market.

Heavy medical equipment manufacturers like Toshiba and Hitachi, which are "muscling into foreign markets," provide a model for Japanese acquisition in the pharmaceutical industry.⁵⁴ Lee, a commentator, asserts that Japanese companies operate by a herd instinct; once a few Japanese companies come into a foreign market, other Japanese competitors will follow. Lee points to similarities between the Japanese entry into the automotive components market and their evolving entry into the US pharmaceutical market.⁵⁵

III. US DEFENSE AGAINST JAPANESE TAKEOVER OF PHARMACEUTICALS

A. Introduction

Japan has dominated certain US markets such as the electronics and automotive industries. Currently the US dominates the pharmaceutical market and enjoys a reputation for producing safe and effective drugs. The US can maintain its position as world leader by; (1) maintaining strong regulation of pharmaceutical drugs to ensure safety and efficacy of US drugs by strengthen-

⁵⁰Yamamoto *supra* note 2; (fifty-four of the bases were established for production; presumably the rest are restricted to sales and/or distribution).

⁵¹Lee, *supra* note 26, at 1.

⁵²Mason, *supra* note 4, at 3.

⁵³*Id.* at 2.

⁵⁴Lee, *supra* note 26, at 11.

⁵⁵*Id.*

ing and reforming the FDA,⁵⁶ and (2) promoting research so that the US can create innovative new drugs to treat disease.

B. FDA is Essential to US Interests

This subsection begins by discussing the policy rationale for the creation of the FDA. Next, it is argued that the FDA, a strong independent regulatory body, is essential to monitor adverse events of drugs because of the inherent difficulty in both; (1) recognizing infrequent adverse events; and (2) in establishing causation between the adverse event and the drug. The FDA provides an essential function because plausible substitutes for the FDA such as market forces and the legal system cannot operate effectively in the pharmaceutical arena for several reasons. First, because of information asymmetry and the infrequency of serious adverse events in this complex field, the public lacks the necessary information to make an informed decision about the safety of a drug. Second, to acquire the data necessary for an informed decision requires extensive data collection and analysis. Such data are not readily available to either the doctors treating patients nor to the public. Third, there is a moral hazard problem. Without FDA regulations, pharmaceutical companies may lack the motivation to recognize and rigorously analyze adverse events, a costly process without any immediate monetary reward. Fourth, the legal system cannot protect the public, but instead has harmed both pharmaceutical companies and the public with its attempt to deal with adverse events. In response to large and unpredictable jury verdicts, pharmaceutical companies have not only removed useful drugs from the market, but have curtailed the development of new drugs with potential liability.⁵⁷

Finally, this subsection concludes by describing the FDA's direct accountability to the public because of legislative and executive control over the agency. Such accountability is lacking in both the market and in the legal system. Those who call for deregulation of the FDA ignore the viable advantageous option to improve the FDA and to thereby preserve the strong US public policy of protecting individuals who do not have adequate information to assess the risk of a product. Additionally, a strong FDA may prevent easy access of Japanese pharmaceutical companies into the US market.⁵⁸

⁵⁶ While reformation of the FDA is of critical importance, suggestions for mechanisms to reform the FDA are beyond the scope of this paper.

⁵⁷ See *infra* § III.B.3.

⁵⁸ See *infra* § III.B.7.

1. FDA Provides Extensive Protection in a Complex Field

a. Approval Process in the US; Role of the FDA

The FDA regulates the approval and monitors the safety of prescription drugs under the Food, Drug, and Cosmetic Act of 1938 (FD&C Act).⁵⁹ Under the FD&C Act, the FDA protects public safety by ensuring that prescription drugs are safe and effective and ensures that the benefits of a prescription drug outweigh its risks.⁶⁰ The FDA fulfills this mission with active control of testing, manufacturing and placing of warning labels on prescription drugs.⁶¹ In addition to the approval process, the FDA conducts on site visits to regulate the compliance of manufacturing plants with proper manufacturing processes. Additionally, the FDA has comprehensive post-market surveillance to ensure the safety and efficacy of licensed medications.⁶² FDA protection of consumers from dangerous prescription drugs is greater than consumer protection from any other marketed product.⁶³

b. History of the FDA Regulatory Process and Public Policy

Before the Federal Pure Food and Drug Act forced manufacturers to label drugs in 1906, consumers could not identify the ingredients of their medications.⁶⁴ Although the 1906 Act forbade false statements about the contents of a drug, it did not regulate either safety or efficacy.⁶⁵ Even with these limitations, the 1906 Act provided the first comprehensive national attempt to regulate drugs by barring adulterated and misbranded products from interstate commerce.⁶⁶

The next major change occurred in 1938 when Congress passed the Food, Drug and Cosmetic Act (FD&C Act)⁶⁷ in response to a national tragedy. The manufacturer of a sulfanilamide elixir (the principle antibiotic of the time), changed the solvent for the antibiotic solution without testing the safety of the new solvent. The new solvent contained impurities which caused over one hundred deaths, which led to public outrage and the subsequent passage of

⁵⁹21 U.S.C. §§ 301-393.

⁶⁰50 Fed. Reg. 7452 (1985).

⁶¹*Id.*

⁶²*Id.*

⁶³*Grundberg v. Upjohn Co.*, 813 P.2d 89.96 (Utah 1991).

⁶⁴David W. Jordan, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND. J. TRANSNAT'L L. 471, 475 (1992).

⁶⁵*Id.* (referring to PETER TEMIN, *TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES* 33 (1980)).

⁶⁶Pure Food and Drugs Act, ch. 3915, 34 Stat. 768 (1906)(subsequently amended).

⁶⁷21 U.S.C. §§ 301-392.

the FD&C Act.⁶⁸ Although the 1938 amendments required manufacturers to perform studies to evaluate safety and toxicity before marketing a new prescription drug, the regulations did not require proof of efficacy.

A new frontier for the FDA followed the passage of the 1962 amendments, when, for the first time, the FDA required that manufacturers prove that new drugs were not only safe but were also effective.⁶⁹ The thalidomide tragedies in Europe triggered Congress to pass the 1962 amendments to the FD&C Act. Babies of pregnant women, who took thalidomide, a sedative used to treat morning sickness, were born with absent or defective limbs.⁷⁰ In response to these tragic results from a nonessential drug, the 1962 amendments required not only proof of safety, but also proof of efficacy through extensive pharmacological and toxicological research. The FDA uses evidence of efficacy in addition to relative safety to determine a risk-to-benefit ratio for pharmaceutical drugs.⁷¹ The amendment also required retroactive proof of efficacy for all new drugs marketed between 1938 and 1962.⁷² Thus, the 1962 amendments greatly expanded the scientific, technical and administrative requirements for approval of new drugs in the United States.⁷³

The next major amendment occurred in 1976. It arose in response to fatal infections caused by the Dalkon Shield, a contraceptive device.⁷⁴ With the increased regulation which followed these serious side effects, the FDA demands the most careful drug safety testing of any regulatory agency in the world⁷⁵ requiring comprehensive monitoring of pharmaceutical drug production and testing.⁷⁶ Public policy has made FDA regulatory control over

⁶⁸Pennington P. Landen, *Federal Preemption and the Drug Industry: Can Courts Co-Regulate?*, 43 FOOD & DRUG COSM. L.J. 85, 96 [hereinafter *Co-Regulation*] (referring to Christopher, *Food and Drug Legislation in the United States: Introductory Comments on its History*, 24 SW. L.J. 403, 404 (1970)).

⁶⁹J. Paul Hile, *The 1960s: A Time of Unparalleled Change*, 45 FOOD & DRUG COSM. L.J. 47, 53 (1990).

⁷⁰Thalidomide was a widely prescribed sleeping pill in Europe. ALFRED GILMAN, ET AL., *GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS* 59 (1991).

⁷¹The ratio depends on the severity of the disease treated; a greater risk of adverse effects is allowed for a more serious illness. *Id.* at 59-60.

⁷²*Id.* at 59.

⁷³Kleinfeld et. al. *Human Drug Regulation: Comprehensiveness Breeds Complexity*, 51 FOOD & DRUG L.J. 242, 245 (1984).

⁷⁴Elixir of Sulfanilamide killed hundreds; thalidomide for morning sickness deformed babies in Europe; the Dalkon shield related infections killed at least eighteen women. FIN. POST, Aug. 23, 1995, at 53 [hereinafter FIN. POST].

⁷⁵*Co-Regulation supra* note 68, at 98 (quoting Stolley, *Assuring the Safety and Efficacy of Therapies*, 4 INT'L J. OF HEALTH SERVICES 131, 142 (1974)).

⁷⁶The Bureau of Chemistry, forerunner of today's Food and Drug Administration (FDA), was part of United States Department of Agriculture (USDA) from 1901-1927. The current process for approval begins with an investigational new drug submission (IND) which allows the FDA to evaluate the chemistry, manufacturing, pharmacology

the approval and distribution of prescription drugs more elaborate and extensive than regulation over any other class of products in our society.⁷⁷

2. Market Not Able to Protect Consumer

a. Information Asymmetry

The FDA provides necessary protection in a field where market control is imperfect due to information asymmetry between manufactures of drugs and the consumer. Although drug testing prior to marketing involves thousands of subjects, adverse reactions often cannot be detected without detailed data collection and analysis. In addition, detection of adverse reactions with a very low frequency may only be possible after a drug is marketed and hundreds of thousands of patients have been exposed to the prescription drug.⁷⁸ Pharmaceutical companies are mandated by the FDA to collect and analyze adverse events and to report their findings to the FDA. The FDA monitors these findings and compares them with the spontaneous reports from physicians and patients who have been exposed to the drug. If the FDA suspects problems with a pharmaceutical drug, it may ask the company to collect demographic data to further evaluate safety or even to remove the drug from the market.⁷⁹

i. Difficulties Identifying and Interpreting Adverse Events

US public policy protects consumers when market forces fail to provide adequate information to allow consumers to make rational and informed

and toxicology of new compounds. (21 U.S.C. § 355(b)(1) (Supp. 1991); 21 C.F.R. § 312.21 (1990)). Once a compound has been studied in extensive clinical trials to evaluate both safety and efficacy, the manufacturer submits a new drug application (NDA) to the agency. The NDA includes detailed summaries of animal and clinical testing, descriptions of adverse reactions, and reports from the world-wide scientific literature. (21 U.S.C. § 355(b) (Supp. 1991); 21 C.F.R. § 314.50 (1990)). Following approval, the FDA continues to monitor the safety of a prescription drug. The company must submit data from any post-marketing studies. Adverse events are reported to the company either from marketed use or during the course of studies conducted in the United States or in any foreign country. In addition, reports from the scientific literature relating to safety and/or efficacy of the prescription drug are submitted to the FDA. (21 C.F.R. §§ 314.80(b), 314.80(c)). Additionally, the FDA may require further clinical testing or Phase IV studies. (21 C.F.R. § 314.85 (1993) (requiring additional information about the risk, benefits and/or optimal use of a drug; studies usually performed by the manufacturer for new indications rather than at insistence of the FDA).) Failure of a company to comply with FDA regulations may result in severe civil and/or criminal penalties. (21 U.S.C. §§ 332-33 (1972 & Supp.1991)). See generally, PETER B. HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW 477-580 (1991).

⁷⁷Grundberg v. Upjohn Co., 813 P.2d 89, 96 (Utah 1991). See also 21 U.S.C. §§ 301-393.

⁷⁸Co-Regulation, *supra* note 68, at 120-21; a new form of tetracycline that later resulted in tooth discoloration in children was introduced in 1959. Lederle, the manufacturer produced an internal memorandum about the discoloration in 1962. The FDA issued a warning letter in 1963.

⁷⁹See *infra* § III.B.1.b.

decisions about product risks. The FDA, through mandatory reporting and analysis of adverse events, not the market, is poised to deal with the problems of emerging adverse events and to protect our population.

To identify adverse effects of prescription drugs, the FDA must differentiate between reports of valid side effects and a multitude of reports that ultimately show no link between the prescription drug and the adverse event. Two types of errors occur. First, serious and unexpected conditions may be too infrequent to be readily detected during clinical trials and may go unnoticed without ongoing monitoring and examination of the correlation between the drug treatment and the adverse event. Second, reports of serious events may not result from drug treatment but instead may be associated with a patient's underlying condition. Without a systematic approach to establish causation of an adverse event by a drug, symptoms unrelated to drugs may erroneously be blamed on an appropriate and effective treatment and lead to the removal of useful drugs from the market.⁸⁰

A prime example of failure to differentiate between the association of a disease with a drug and causation of the disease by the drug is the recent silicon breast implant fiasco. Scientific epidemiological studies have failed to show an increased risk of autoimmune disease in women following silicone breast implantation.⁸¹ Instead of silicone breast implants causing autoimmune disease, a chance association occurs because both occur predominantly in the same population of middle aged women; autoimmune diseases have a peak incidence in middle aged women, and middle aged women represent the largest population with breast implants. Instead of requiring proof that the implants cause autoimmune disease, juries have acted out of sympathy to give plaintiffs large awards, such as the \$14 million recently awarded by a Nevada jury.⁸² As a result, other women are deprived of potentially beneficial treatment with a silicone breast implant following mastectomy for breast cancer. Additionally, some women may delay seeking treatment for breast cancer because they fear disfigurement from surgery and now are also needlessly afraid of an implant.⁸³

⁸⁰See *infra* § III.B.3.c.

⁸¹See, e.g. Jorge Sanchez-Guerrero et al., *Silicone Breast Implants and the Risks of Connective Tissue Diseases and Symptoms*, 332 (25) N.E.J. MED. 1666-70 (1995); John A. Goldman, et. al, *Breast implants, rheumatoid arthritis, and connective tissue disease in a clinical practice*, 48(4) J. CLIN. EPIDEMIOLOG. 571-82 (1995); Frank B. Vasey, *Observation on women with breast implants*, 82 J. FLA. MED. ASSOC. 348-51 (1995).

⁸²Marilyn Lloyd, *The Real Tragedy Behind Silicone Breasts*, CHICAGO TRIB., Nov. 9, 1995 (Marilyn Lloyd is a former member of Congress from Tennessee, a breast cancer survivor and a recipient of silicone breast implants).

⁸³*Id.*

b. Lack of Readily Accessible Information

Spontaneous reporting of adverse events by physicians and patients does not provide adequate data to distinguish between causation and a chance association between an adverse event and drug treatment. Although the FDA spontaneous reporting system has been collecting reports since 1960, the number of reported drug reactions is low.⁸⁴ In addition to spontaneous reports of drug reactions, the FDA requires the systemic collection of reports from physicians, patients and the pharmaceutical industry, and provides an impartial detailed analysis and interpretation of the data.

i. Physicians Lack Sufficient Data to Assess Infrequent Adverse Events

Not only do consumers lack the expertise to appreciate the risks associated with drug treatment, but doctors may also fail to recognize adverse events in their patients. Some contend that physicians fail to report adverse events because they fear involvement in litigation.⁸⁵ More likely, however, physicians fail to recognize an adverse event either because the adverse event is uncommon or because they fail to link the patient's symptoms to a drug reaction. Instead of recognizing a drug reaction, the physician may erroneously assume that an associated illness, and not the drug, is responsible for the patient's symptoms.⁸⁶ Physician training to improve their awareness of potential adverse drug effects has resulted in significant gains in physician reporting of adverse events.⁸⁷ Thus, increased physician awareness is a source of potential improvement in the current reporting system. However, more frequent physician reporting alone is not enough to protect the public. The FDA must also accurately and systematically monitor and analyze massive amounts of data to distinguish causation of symptoms following drug treatment from a mere association between symptoms and the drug.

The need for a central and impartial agency, such as the FDA to monitor drug safety is even more pronounced with the advent of HMOs. Managed care organizations are primarily concerned with the cost-effectiveness of a new drug rather than with safety and efficacy, and may not act as "honest agents" for the patient.⁸⁸

⁸⁴Michael B. Kaufman, et al., *Physician's liability for adverse drug reactions*, 87(8) S. MED. J. 780-84 (1994).

⁸⁵*Id.* at 780.

⁸⁶Linda M. Lucas & C.A. Colley, *Recognizing and reporting adverse drug reactions*, 156 W.J. MED. 172-75 (1992).

⁸⁷H.D. Scott, et al., *Physician Reporting of Adverse drug reactions. Results of Rhode Island adverse drug reaction reporting project*, 263(13) JAMA 1785-88 (1990)(reported a seventeen-fold increase in reports by physicians after two years of training; similar increases were not seen nationally).

⁸⁸FDA Reform and the European Medicines Evaluation Agency, 108 HARV. L. REV. 2009, 2017 (1995)[hereinafter *FDA Reform*].

c. Moral Hazard Problem

Unlike the market or the legal system, the FDA is subject to external controls to regulate its activities. The FDA is under the control of the legislature and the executive branch and through these bodies is responsive to input from the public. Congressional oversight committees also monitor FDA activities. For example, after Senator Orrin Hatch issued a scathing attack on the FDA's approach to dietary supplements,⁸⁹ the FDA responded by modifying its position.

i. Market Lacks Motivation for Regulation

The market presumably regulates inferior or defective products through decreased sales once the public becomes aware of the product's impaired reputation. However, as noted above, physicians and patients are unlikely to recognize adverse events resulting from drugs because they lack the resources necessary to collect and analyze data from large segments of the population. Arguably, the pharmaceutical industry lacks a financial motivation to collect and to publicly report adverse events. Not only is the process time consuming and expensive, but reports of adverse events are likely to result in lost profits. Deregulation with reliance on market forces cannot protect the public. Even with legally mandated reporting of adverse events, estimates show significant under-reporting to the FDA.⁹⁰ Critics clamor for increased FDA vigilance when adverse events occur after drugs are marketed. Despite FDA monitoring and penalties for failure to comply with regulations, some manufacturers fail to adequately inform the FDA of emerging problems.⁹¹ Complaints of under-reporting would be significantly compounded by deregulation of the FDA. Companies would no longer face penalties for failure to report adverse events and may lack the incentive for vigilant monitoring, a tedious and unprofitable exercise.

Corporations assess the risks and benefits of a product and balance the effect on human life and profit.⁹² The calculations made by the Ford Motor Company when it weighed the cost of correcting defects in the Pinto model to prevent explosions in rear-end accidents provide an example of the moral hazard arising from the temptation to place profit above human welfare.⁹³ Ford found the expense of correcting a defective design in their Pinto model greater than the cost of defending suits for the loss of human life. This case argues against

⁸⁹STAFF REPORT TO SENATOR ORRIN G. HATCH, *False and Misleading: FDA's Report: Unsubstantiated Claims and documented Health Hazards in the Dietary Marketplace*, Oct. 21, 1993.

⁹⁰*Co-regulation*, *supra* note 68.

⁹¹*Id.* at 117-121; *See also Grundberg*, 813 P.2d at 100, 104 (Stewart, J., dissenting).

⁹²Gary T. Schwartz, *The Myth of the Ford Pinto Case*, 43 RUTGERS L. REV. 1013, 1020 (1991) (discussion of risk-benefit analyses routine for manufacturers).

⁹³*Id.*

relying upon the market to monitor and correct adverse effects. This is especially true when the public cannot readily detect defects in the product and monitoring for defects is costly for the manufacturer. The US legal system changed the equation for Ford,⁹⁴ but only because damaging testimony revealed to the public the details of Ford's cost-benefit analysis and the \$200,000 value that Ford placed on a human life.⁹⁵

In the pharmaceutical arena, detailed scientific analysis is required to show causation between drug treatment and an adverse event.⁹⁶ As in the automotive industry, where corporate equations of profit versus the value of human life do not mesh with public interest, pharmaceutical companies may not place the same value on human life as does the public. Arguably, without the FDA to protect the public interest, a marked increase in adverse events may result from a corporate risk-benefit analysis driven by the need to maximize shareholder profits.

3. Legal System Ineffective in Regulation of Drugs

Some critics have proposed that the FDA should be deregulated because the legal system can effectively protect the public from dangerous drugs.⁹⁷ The legal system, however, has already rendered inconsistent decisions which vary between jurisdictions. Without FDA regulation, the legal system cannot protect the public from exposure to dangerous drugs or from the loss of effective drug

⁹⁴Grinshaw v. Ford Motor Co., 174 Cal. Rptr. 348, 119 Cal. App. 3d 757 (1981) (Ford fined \$125 million in punitive and \$2 million in compensatory damages; punitive damages remitted to \$3.5 million).

⁹⁵Human life assessed at \$200,000 per person. Schwartz, *supra* note 92.

⁹⁶See *supra* §§ III.B.2.a; III.B.2.a.i; III.B.2.b.

⁹⁷See Peter Stone, *The Demolition: Prescription Industry Leaders and Lawmakers Want to Overhaul the Food and Drug Administration*, ORLANDO SENTINEL Mar. 26, 1995, at G1. A coalition of conservative groups including the Progress & Freedom Foundation affiliated with House Speaker Newt Gingrich, and powerful Republican lawmakers including Newt Gingrich, the "godfather of the FDA reform movement" and Thomas J. Bliley Jr., R-Va., who heads the House Biotechnology Caucus, are launching a well-financed campaign including fund raising and advertising campaigns to overhaul the FDA. *Id.* at 1. The group has raised \$400,000 from drug, biotech and medical device companies. *Id.* at 3. According to Rep. Henry Waxman, senior Democrat on the Commerce Subcommittee on Health and Environment, the Republicans, especially Gingrich, would like to "eviscerate the FDA" or at the least to intimidate the FDA. Waxman claimed to be stunned by the supercharged words that Gingrich used against Kessler. *Id.* at 2. Gingrich has gone so far as to introduce legislation and intercede with the FDA on behalf of Solvay Pharmaceuticals, a Belgium-based company. *Id.* at 4.

See also, No, *The FDA is not Killing People*, CONSUMER REP. Apr. 1, 1995, at 218. The FDA is being attacked by politicians and by foundations that include the Washington Legal Foundation. These groups rely on funding from drug companies which could profit from deregulation, including Burroughs Wellcome, Eli Lilly, Genzyme, Glaxo, Johnson & Johnson, Pfizer, Searle, Siemens and Solvay. Merck, on the other hand, stated that it opposed deregulation.

therapy after pharmaceutical drugs have been erroneously linked to adverse effects.⁹⁸

Furthermore, in the face of increasing tort reform with caps on nonpecuniary damages and punitive damages, tort law may not adequately protect the consumer or deter the manufacturer. Thus, tort law reform coupled with the deregulation of the FDA would remove deterrence from manufacturers to ensure public safety.⁹⁹

a. Misuse of Strict Liability for Pharmaceuticals

Strict liability claims against pharmaceutical companies undermine regulation by the FDA, contribute to the escalation of medical costs and inhibit the development of new prescription drugs.¹⁰⁰

Under our adversarial legal system, pharmaceutical companies are forced to prove to juries of twelve lay persons that the same prescription drug is safe and effective at multiple trials in different jurisdictions.¹⁰¹ Juries do not evaluate all of the available data because legal rules of evidence and procedure are limited to the testimony of paid witnesses. Juries reach legal conclusions; they do not make scientific determinations.¹⁰² In contrast, FDA scientists and physicians examine extensive data to evaluate whether new prescription drugs are safe and effective.¹⁰³

Although strict product liability gained popularity in the 1960s,¹⁰⁴ Dean Prosser, the reporter for the Second Restatement of Torts in 1965, added comment k to the Restatement (Second) of Torts because he did not intend to apply the same standard of strict liability to prescription drugs and vaccines as to other products.¹⁰⁵ Comment k sought to limit strict liability for desirable

⁹⁸ See *infra* §§ III.B.3.a; III.B.3.b; III.B.3.c.

⁹⁹ FDA Reform, *supra* note 88 at 2017.

¹⁰⁰ Note, *A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals*, 103 HARV. L. REV. 773 (1990).

¹⁰¹ See *In re Bendectin Litig. v. Merrell Dow Pharms., Inc.*, 857 F.2d 290 (6th Cir. 1988) (discussing 1180 claims in 844 multidistrict courts); *Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349 (6th Cir), *cert. denied*, 113 S. Ct. 84 (1992) (summarizing Bendectin litigation).

¹⁰² See PETER W. HUBER, GALILEO'S REVENGE: JUNK SCIENCE IN THE COURT ROOM (1991); *Daubert v. Merrell Dow Pharms., Inc.*, 113 S. Ct. 2786 (1993) (held in Bendectin case that general acceptance of expert's opinion by scientific community not necessary precondition to admissibility of expert's scientific evidence under Federal Rules of Evidence).

¹⁰³ See *supra* §§ III.B.1.a; III.B.1.b.

¹⁰⁴ *Greenman v. Yuba Power Prods.*, 377 P.2d 897, 898 (Cal. 1963) (Seminal case: manufacturer of power tool held liable for injuries despite lack of knowledge of danger); See RESTATEMENT (SECOND) OF TORTS § 402A (1965).

¹⁰⁵ RESTATEMENT (SECOND) OF TORTS § 402A cmt. k, providing narrow exemption for useful and desirable products which are unavoidably unsafe; refers explicitly to drugs

products such as prescription drugs and vaccines which are "unavoidably unsafe," because of the probability that someone will have an adverse reaction no matter how perfectly the product is designed.¹⁰⁶

However, by 1984, following an explosion in strict liability litigation, Keeton, Prosser's succeeding editor, seemed to ignore Prosser's admonitions to keep prescription drugs out of the arena of strict product liability. Keeton merely noted that it is "suggested" that prescription drugs be treated differently from other products.¹⁰⁷

Modern courts have reached inconsistent conclusions. Many courts have held manufacturers of prescription drugs to standards of strict liability, or have held manufacturers responsible for design defects despite FDA approval. These courts fail to distinguish between pharmaceutical drugs and other products, and assume that manufacturers of prescription drugs should insure the safety of their products. For example, in a large number of recent cases ranging from vaccinations,¹⁰⁸ to birth control pills,¹⁰⁹ copper seven intrauterine devices (IUDs),¹¹⁰ antibiotics¹¹¹ and psychoactive compounds,¹¹²

and vaccinations.

¹⁰⁶*Id.*

¹⁰⁷W. PAGE KEETON, ET. AL., PROSSER & KEETON ON THE LAW OF TORTS (5th ed. 1984) § 99 at 701 (5th ed. 1984).

¹⁰⁸*E.g.*, *Hurley v. Lederle Labs. Div. of Am. Cyanamid Co.*, 863 F.2d 1173 (5th Cir. 1988)(federal law did not implicitly exempt product liability state law for DPT vaccine); *Abbott v. American Cyanamid Co.*, 844 F.2d 1108, 1109 (4th Cir.); *cert. denied*, 109 S. Ct. 260 (1988);(no preemption of Virginia common-law liability for defective design or failure to warn); *Graham v. Wyeth Labs., a Div. of Am. Home Prods. Corp.*, 906 F.2d 1399, 1406, 1419 (10th Cir.); *cert. denied*, 111 S. Ct. 511 (1990);(federal law does not preempt Kansas strict liability tort law for DPT vaccination; new trial after \$15 million award on evidentiary basis); *MacGillivray v. Lederle Labs. Div., Am. Cyanamide Co.*, 667 F. Supp. 743 (D. N.M. 1987)(federal regulation did not preempt strict product liability on defective design of pertussis vaccine).

¹⁰⁹*E.g.*, *Brochu v. Ortho Pharm. Corp.*, 642 F.2d 652 (5th cir. 1981)(manufacturer of oral contraceptive held liable for design defect inherent in high estrogen pill).

¹¹⁰*E.g.*, *Adams v. G.D. Searle & Co., Inc.*, 576 So.2d 728 (2d Cir. 1991)(whether copper seven intrauterine device (IUD) protected from defective design claim by comment k a question of fact); *Callan v. G.D. Searle & Co.*, 709 F. Supp. 662 (D. Md. 1989)(tort claims not preempted by FD&C Act); *Tarallo v. Searle Pharm., Inc.*, 704 F. Supp. 653 (D. S.C. 1988)(tort claim not preempted by federal law).

¹¹¹*E.g.*, *Feldman v. Lederle Labs., a Div. of Am. Cyanamid Co.*, 592 A.2d 1176 (N.J. 1991)(prior approval of FDA and FDA delay in requiring warning letter of problem did not preempt state law for failure to warn of tooth discoloration after use of tetracycline); *In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989).

¹¹²*Shanks v. Upjohn Co.*, 835 P.2d 1189 (Alaska 1992)(reversed superior court; held prescription drug manufacturers not exempt from strict liability design defect claims in case involving Xanax, used to treat anxiety in a patient taking many other active drugs); *Noyola v. Johnson & Johnson & McNeilab, Inc.*, 1987 WL 13586 (N.D. Ill. 1987) (lack of express language in FD&C Act coupled with court's presumption against preemption

state and federal courts have held pharmaceutical manufacturers liable for drug design defects, a strict liability standard, despite FDA approval using a rigorous risk-benefit analysis for the drug. Courts have not only granted large awards, but at times have also allowed punitive damages. For example, the Illinois District Court not only held a pharmaceutical company to a strict liability standard, but even imposed punitive damages. Punitive damages ordinarily do not apply to strict liability since punitive damages are supposed to alter behavior. Without fault, behavior cannot rationally be modified.¹¹³

The argument offered by the Alaska Supreme Court to impose strict liability on manufacturers of pharmaceutical drugs depended on the use of strict liability to protect powerless injured persons. However, the Alaska Supreme Court acknowledged the danger of that philosophy; product liability litigation may impair a prescription drug manufacturer's ability to get liability insurance and may force a pharmaceutical company to withdraw beneficial prescription drugs from the market.¹¹⁴ Thus, the court acknowledged that its ruling would deter pharmaceutical companies from marketing beneficial prescription drugs even when legal liability is not grounded in scientific fact.¹¹⁵ Despite this acknowledgement, instead of looking at causation, the court required the manufacturer to act as an insurer to absorb the costs of any illness that arose while a patient was taking a drug even without showing that the drug caused the illness. The court cavalierly suggested that pharmaceutical manufacturers can obtain insurance (which it acknowledged manufacturers may have difficulty obtaining) and charge more for its products.¹¹⁶ Thus, patients who require treatment must pay more to cover costs incurred by legal suits brought by other parties for symptoms which may be totally unrelated to the prescription drug.

On the other hand, some courts have refused to apply a strict liability standard to prescription drugs and have held that FDA approval preempts state claims of design defect for cases involving sleeping pills,¹¹⁷ vaccines,¹¹⁸

precluded preemption; court also differentiated the pharmaceutical drug Haldol (used to treat psychosis) in this case from vaccines which the court labelled a 'biologic').

¹¹³*Noyola*, 1987 WL 13586 1, at *2-4.

¹¹⁴*Shanks*, 835 P.2d at 1195.

¹¹⁵*Id.* at 1196.

¹¹⁶*Id.*

¹¹⁷*Grundberg v. Upjohn Co.*, 813 P.2d 89, 90 (Utah 1991).

¹¹⁸*Mazur v. Merck & Co., Inc.*, 964 F.2d 1348, 1355 (3d Cir. 1992) *rehearing and hearing en banc* (no strict liability for mumps, measles and rubella vaccine (MMR II) when learned intermediary informed of risks); *Jones v. Lederle Labs.*, a Div. of Am. Cyanamid Co., 982 F.2d 63 (2d Cir. 1992) (DPT vaccine not unreasonably unsafe when given to plaintiff in 1979, absent evidence that a safer alternative could have been produced); *Toner v. Jones v. Lederle Labs.*, a Div. of Am. Cyanamid Co., 779 F.2d 1429, 1431 (9th Cir. 1986) (failure to develop a potentially safer DPT vaccine not a reason to find vaccine

steroid injections,¹¹⁹ birth control pills,¹²⁰ antibiotics,¹²¹ and diethylstilbestrol (DES), a prescription drug to prevent miscarriages.¹²² For example, the California Supreme Court highlighted the stifling economic impact of strict liability claims on pharmaceutical companies, and stressed that strict liability of pharmaceutical drugs is not associated with any realistic expectation of improvement of safety.¹²³ The Utah Supreme Court echoed the same philosophy noting that allowing individual courts and/or juries to continually reevaluate a prescription drug's risks and/or benefits ignores the extensive and expert regulation by the FDA.¹²⁴

b. Economic Impact of Legal System on Pharmaceutical Market

The large number of claims and the extensive litigation related to alleged design defects in prescription drugs over the past decade have had a dramatic impact on the pharmaceutical industry.¹²⁵ Damage awards have been large, and the cases complicated, often with several appeals and protracted

defective when FDA refusal to license the vaccine would have made use of the vaccine a criminal offense under the FD&C Act).

¹¹⁹Hahn v. Richter, M.D., 628 A.2d 860, 868 (Pa. Super. Ct. 1993)(Pennsylvania applies Comment k to all prescription drugs; precluded strict liability for Depo-Medrol injected intrathecally for back pain).

¹²⁰Glassman v. Wyeth Labs., Inc., 606 N.E.2d 338 (Ill. App. Ct. 1992)(comment k exception to strict liability should apply to oral contraceptive).

¹²¹Incollingo v. Ewing, 282 A.2d 206 (Pa. 1971)(strict liability precluded by Comment k for chloromycetin, a broad spectrum antibiotic).

¹²²Brown v. Superior Ct., 751 P.2d 470 (Cal. 1988); Castrignano v. E.R. Squibb & Sons, Inc., 546 A.2d 775 (R.I. 1988)(exemption from no-fault strict liability a defense to allegations of design defect but not a defense to allegations of failure to warn), *aff'd* 900 F.2d 455 (1st Cir. 1990).

¹²³The California Supreme Court recognized that strict liability for design defects does not apply to prescription drugs (*Brown*, 751 P.2d 470. The court only held manufacturers liable for failure to warn of dangers that they knew or could have reasonably known of when the prescription drug was released. The court reasoned that the policies underlying strict liability, to insure that the manufacturer would guard against recurrent hazards and to distribute the costs of injury among consumers, did not apply to prescription drugs. *Id.* at 474. Strict liability applied to prescription drugs would harm the public, stifling medical research and increasing the cost of prescription drugs. *Id.* at 475 (referring to 38 ALI Proc. 19, 990-92, 98 (1961) (discussing reasons why prescription drugs should be exempted from strict liability)). The court distinguished prescription drugs, which alleviate pain and suffering and sustain life, from other products which serve the less vital functions of making work easier or increasing pleasure. *Id.* at 479.

¹²⁴*Grundberg*, 813 P.2d at 90. (Plaintiff claimed she shot her mother to death because of Halcion-induced intoxication. Complaint stated several causes of action; the certified question to the Utah Supreme Court involved only claim of design defect). Note: Halcion is a triazolam sleeping pill produced by Upjohn.

¹²⁵See Gregory C. Jackson, *Pharmaceutical Product Liability May Be Hazardous To Your Health: A No-Fault Alternative to Concurrent Regulation*, 42 AM. U. L. REV. 199, 199-201

litigation.¹²⁶ As an example of excessive liability, in a vaccine case, the *Toner* court established that the defendant, Lederle Laboratories, did not sell a defective vaccine through certified questions to the Idaho Supreme Court. Despite this finding, the court allowed a damage award of \$1,131,200.¹²⁷ Oddly, the Ninth Circuit found Idaho law, which precluded strict liability for the vaccine, consistent with a jury finding of negligence despite the finding that the manufacturer could not have made a safer product. Instead of using the standard criteria for negligence, the court allowed the jury to assert that the manufacturer should have developed a safer alternative vaccine despite the absence of available technology and research to produce a safer product.¹²⁸ Such a decision, allowing a novel definition of negligence to substitute for strict liability, flies in the face of the accepted definition of strict liability.¹²⁹

Costly litigation affects the average consumer because prices of prescription drugs increase while the availability of products decreases. One producer of a diphtheria-tetanus-pertussis (DPT) vaccine gave "extreme liability exposure, cost of litigation and the difficulty of ... obtaining adequate insurance" as its reason for withdrawing its product from the vaccine market.¹³⁰ By 1986, only two producers of the DPT vaccine remained in the market. The cost of each dose had risen from eleven cents per vaccination in 1982 to \$11.40 in 1986; \$8.00 of this cost resulted from the increased price of insurance following costly litigation.¹³¹

(1992).

¹²⁶For example, see *Toner v. Jones v. Lederle Labs., a Div. of Am. Cyanamid Co.*, 779 F.2d 1429 (failure to develop a potentially safer DPT vaccine not a reason to find vaccine defective when FDA refusal to license the vaccine would have made use of the vaccine a criminal offense under the FD&C Act); *Toner v. Jones v. Lederle Labs., a Div. of Am. Cyanamid Co.*, 828 F.2d 510 (9th Cir. 1987) (held that Idaho law that drug manufacturer not strictly liable for paralysis consistent with jury finding that manufacturer negligent for failure to develop safer alternative vaccine); *Toner v. Jones v. Lederle Labs., a Div. of Am. Cyanamid Co.*, 732 P.2d 297 (Idaho 1987) (comment k excepted vaccine from liability claims of defective design, but did not shield manufacturers from claims of negligence); *Toner v. Jones v. Lederle Labs., a Div. of Am. Cyanamid Co.*, 831 F.2d 180 (9th Cir. 1987) (clarification of ambiguities of 1986 opinion); *cert. denied* 485 U.S. 942 (1988).

¹²⁷*Toner v. Jones v. Lederle Labs., a Div. of Am. Cyanamid Co.*, 732 P.2d 297 (Idaho 1987) (comment k excepted vaccine from liability claims of defective design, but did not shield manufacturers from claims of negligence).

¹²⁸*Id.*

¹²⁹W. PAGE KEETON, ET. AL., *PROSSER AND KEETON ON THE LAW OF TORTS* § 75 at 534-38 (liability without fault) (5th ed. 1984).

¹³⁰*Hearings Before Subcomm. on Health and the Environment of House Comm. on Energy and Commerce on Vaccine Injury Compensation*, 98th Cong., 2d Sess. 295 (1984).

¹³¹See *Brown v. Abbott Lab.*, 751 P.2d 470, 480-92 (Cal. 1988) (quoting 232 SCIENCE June 13, 1986, at 1339).

c. *Chilling Effect on Research and Available Treatment*

In addition to escalating costs and decreased availability of prescription drugs, fear of litigation has affected the development of new products. Pharmaceutical companies have abandoned promising research, including a potential cure for AIDS,¹³² and a treatment for blepharospasm, a condition resulting in violent spasms of the eyelid muscles which can lead to functional blindness.¹³³

Excessive litigation has also resulted in the loss of existing therapies. A large pharmaceutical company, E.R. Squibb removed Bendectin, the only prescription drug to treat nausea in pregnancy, from the market in 1983 after an onslaught of lawsuits that alleged that Bendectin cause deformities in newborn babies.¹³⁴ Estimates show that over 30 million women worldwide¹³⁵ and 17.5 million women in the United States between 1956 and 1983 took Bendectin.¹³⁶ It is generally agreed that limb defects appear in slightly less than one in 1,000 live births whether or not the mothers took Bendectin.¹³⁷ Thus, because of the large consumption of Bendectin by pregnant women, plaintiffs blamed Bendectin for limb defects that would have likely occurred without the drug. Although over thirty-five extensive studies have failed to establish a causal link between Bendectin and limb deformities,¹³⁸ the company could no longer bear the cost of litigation.¹³⁹ The price of insurance almost equalled

¹³²See *The Impact of Product Liability Law on the Development of a Vaccine Against the AIDS Virus*, 55 U. CHI. L. REV. 943, 955 (1988).

¹³³Philip M. Boffey, *Loss of Drug Relegates Many to Blindness Again*, N.Y. TIMES, Oct. 14, 1986 at 10.

¹³⁴In *Re Bendectin Litig. Hoffman v. Merrell Dow Pharm., Inc.*, 857 F.2d 290 (6th Cir. 1988) (Eleven hundred eighty claims in approximately 844 multidistrict cases representing only a part of bendectin cases in state and federal courts in the nation), *cert. denied*, 488 U.S. 1006 (1989).

¹³⁵*Merrell Dow Pharms. Inc. v. Thompson*, 478 U.S. 804 (1986)(suits filed by noncitizens against U.S. Pharmaceutical companies).

¹³⁶*Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1350 (6th Cir.), *cert. denied*, 506 U.S. 826 (1992).

¹³⁷*Id.* at 1353.

¹³⁸*Id.* at 1353; *cf. Turpin v. Merrell Dow Pharms. Inc.*, 736 F. Supp. 737 (E.D. Ky. 1990)(district court granted summary judgment granted on basis of epidemiological studies); *see also Ealy v. Richardson-Merrell, Inc.*, 897 F.2d 1159 (D.C. Cir. App.)(reversed lower court finding for plaintiff based on expert opinion of no scientific evidence for teratogenic effects), *cert. denied*, 498 U.S. 950 (1990); *Brock v. Merrell Dow Pharms., Inc.*, 874 F.2d 307 (5th Cir. 1989)(lack of conclusive epidemiological proof fatal to plaintiff's case), *cert. denied*, 494 U.S. 1046 (1990); *Longmore v. Merrell Dow Pharms., Inc.*, 737 F. Supp. 1117 (D. Idaho 1990)(motion for summary judgment denied; epidemiological studies indication no casual connection between Bendectin and birth defect).

¹³⁹For an excellent summary of the extensive litigation over Bendectin *see Turpin*, 959 F.2d 1349.

income from the prescription drug, while the price to the consumer had increased over 300 percent.¹⁴⁰

In summary, in response to escalating litigation, including liability for risks that could not have been known when the prescription drug was sold,¹⁴¹ pharmaceutical companies have raised prices of prescription drugs, limited research to find new cures for diseases, and removed useful drugs from the market.¹⁴²

Not only is the legal system too costly, but it is not effective in the scientific evaluation of the risk-benefit ratio of prescription drugs.¹⁴³ While FDA scientists examine a full range of data, a lay jury must make decisions constrained by their lack of technical knowledge and their limited access to data governed by legal rules of evidence.¹⁴⁴ The "truth" of the court room differs from scientific truth.¹⁴⁵ Unlike FDA evaluations, which are subject to continued assessment to discover whether a prescription drug remains safe and effective, legal rules of evidence are designed to resolve a legal dispute at one point in time.¹⁴⁶ Scientists have called drugs which cause lawsuits, instead of physical injuries, "litogens."¹⁴⁷ As a result of strict liability applied to prescription drugs, litogens result in decreased availability of drugs without scientific evidence that the prescription drug caused any injury.¹⁴⁸

Over a hundred years ago the Supreme Court defined the role of juries.¹⁴⁹ The Court described a jury as twelve average people, some educated, some of little education, from all walks of life who apply their separate experiences in life to draw a unanimous conclusion.¹⁵⁰ The court assumed that these twelve people know more about the common affairs of society and can make safer and

¹⁴⁰*Lawsuits kill off a pregnancy drug*, CHEMICAL WK., June 22, 1983, at 14.

¹⁴¹RESTATEMENT (SECOND) OF TORTS § 402A cmts. h, j (1965).

¹⁴²See Louis Lasagna, *The Chilling Effect of Product Liability on New Drug Development*, in THE LIABILITY MAZE: THE IMPACT OF LIABILITY LAW ON SAFETY AND INNOVATION 334-341 (P. Huber & R. Litan eds. 1991); see also Kuhlik & Kingham, *The Adverse Effects of Standardless Punitive Damage Awards on Pharmaceutical Development and Availability*, 45 FOOD & DRUG COSM. L.J. 693-708 (1990).

¹⁴³*Grundberg*, 813 P.2d at 98-99; See generally PETER W. HUBER, GALILEO'S REVENGE: JUNK SCIENCE IN THE COURT ROOM (1991).

¹⁴⁴HUBER, *supra* note 143.

¹⁴⁵*Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993).

¹⁴⁶See *id.* at 2798-99 (discussing scientific evidence and rules of evidence).

¹⁴⁷Mill & Alexander, *Teratogens and "Litogens"*, 315 N. ENG. J. MED. 1234 (1986).

¹⁴⁸*Id.*; see also *Brown*, 751 P.2d at 477-480 (public policy demand for prescription drugs demands different policy from strict liability for other products); see also *supra* notes 5-6 (removal of beneficial prescription drug unsupported by scientific evidence).

¹⁴⁹*Railroad Co. v. Stout*, 84 U.S. 657, 663-64 (1873).

¹⁵⁰*Id.*

wiser conclusions than a single judge.¹⁵¹ However, instead of asking the jury to deal with common events of life, cases involving the risk-benefit of prescription drugs require twelve lay persons to become a "super FDA," creating their own labelling requirements on a case-by-case basis.¹⁵²

Given the FDA's increasingly rigorous regulation of the drug industry, courts and juries are less capable than the FDA of dealing competently and impartially with complex scientific issues.¹⁵³ The judicial system cannot consistently regulate the safety of pharmaceutical drugs for the general population because the job of the courts is to respond to discrete privately initiated controversies and to determine issues of fault and veracity,¹⁵⁴ not to make scientific evaluations to protect the public.

Thus, the legal system already poses a significant threat to the pharmaceutical industry. Even with FDA oversight, plaintiffs bring scores of costly lawsuits. Without the FDA, both the safety and efficacy of drugs and the public's confidence in drugs may decrease even further, leading to an increase in lawsuits. Thus, deregulation can only magnify the threat of costly litigation, perhaps to the extent of rendering the US pharmaceutical industry stagnant and unwilling to produce innovative drugs for fear of excessive liability.

4. FDA Needed to Regulate Drugs

To summarize, without the FDA, there would be no coherent monitoring of adverse events. Currently, reports of adverse events by pharmaceutical manufacturers to the FDA allow the agency to re-assess the safety and efficacy of drugs and to either issue additional warnings about unanticipated adverse effects or to withdraw the products from the market.¹⁵⁵ In addition, the currently available alternative control mechanisms, the market and the legal system, are inferior to the FDA to insure public safety.

¹⁵¹*Id.*

¹⁵²Joseph A. Mahoney, *Senate Bill 640: Proposed Product Liability Reform and its Potential Effect on Pharmaceutical Cases and Punitive Damages Claims*, 36 ST. LOUIS L.J. 475, 491 (1992) (citing D. VINSON & A. SLAUGHTER, *PRODUCTS LIABILITY: PHARMACEUTICAL DRUG CASES*, 196-97 (1988)).

¹⁵³*Co-Regulation*, *supra* note 68, at 121.

¹⁵⁴Cass Sustein, *Cost-Benefit Analysis and the Separation of Powers*, 23 ARIZ. L. REV. 1267, 1270 (1981).

¹⁵⁵Michael McDonald, Comment, *Products Liability - Utah Extends Comment k Protection for Strict Products Liability to All Prescription Drugs - Grundberg v. Upjohn Co.*, 26 SUFFOLK U.L. REV. 321 (1992) (quoting Donald C. Dilworth, *Half of FDA-Approved Drugs Show Harmful Side Effects*, TRIAL, Aug. 1990, at 14).

5. Problems With Proposed Deregulation of the FDA

a. Critics Exaggerate Problems and Ignore FDA Improvement

Republicans, especially Newt Gingrich, assert the need for FDA reform and advocate privatization or deregulation of the FDA.¹⁵⁶ Calling the FDA Commissioner David Kessler a "thug and a bully," Gingrich wants to relegate the FDA to the role of an oversight agency without the ability to effectively regulate or approve of new drugs.¹⁵⁷ However, the critics ignore crucial differences between deregulation of the FDA's drug approval process and the typical "conservative" deregulation.¹⁵⁸ For most regulated agencies, such as the Environmental Protection Agency, the conflict of interest is between the healthy public and regulated industries.¹⁵⁹ However, for prescription drugs individual patients must assume the risk inherent in all drugs in exchange for the benefit of treatment; a risk that varies with the uncertain nature of illness.¹⁶⁰ It is virtually impossible for the public at large to make this determination; even the FDA struggles to strike an acceptable balance between risk and benefit.¹⁶¹

Critics allege multiple problems with the FDA, claiming that the FDA is a slow, overly cautious bureaucratic organization riddled by voluminous paperwork. Critics of the FDA assert that agency requirements for approval are responsible for delays and increased costs in drug development, causing pharmaceutical companies to move the development of new drugs to foreign countries to minimize their administrative burden.¹⁶²

However, Mr. Gingrich and his colleagues ignore recent advances made by the FDA. For example, the FDA estimates that new regulations requiring manufacturers to pay a user fee for each New Drug Approval (NDA) will

¹⁵⁶FIN. POST *supra* note 74, at 2.

¹⁵⁷FDA Reform, *supra* note 88, at 2009 (citing Laurie McGinley, *GOP Takes Aim at FDA, Seeking to Ease Way for Approval of New Drugs, Medical Products*, WALL ST. J., Dec. 12, 1994, at A16).

¹⁵⁸*Id.*

¹⁵⁹*Id.*

¹⁶⁰*Id.* at 2009-10.

¹⁶¹*Id.* at 2010.

¹⁶²In the early 1960s, the process from pre-clinical testing through new drug approval required an average of four years, by the mid-1970s, approval time increased to seven years (See Henry C. Grabowski, *Regulation and the International Diffusion of Pharms.*, in THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM 5 (Robert Helms ed., 1980)), and by 1991 an estimated ten years.(COUNCIL ON COMPETITIVENESS, IMPROVING THE NATION'S DRUG APPROVAL PROCESS 2 (1991)). The cost to develop a new drug also rose from an estimated 50 million dollars in the mid-1970s to over 230 million dollars in 1991. (Paul Abrahams, *A Tricky Balancing Act for Regulators*, FIN. TIMES (London) Nov. 15, 1991, § 1, at 19 (quoting a spokesman for the Pharmaceutical Manufacturers Association of America)).

reduce the approval time for new drugs by fifty percent in 1997.¹⁶³ User fees give the FDA additional resources to hire more staff to review drug applications, to streamline the review process and to use additional computer technology to evaluate data.¹⁶⁴ The FDA plans to hire 700 new drug reviewers and support staff by the end of fiscal 1997 to reduce the approval time of a new drug.¹⁶⁵ Interestingly, Japan had user fees in place for over a decade before the US.¹⁶⁶

Another FDA innovation includes the recent loosening of restrictions to allow treatment of some patients while a new drug is still in the investigational stage.¹⁶⁷ Additionally, the FDA has a "fast track" for life-threatening and severely debilitating diseases,¹⁶⁸ which shortened approval times to 22 months in 1990,¹⁶⁹ and to 10.4 months in 1994.¹⁷⁰ Recent FDA changes have also shortened overall approval time for new drug applications. Approval times for routine drugs fell from 26.7 months in 1993 to 13.5 months in 1994 under the new Prescription Drug User Fee Act of 1992.¹⁷¹

Many assertions by the critics and experts are misplaced. For example, critics assert that FDA delays have cost thousands of lives. One commentator stated that the delay in the approval of Septra, an antibiotic, cost 80,000 lives.¹⁷² This commentator failed to note that other more potent antibiotics were available

¹⁶³*User Fee Breakthrough in U.S.*, DRUG & COSMETIC INDUSTRY, Nov. 1, 1992 at 12. See the Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified as amended at 21 U.S.C. § 379(h) 1992)).

¹⁶⁴Alicia Ault Barnett, *Amid frenetic restructuring to keep pace with market reform, manufacturers are leaving tradition behind and forging new managed care alliances; includes article about changes to Food and Drug Administration's drug approval process*, 13 HEALTH & BUS. 41, (1995).

¹⁶⁵*Id.*

¹⁶⁶STANDARDS AND CERTIFICATION SYSTEMS CONCERNING DRUGS IN JAPAN, INCLUDING PHARMACEUTICAL AFFAIRS LAW 83 (Pharmaceutical Affairs Bureau, Ministry of Health and Welfare ed., 1985) [hereinafter Health Ministry].

¹⁶⁷FDA Reform, *supra* note 88, at 2015.

¹⁶⁸21 C.F.R. §§ 312.80-85 (1993).

¹⁶⁹Jack M. Rosenberg & Nicholas LaBella, Jr., *New Drug Developments in the U.S.*, STRAUSS'S PHARMACY L. EXAMINATION REV., 137, 140 (Steven Strauss ed., 2d ed. 1990)(the approval time is comparable with that in foreign countries).

¹⁷⁰See *The FDA and the Future of the American Biomedical and Food Industries Hearings before the Senate Comm. on Labor and Human Resources*, 104th Cong., 1st Sess. 97 (1995) (statement of David A. Kessler, FDA Commissioner).

¹⁷¹Pub. L. No. 102-571, 106 Stat. 4491 (Prescription Drug User Fee Act of 1992, (codified as amended in scattered sections of 21 U.S.C. (Supp. IV 1992))).

¹⁷²Van de Kamp, *Van de Kamp and RU 486 Testing*, L.A. TIMES, Mar. 29, 1990 at B6, (quoting George Higgins, co-winner of 1988 Nobel Prize in medicine who asserted that 5 year delay in approval of Septra cost 80,000 lives).

to treat infections. Septra is not a first line drug, but an alternative to other effective drug therapy.

Another commentator contended that delay in approving Tacrine, a treatment for Alzheimer's Disease, prevented 40% of patients suffering from the disease from obtaining effective treatment.¹⁷³ However, the commentator failed to note that Tacrine is not a therapeutic breakthrough in the treatment of Alzheimer's disease. In fact, researchers note uncertainty in the efficacy and safety of the treatment¹⁷⁴ since only a low proportion of patients respond to treatment and patients experience a high incidence of liver toxicity.¹⁷⁵ Furthermore, Tacrine fails to provide any benefit for forty percent of the patients who suffer from Alzheimer's disease.

Similar complaints arose following reported FDA delays in approving a chickenpox vaccine. Critics asserted that FDA approval should be based on adequate testing programs in Japan. However, commentators failed to note that the strain of virus used in Japan is different than that used in the US and that several experts remain ambivalent about the value of this vaccine.¹⁷⁶ Additionally, since the duration of immunity following chickenpox vaccination is unknown, the possibility remains that vaccination may shift chickenpox outbreaks toward older age groups where the infection can result in more serious complications.¹⁷⁷

Critics also contend that foreign regulatory bodies approve drugs faster than the FDA. Although critics argue that in 1988 foreign review of the same products took approximately half the time of a comparable review by the FDA, foreign review time failed to include preclinical testing conducted in the United States.¹⁷⁸ The reported approval time of eighteen months for Japan, when compared with thirty-one months in the US, also failed to include the time spent by applicants in answering Ministry questions when seeking approval in Japan.¹⁷⁹ One commentator noted that although the actual review time may

¹⁷³Malcolm S. Forbes, Jr., *Fact and Comment: (Low Fat) Bread and Circuses*, FORBES, July 8, 1991, at 23, 24.

¹⁷⁴Christopher M. Filley, *Alzheimer's Disease: It's Irreversible but not Untreatable*, 50 GERIATRICS, 18-22 (1995).

¹⁷⁵A. J. Wagstaff and D. McTavish, *Tacrine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in Alzheimer's disease*, 4(6) DRUGS AGING 510-40 (1994).

¹⁷⁶Kristine M. Severyn, *Is chickenpox vaccine a good idea?*, DAYTON DAILY NEWS, June 3, 1995, at 13A.

¹⁷⁷M. Elizabeth Halloran, et al., *Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States*, 140 AM. J. EPIDEMIOLOGY 81 (1994).

¹⁷⁸JAMES R. NIELSON, HANDBOOK OF FEDERAL DRUG LAW 30 (2d ed. 1992).

¹⁷⁹Kanusky *supra* note 8, at 686. Review time decreased from 28 months in 1981). See U.S. Int'l Trade Comm'm, *Global Competitiveness of U.S. Advanced-Technology Manufacturing Industries: Pharms. 3-6* (1991); *summary available in LEXIS, ITRADE*

not be different, perceived differences prompt U.S. companies to seek initial approval in foreign countries.¹⁸⁰

In addition, proponents of FDA deregulation such as Tom Leonard of the Progress and Freedom Foundation, a right wing think tank associated with Newt Gingrich, who want to privatize the drug approval process forget that quack treatments deplete desperate people not only of their money, but of their chance to benefit from proven therapy.¹⁸¹ Countries with less strict regulation make guinea pigs out of their citizens allowing the FDA to learn about unforeseen side effects of new medications.¹⁸² Additionally, critics tend to exaggerate health costs of slow approval, while failing to credit the FDA for the lives saved by prudent controls and monitoring.¹⁸³ Most importantly, critics forget that improvement and support of the FDA are preferable options to deregulation.¹⁸⁴

b. Critics Ignore FDA Benefits to Public

Benefits of FDA protection can be measured by both: (1) the numbers of drugs not approved in the US that cause serious side effects and deaths in other countries; and (2) the rapid removal of dangerous drugs or the provision of warnings about adverse events that occur either during clinical investigations or after approval of a drug when unexpected adverse events emerge after widespread use of the pharmaceutical drug therapy.

i. Dangerous Drugs Not Approved in the US

Critics ignore potentially promising drugs not approved by the FDA that later show serious, and at times fatal, adverse effects.¹⁸⁵ A study by the Public Citizens Health Research Group compared the number of drugs withdrawn from the market in four countries between 1970 and 1992; fifty-six drugs were

Library, ALLITC File.

¹⁸⁰FIN. POST *supra* note 74, at *2.

¹⁸¹*Id.*

¹⁸²See *Study Says U.S. has Better Barrier to Bad Drugs than Europe*, WASH. POST, Feb. 3, 1995, at 9 (quoting Sidney Wolfe, executive director of Health Research Group) [hereinafter *Better Barrier*].

¹⁸³These critics contend that FDA delays cost 200,000 lives over thirty years. Additionally, Gingrich supporters contend that the FDA took too long for chickenpox vaccine approval, contending that the vaccine was approved in Europe fifteen years before approval in the US. Again, the critics fail to recognize the serious dangers of many vaccines, including those still on the market. Additionally, the chickenpox vaccine is not a proven entity; researchers are still uncertain about whether or not immunity from vaccination will persist into adult years. FIN. POST, *supra* note 74, at 2.

¹⁸⁴Steve Berchem, a spokesperson for the Pharmaceutical Manufacturer's Association stressed the need for high safety standards at the FDA with the goal to improve, not to dismantle the agency. *Better Barrier*, *supra* note 182, at 9.

¹⁸⁵*Id.*

withdrawn:¹⁸⁶ France (thirty-one); Germany (thirty); Great Britain (twenty-three) and the US (nine).¹⁸⁷ Furthermore, in three of the US cases, manufacturers pleaded guilty to criminal charges of withholding information from the FDA,¹⁸⁸ stressing problems of compliance even with strong regulation, problems likely to worsen in the absence of FDA regulation.

Failure to approve these compounds saved lives in the US. Examples of adverse effects seen in other countries due to drugs not approved in the US include: clometacin, an anti-inflammatory drug linked to 130 reports of liver damage and nine deaths in France; Indomethacin-R, marketed and later withdrawn in Great Britain and Germany, linked to 717 reports of adverse events and thirty-six deaths; and terodiline, a drug to treat urinary incontinence in Britain and Germany, linked to sixty-nine reports of irregular heart rhythm and fourteen deaths.¹⁸⁹

ii. Dangerous Drugs Withdrawn From US Market

The FDA also serves the public by identifying adverse events after drugs are marketed or during clinical trials by removing the drugs rapidly so that more people are not injured. Without such surveillance, it would take much longer to identify adverse events (or they may be missed entirely) and would expose more people to needless harm. A few examples of these events are described below.

Abbott Laboratories marketed temafloxacin (omniflox, a fluoroquinolone), a broad-spectrum antibiotic, in February, 1992.¹⁹⁰ By June 1992, the FDA received fifty reports of serious adverse reactions and required Abbott to remove the drug from the market.¹⁹¹ These adverse events did not occur in preapproval clinical trials which involved over 4,000 patients. However, during the first three months of marketing, more than 200,000 patients received the drug, and fifty patients experienced severe or life-threatening adverse reactions.¹⁹² Neither Abbott nor the FDA expected these adverse reactions since other drugs from a similar class of antimicrobial drugs (fluoroquinolones) did not show these adverse reactions.¹⁹³ Thus, careful monitoring by the FDA

¹⁸⁶The numbers do not add up because many of the drugs were withdrawn by more than one country.

¹⁸⁷*Better Barrier*, *supra* note 182, at 9.

¹⁸⁸*Id.*

¹⁸⁹*Id.*

¹⁹⁰FDA MED. BULL., Sept. 1, 1992.

¹⁹¹*Id.* Adverse reactions included hemolytic anemia, other hematologic problems and renal failure which required dialysis in 50% of those affected.

¹⁹²*Id.*

¹⁹³*Id.*

resulted in prompt removal of a dangerous drug, averting further danger or illness and/or death.

In other cases the FDA helped to differentiate adverse events which occurred during drug treatment from signs and symptoms associated with the patient's underlying illness, but not caused by drug treatment. For example, many asserted that Prozac, marketed by Eli Lilly & Co. for depression, caused patients to develop suicidal thoughts.¹⁹⁴ However, clinical studies showed that patients on Prozac were actually less likely to develop suicidal thoughts than those on other antidepressants or on a placebo.¹⁹⁵ Suicidal thoughts are common in depression; as many as eighty per cent of depressed patients consider suicide at some point and fifteen percent actually kill themselves.¹⁹⁶

Additionally, even without actually removing a drug from the market, FDA monitoring can identify potential problems so that patients and doctors are aware of risks and modify treatment accordingly. For example, Wallace Laboratories marketed Felbatol to treat seizures in August 1993.¹⁹⁷ Although Felbatol seemed to be a miracle drug for some patients, the FDA received warnings that the drug could cause aplastic anemia, a rare form of bone marrow failure.¹⁹⁸ After the FDA received reports of ten cases of aplastic anemia resulting in four deaths, the agency recommended that physicians use Felbatol only for patients with severe epilepsy in whom the benefits outweighed the risks.¹⁹⁹ In fact, some patients chose to remain on the drug despite the risks because their epilepsy did not respond to other treatment.²⁰⁰ Thus, the FDA did not deprive these select patients of treatment. The FDA performed a similar function in alerting doctors and patients to the increased danger of heart attacks associated with the nicotine patch used to break smokers from their addiction to cigarettes.²⁰¹

¹⁹⁴Leslie Scanlon, *Firm disputes Prozac link to suicide*, CIN. ENQUIRER, Nov. 17, 1994, at B8.

¹⁹⁵*Id.*

¹⁹⁶*Id.*

¹⁹⁷Tracy Everbach, *Family blames epilepsy drug for woman's impairment. Felbatol benefits outweigh risk, many doctors say*. DALLAS MORNING NEWS, Nov. 18, 1994, at 29A.

¹⁹⁸*Id.*

¹⁹⁹*Id.*

²⁰⁰*Id.* author quoted Dr. Delgado, chairman of the Dallas Epilepsy Association who commented that all medications have side effects and must be monitored carefully; notes most treatment for epilepsy is associated with serious, albeit infrequent risk of liver damage and other side effects and patients must weigh risk versus benefit. Some patients controlled with Felbatol are alert, happy and functioning for the first time.

²⁰¹FDA Panel to Discuss Labelling on Nicotine Patches, DOW JONES NEWS SERV., July 14, 1992. FDA to reexamine current labelling because of reports of heart attacks in patients wearing the patch. Patients found to be smoking while wearing the patch resulting in an overdose of nicotine.

The FDA also protects against the promulgation of adverse effects from drugs under investigation. For example, a drug used to treat hepatitis, fiauluridine or FIAU²⁰² was associated with five deaths during clinical trials in 1994.²⁰³ The FDA criticized the clinicians involved for not spotting the adverse events quickly enough.²⁰⁴ The study was canceled after thirteen weeks because of liver failure in a patient. Researchers initially missed the association between the drug and the patient's death because the patient's symptoms resembled those of the underlying disease.²⁰⁵ This study highlights the difficulty in identifying adverse events, especially in extremely ill or dying patients, where drug effects may mimic the underlying disease. More importantly, the study also highlights the critical role of the FDA; without FDA oversight, trained researchers acting competently missed the association between treatment and the resulting fatalities.²⁰⁶ FDA oversight identified causation and halted the studies, saving additional lives that might have been lost if other patients had been treated with the drug.

c. FDA Bias for Caution Consistent With US Public Policy

Critics argue that the FDA delays approval of drugs because of excessive agency caution.²⁰⁷ While the FDA faces severe criticism for allowing dangerous drugs on the market, critics assert that there are no significant penalties for delay in approval of a drug.²⁰⁸ However, this criticism not only ignores the response of the FDA to speed up approval time by implementing changes including the institution of user fees, but the FDA's mandate to implement US public policy. Public policy mandated that the FDA calculate a risk-benefit ratio for pharmaceutical drugs to protect the public against undue risks. This same policy underlies US tort law, particularly strict liability cases, where responsibility for harm, even without negligence or fault of the manufacturer,

²⁰²A drug that showed promise in treatment of hepatitis B, a virus that kills 6,000 annually in the US. See Laura McGinley, *Review Exonerates Researchers in Test of Hepatitis Drug that Led to 5 Deaths*, WALL ST. J., Mar. 17, 1995, at B2.

²⁰³*Id.*

²⁰⁴*Id.*

²⁰⁵*Id.*

²⁰⁶See Rex Dalton, *Report backs scientists in fatal tests*, SAN DIEGO UNION & TRIB. Mar. 17, 1995, at B2.

²⁰⁷*FDA Reform*, *supra* note 88 at 2010-11: prescription drug injuries are often conspicuous while adverse health effects of nonapproval are frequently invisible giving the FDA an incentive for excess caution. Members of Congress, concerned with public opinion, also hesitate to advocate approval of specific new drugs which might later produce well-documented adverse effects on consumers.

²⁰⁸Larry Kramer, *Gambling with the FDA in Nevada: Businessman Wins State Approval to Market Drug: State Approves Drug that Claims to Help the Elderly*, WASH. POST Nov. 13, 1995, at F1 (intrastate approval legal as long as all production, distribution and consumption of the drug is within the state's borders).

is inferred because of the inability of the consumer to discern risk.²⁰⁹ These policies arise from the high value placed on human life in the US.

d. FDA Requires Reform, Not Deregulation

The FDA has responded to political pressure in recent years. Recently, the FDA approved two drugs faster than in other countries: Tacrine, used to treat Alzheimer's disease and Taxol to treat cancer.²¹⁰ Additionally, there has been a marked increased speed in the overall approval rate of new drugs.²¹¹

Critics point to the FDA's depressed physical plant, low salaries and unfilled positions to show that the FDA does not operate effectively.²¹² Critics also assert that the agency is not equipped to understand scientific advances or effectively evaluate new drugs because of the lack of qualified personnel.²¹³

However, instead of choosing a market driven process, critics should improve the FDA by enhancing salaries and its physical plant to increase FDA efficiency in approving safe and effective drugs. Marketing ineffective drugs and waiting to see what adverse events emerge puts our population at great risk. Dismantling the FDA may result in a temporary financial benefit for manufacturers who produce ineffective or marginally effective drugs that may show market failure only after a long period. Meanwhile, many may suffer from resultant morbidity and mortality due to unidentified adverse events. Ultimately, however, with the emergence of adverse events without data to rebut or ascertain causation, liability costs may rapidly outstrip profits.

Finally, a strengthened FDA with more rapid approval times could result in savings for pharmaceutical companies if federal preemption barred strict liability claims of defective product design. Some of the salvaged legal costs resulting from the adoption of preemption could be funnelled into research and development and into user fees to strengthen the FDA. Plaintiffs would still have a cause of action against pharmaceutical companies in cases of negligence and fraud, including cases where companies failed to report adverse events to the FDA.²¹⁴

²⁰⁹FDA Reform, *supra* note 88, at 2010-11.

²¹⁰FIN. POST, *supra* note 74, at 2.

²¹¹*Id.* (quoting report from Sandra Raymond of the National Osteoporosis Foundation).

²¹²Louis Lasagna, *Promising New Drugs Deserve Faster Approval Health: The FDA is determined not to permit drugs that don't merit approval But blocking effective ones may be a worse sin*, L.A. TIMES, Oct. 19, 1989, at B7.

²¹³Carol Griffiee, *Dream Buster: Hopes for a Biotechnology Corridor Dying Due aid New Federal Mandates at NCTR*, ARK. BUS., July 22, 1991 § 1, at 18.

²¹⁴Details of this proposition are beyond the scope of this paper.

6. FDA Protection Forces Higher Standards in a Global Market

a. Impact of Harmonization

Over the last decade regulatory authorities and manufacturers in different countries have worked toward developing complementary if not reciprocal regulation for the approval of pharmaceutical agents.²¹⁵ The International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) is a long-term project involving both regulatory bodies and manufacturers from the US, the EC, and Japan attempting to standardize requirements for new pharmaceutical licensing.²¹⁶

The goal of harmonization is to reduce differences in the conduct of clinical studies between countries and to implement mechanisms for joint regulatory approval. Harmonization seeks to promote more rapid approval of safe and effective drugs by decreasing delays due to duplicative research to meet divergent regulatory requirements in different countries.²¹⁷

If strict standards are preserved for drug approval, harmonization may provide an impetus for increased quality of research. Improvement in the quality of Japanese research supports this contention.²¹⁸

Despite progress in harmonization, some differences are likely to remain. For example, the Japanese Ministry of Health and Welfare requires pharmaceutical companies to conduct absorption, distribution, metabolism and excretion, dose ranging studies and Phase III studies (to show safety and efficacy) in Japan to support New Drug Applications because of differences in race. Such requirements mirror newer FDA requirements to evaluate the effects of new drugs which relate to age, gender, and race.

Until 1984, most drug studies for US approval were conducted in the US because of FDA reluctance to accept foreign data.²¹⁹ However, in 1985, the FDA adopted guidelines to accept international research into domestic Investigation New Drugs (INDs) and New Drug Applications (NDAs) and has subsequently approved NDAs based on a mix of foreign and domestic data, and some based solely on foreign data.²²⁰ Thus, the FDA, in response to political and industry pressure, has not only accepted foreign data in recent years, but has taken an

²¹⁵Renato Altissimo, *Welcoming Remarks*, in PROCEEDINGS OF THE 2ND INTERNATIONAL CONFERENCE OF DRUG REGULATORY AUTHORITIES vii, v11 (Dulilo Poggiolini, ed., 1983). One of the first international conferences for pharmaceutical regulation was held in Rome in 1979, with efforts to draft uniform regulations continuing since that time. *Id.* at vii-ix.

²¹⁶See *Meeting Notice*, 57 FED. REG. 13105 (1992).

²¹⁷David W. Jordan, Note, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND. J. TRANSNAT'L LAW 471, 492-95 (1992).

²¹⁸See *infra* § III.B.6.c.

²¹⁹See NIELSEN, *supra* note 178, at 30.

²²⁰21 C.F.R. § 314.106 (1993); See also John J. Gorski, *An FDA-EEC Perspective on the International Acceptance of Foreign Clinical Data*, 21 CAL. W. INT'L L.J. 329 (1990-1991).

active role in harmonization efforts to reduce duplicative testing in the US and abroad.

With globalization, the FDA must preserve its standards for quality control in the pharmaceutical market to preserve the US role of leadership in the pharmaceutical industry, as well as to protect our citizens. The US provides the most stringent standards in the world for the regulation of pharmaceutical drugs because of the importance of individual safety to the US public. Preservation of high US standards is important because of increasing numbers of joint ventures. The US has entered the Japanese market, while Japan (and other countries) are eager to market their drugs in the US. Thus, our example of scientific regulation may protect not only the health of US citizens, but potentially the health of citizens worldwide.

*b. Approval Process in Japan*²²¹

Most of the Japanese regulations for the approval and licensing of prescription drugs appear similar to those in the US.²²² To compete effectively in the global market, Japanese standards emulate FDA standards. Over the past twenty years, Japan has also implemented regulatory processes which emulate those in the US. For example, to formulate their Good Laboratory Process, the Japanese government exchanged information with the US and Switzerland.²²³ In addition, Japan has joined the World Health Organization (WHO) international monitoring system to exchange information with WHO.²²⁴

Pharmaceutical Affairs Law regulates the sale and distribution of pharmaceuticals in Japan under the Japanese Ministry of Health and Welfare.²²⁵ An investigative board, the Central Pharmaceutical Affairs Bureau

²²¹For an excellent description of the Japanese regulatory process see Health Ministry, *supra* note 166. Flow charts summarize laws at 39, 59; For comprehensive summary see also K. Shiota, *Drug Registration in Japan*, in PROCEEDINGS OF THE 2ND INTERNATIONAL CONFERENCE OF DRUG REGULATORY AUTHORITIES. Italian Ministry of Health, Raven Press (1982).

²²²Applications drug approval include preclinical testing conducted according to good laboratory practices issued by the Pharmaceutical Affairs Bureau. The Bureau also distinguishes between generic and new drugs requiring more extensive testing for new drugs. (see Shiota, *supra* note 221 at 66.) (Note: Generic is *not* the same as non-prescription. Generic connotes the 'no brand' edition of a drug with the same chemical structure. The FDA requires less testing for generic drugs because the compound has already been tested extensively. The major difference is now the manufacturing process—not the basic structure.) After initial classification of compounds, subcommittees of the Pharmaceutical Affairs Bureau study submissions. The National Institute of Hygienic Sciences also tests new compounds, while the National Institute for Health tests biologics and antibiotics. The Ministry of health issues final approval. JAPAN PHARMACEUTICAL, MEDICAL, AND DENTAL SUPPLY EXPORTERS' ASSOCIATION, JAPAN PHARMACEUTICAL REFERENCE: ADMINISTRATION AND PRODUCTS IN JAPAN 4, 6 (1st ed. 1989).

²²³Health Ministry, *supra* note 166, at 81.

²²⁴*Id.* at 57.

(CPAC) advises the Ministry about scientific and administrative aspects of pharmaceutical drugs.²²⁶ Various committees of CPAC evaluate the safety, quality and efficacy of new drugs. The Pharmaceutical Affairs Bureau acts as a secretariat for the CPAC to organize the submission of data, to minimize inconsistent policies between CPAC subcommittees and also to oversee efforts at international harmonization.²²⁷

In addition to approval, the Ministry of Health and Welfare requires pharmaceutical companies to obtain a license to import or manufacture a new drug. Before issuing a license, government inspectors investigate plants to ensure that they operate in compliance with good manufacturing practice.²²⁸ As in the US, the Japanese Ministry has a mechanism for post-market surveillance.²²⁹

c. Problems With Japanese Clinical Studies

Despite similarities in regulations, in practice studies in Japan are conducted with fewer scientific controls than in the US. Until 1990, the Health Ministry did not require pharmaceutical companies to inform patients that they were participating in drug trials.²³⁰

Recently, because of American dissatisfaction with Japanese studies, the Japanese industry has admitted to problems with enforcement of its regulations, and has reformed its approval process. Both the Health Ministry and the JPMA are implementing safety measures.²³¹ Significantly, because of efforts to compete in the US market, Japan has begun to evaluate differences between its studies and those conducted in the US.²³² Thus, strict standards imposed by the FDA have helped Japan improve its clinical testing.

²²⁵*Id.*; see also Pharmaceutical Affairs Law No. 145 of 1960, translated in Standards and Certification Systems Concerning Drugs in Japan.

²²⁶Shirota, *supra* note 221, at 66.

²²⁷Takao Hayakawa, *The Japanese Perspective Regarding Regulatory Concerns for Biotechnology Drugs and their Scientific Basis*, in DRUG BIOTECHNOLOGY REGULATION: SCIENTIFIC BASIS AND PRACTICES 468, 470 (Yuan-Yuan H. Chiu & John L. Gueriguan eds., 1991).

²²⁸Kanusky *supra* note 8, at 685-86.

²²⁹JAPAN PHARMACEUTICAL, MEDICAL, AND DENTAL SUPPLY EXPORTERS' ASSOCIATION, JAPAN PHARMACEUTICAL REFERENCE: ADMINISTRATION AND PRODUCTS IN JAPAN 4, 14-22 (1st ed. 1989).

²³⁰Robert B. Leflar, *Beyond Compensation: Personal Injury Compensation Systems in Japan: Values Advanced and Values Undermined*, 15 HAWAII L. REV. 742, 748 (1993).

²³¹*Pharmaceutical Industry of Japan*, DAILY NEWS BIOTECHNOLOGY & MED. TECH. May 18, 1995.

²³²Study by Naokata Shimizy of Teikyo University School of Medicine: US studies conducted in fifty percent of by CROs (19/30); CROs in 1/41 studies in Japan; more patients in US studies for each trial; differences is dosages; double blinding the responsible the investigator in 37/43 Japanese studies while in thirty-eight US trials,

d. Moral Hazard: Differences in US and Japanese Public Policy

While the quest for short term profits may induce US corporations to fail to recognize and track adverse events, US public policy has compelled strict regulation of pharmaceutical drugs through the FDA. In contrast, in the past, the Japanese government has shown less concern with regulation of safety and efficacy than in the economic success of their nation. As with the Ford Pinto saga in the US,²³³ Japanese corporations have at times valued profit more than human safety. In Japan, social hierarchies are the norm and administrative control is by an elite class; ordinary citizens are essentially excluded.²³⁴ Thus, an important difference between Japan and the US is the importance of individual protection in the US.²³⁵

In the past, both corporations and the government in Japan have placed economic development above the welfare of its citizens. The government risked the lives of their children by using a less safe DPT vaccine, while refusing to buy a safer US vaccine, presumably to protect Japanese product technology. This philosophy is at odds with the US policy to protect the individual and not allow businesses or the government to place financial interests above individual rights.²³⁶

In another striking example, the Ministry of Health and Welfare allowed the Japanese public to rely on blood products imported from the US even though the government knew that the blood might be infected with the HIV virus.²³⁷ The government delayed the approval of a foreign company's heat treatment to eliminate AIDS from blood products until October of 1985 to protect the development of a similar treatment by a Japanese company.²³⁸ This delay contributed significantly to the infection of forty percent of all hemophiliacs in Japan with the AIDS virus; many of those infected have either developed AIDS Related Complex and/or AIDS and have died.²³⁹

handled by person connected with sponsor in 15/38, 3rd party in 6/38; and unknown in 7/38. Study part of the harmonization effort. MARKETLETTER, Oct. 2, 1995, at 1-2.

²³³See *infra* §§ II.A. and II.B.

²³⁴Leflar, *supra* note 230, at 744.

²³⁵Studies support differences in American attitudes about risk from other countries. For example, in Britain, scientists and government decision makers recognize risk only when there is persuasive evidence of actual harm while in the US risk may be recognized without direct proof of injury to the public. See Sheila Jasanoff, *Cultural Aspects of Risk Assessment in Britain and the United States*, in *THE SOCIAL AND CULTURAL CONSTRUCTION OF RISK* 359, 385 (Branden B. Johnson and Vincent T. Covello eds., 1987).

²³⁶James Fallows, *What is an economy for?*, ATLANTIC MONTHLY, Jan. 1994, at 76.

²³⁷Yutaka Tejima, *Tort and Compensation in Japan: Medical Malpractice and Adverse Effects from Pharmaceuticals*, 15 HAWAII L. REV. 728, 735-36 (1993).

²³⁸*Id.*

²³⁹*Id.* at 735.

Additionally, litigation to protect individual rights is notoriously less frequent in Japan.²⁴⁰ In 1974, the High Court in Osaka reviewed the actions of Chisso K.K. toward victims suffering from Minamata disease following mercury poisoning from industrial waste. The court found Chisso's corporate treatment of the victim shareholders disgraceful.²⁴¹ Despite the dramatic manifestations of the mercury poisoning, which cannot be easily ignored,²⁴² the corporation failed to atone for dumping mercury into the bay, and only responded to victims' complaints after a massive onslaught of publicity from the press.²⁴³ Even then, the corporation failed to adequately compensate or protect victims from further harm. Although the company knew the cause of the disease as early as 1959, the government only recognized mercury as the cause of the disease in 1968.

Given this Japanese bias, support of the FDA becomes even more imperative to protect consumers in a global market. By maintaining high national standards for pharmaceutical production, the US can motivate Japan and other countries in the international market to adopt similar standards. For example, the Japanese Health Ministry stated the goal of elimination of its trade imbalance with the US and the EC as a motivation for allowing foreign manufacturers to make direct applications to the Health Ministry for new drug approvals.²⁴⁴ Similarly, motivation to trade may pressure the Japanese to require high standards for safety and efficacy prior to drug approval.

7. Deregulation of the FDA May Hasten Japanese Control

FDA regulations not only protect the public, but present a significant barrier for entry of other countries into our pharmaceutical market. Under current regulation, all products must meet US safety and efficacy standards. One commentator considered the regulatory process the chief obstacle delaying entry of Japan into the US market because of the greater intricacies and more stringent requirements for approval of drugs in the US.²⁴⁵

²⁴⁰Leflar, *supra* note 230, at 751. Author notes significant difference between American and Japanese products liability litigation. Litigation is almost absent in Japan for asbestos cases and cases against automobile manufacturers, cases highly litigated in the US. *Id.* at 754: unpredictability in liability litigation also less problematic because of standardized guidelines in Japan based on traffic accident schedules. See also Mark Ramseyer & Minoru Nakazato, *The Rational Litigant: Settlement Amounts and Verdict Rates in Japan*, 18 J. LEGAL STUD. 263, 274-76 (1989) (various factors in Japan much less favorable to plaintiff than in US such as contingent fee arrangements).

²⁴¹Chisso K.K. v. Goto, Osaka H. Ct. 1974.

²⁴²The disease crippled victims who became bedridden and incoherent; forty percent died and the public shunned those survived. (Chisso, K.K. v. Goto, Osaka Dist.Ct, (1974) in YUKIO YANAGIDA, ET AL., LAW AND INVESTMENT IN JAPAN, 500 (1994)).

²⁴³*Id.* at 501.

²⁴⁴Health Ministry, *supra* note 166, at 59.

²⁴⁵Mason, *supra* note 4, at 2.

Deregulation may cause several problems. First, under a deregulated system, without the protection of FDA standards and the threat of withdrawal of dangerous drugs from the market by the FDA, pharmaceutical companies may not track adverse events. Second, an increase in adverse events is likely because of market failure to detect serious infrequent adverse events may result in harmful drugs remaining in the market. Third, useful drugs may be removed from the market because of an association of symptoms with the drug which results in costly litigation even though the drug did not cause the symptoms. Fourth, an increase in costly litigation may also result from increased public reliance on the legal system for protection. Legal cases are likely to result in a concomitant loss of profits to pharmaceutical companies. These costs may contribute to the break-up of corporations with fragmentation providing Japanese companies an easy entree into the US pharmaceutical market.

An additional danger is that while deregulation may result in a decrease in the overall quality of prescription drugs both in Japan and in the US, the impact may be more severe in the US. US manufacturers, without FDA control, may concentrate on inferior, but more immediately lucrative products. In contrast, the Japanese may look to long term market development and invest in the necessary research to develop breakthrough drugs with more sustained long-term profit.²⁴⁶ Thus, the decline in quality for Japanese products may be less than the decline in US quality. The Japanese may differentiate their drugs from those manufactured in the US by providing superior quality (as they did in the automotive and electronic industries) leading to a greater public confidence in Japanese drugs than in US drugs. Note that without FDA controls, even the quality of these Japanese drugs may be significantly less than the quality of pharmaceutical drugs enjoyed by consumers at the present time. As with the automotive industry, once the US reputation for quality is lost it may be difficult to regain.

IV. ROLE OF RESEARCH: MAINTAIN US LEADERSHIP IN THE PHARMACEUTICAL MARKET

Business prosperity depends solely on the capability of research and development to discover epoch making new drugs.²⁴⁷ This time consuming process is expensive and the results of research are uncertain; drugs which initially seem promising ultimately lack sufficient efficacy or produce unforeseen severe side effects. Each year, only a handful of genuinely new drugs are commercialized. Furthermore, the number of new drugs is declining because rival companies find it more profitable to emulate a successful drug of their competitors than to find truly new compounds.²⁴⁸ In addition, the share

²⁴⁶See *supra* § II.B.

²⁴⁷*The Pharmaceutical Industry of Japan*, DAILY NEWS BIOTECHNOLOGY & MED. TECH. May 18, 1995.

²⁴⁸Claudio Tarabusi & Graham Vickery, *Globalization and pharmaceuticals*, OEDC OBSERVER, Dec. 1993.

of US government funding in research and development is less than two percent. In contrast, intensive government spending in other research and development intensive industries such as aerospace, computers and electronics are heavily funded by the government because of their importance for defense.²⁴⁹ Senator Pyror recently stressed the need for researchers at federal laboratories such as the National Institutes of Health to contribute to the discovery of new drugs in the US. However, according to Gerald Mossingoff, president of the Pharmaceutical Research and Manufacturers of America (PMA), over ninety percent of all new medicines are discovered, developed, and produced by the drug industry.²⁵⁰

There is significant controversy over the effort of pharmaceutical companies to invest in research. Many contend that monies are diverted for advertising and promotion and not enough is spent in development of new compounds.²⁵¹ President Clinton lambasted the pharmaceutical industry contending that they spent \$1 billion more in advertising than on research and development.²⁵² Based on documents filed with the FDA, Dr. Schondelmeyer, professor of pharmaceutical economics at the University of Minnesota, estimated that the typical drug company spends about sixteen percent of its budget on promotion as compared to two percent in most other consumer based companies (although some beer and cosmetic companies spend ten percent or more).²⁵³ The industry defends these expenditures because some of the marketing expense is used to educate physicians. Additionally, pharmaceutical companies assert the need to recoup profits rapidly because their patent protection lapses after ten to fifteen years.²⁵⁴

In fact, many of the larger pharmaceutical companies lack upcoming innovative new compounds.²⁵⁵ Ultimately, without the development of new compounds, pharmaceutical companies will fail. In contrast, if the Japanese are

²⁴⁹*Id.*

²⁵⁰*Is Government getting its Research Rewards?* MARKETLETTER Mar. 3, 1993.

²⁵¹Elizabeth Rosenthal, *Health economists question drug industry's profits*, AUSTIN AM. STATESMAN Feb. 22, 1993, at A1.

²⁵²*Id.* Based on Pink sheet estimate that in 1991 companies spent \$10 billion on research and development and \$11 billion on marketing.

²⁵³*Id.*

²⁵⁴*Id.*

²⁵⁵American Home Products (AHP), although employing 46,000 employees and owning high-profile brand-name drugs like Advil and Anacin is most limited by the lack of a steady flow of new drugs in its pipelines. Analysts states that this problem plagues not only AHP but other pharmaceutical companies.*6. Margaret Jacobs, *AHP emerging from seclusion*, STAR-LEDGER Mar. 1, 1992, at 1. The pipeline of new drugs at Ciba is running out. *Ciba expects "slower" 2nd half*, 8/31/95 AFX NEWS 11:46:00; Eli Lilly, hit by patent expirations and a near-dry pipeline had its first quarterly losses in September, 1992. Nancy Hass, *Serious Medicine: can a telephone man clear the static at Eli Lilly*, FIN. WORLD, Nov. 9, 1993, at 6.

more effective in promoting substantive research, and develop innovative drugs, their twenty-year goal of domination of the pharmaceutical industry may be met. Thus, it is imperative that US pharmaceutical companies make a larger commitment to substantive research to secure their position as world leaders.

Unlike companies which have survived on the promotion of existing drugs, but stagnated because of lack of expansion, other large and successful companies like Merck which have invested heavily in research have reaped the rewards of large profits, stability and growth.²⁵⁶ Merck also abides by the principle that safety sells products.²⁵⁷ A novel drug that captures a large share of the market can produce huge profits.²⁵⁸

Misplaced government cost cutting is placing the US's once undisputed position as a world leader in scientific research in jeopardy.²⁵⁹ To ensure our position of leadership and innovation, the US must infuse more funds into education and research, an approach that has worked successfully for this nation in the past.²⁶⁰ One dramatic example of the payoff of research is that of the polio vaccination which has saved billions of dollars in the cost of iron lungs and the chronic care of debilitated young patients.²⁶¹ Had the vaccine not been developed, the amount spent for victims today would be astronomical.²⁶² Arguably, research does not mesh well with an immediate bottom line philosophy. Some waste is inevitable in research; scientists need to explore blind alleys. Experiments are called experiments because the result of research is not known in advance. Furthermore, research which initially seems absurd to the lay person has resulted in unexpected advances in science. For example, genetic differences in the color of fruit fly's eyes may have been the forerunner of genetic engineering to provide treatment or to reverse deadly genetic diseases which are quite costly to treat.

Research could offer Americans unprecedented treatment for conditions ranging from Alzheimer's disease to cocaine addiction; ailments where billions are spent for supportive treatment which must be continued indefinitely be-

²⁵⁶Freudenheim, *supra* note 10.

²⁵⁷*Id.* (quoting Linda Lipsen, Washington Legislative counsel with Consumer's Union).

²⁵⁸*Id.* For example, Bristol-Meyer's new drug to lower cholesterol, Pravochol, was expected to earn \$100 million in 1992.

²⁵⁹Thomas Everhart, *Science in Jeopardy*, WASH. POST, Aug. 29, 1995, at A19.

²⁶⁰*Id.*

²⁶¹Polio struck millions of children; in 1952, 58,000 children were affected. The oral vaccine was developed after 30 years of research. Heloisa Sabin, *Animal Research Saves Human Lives*, WALL ST. J., Oct. 18, 1995, at A20.

²⁶²Bradley Southern, *Medicare's end-stage renal disease program: its development and implications for health care*, 26 HARV. J. ON LEGIS. 225, 250 (1989).

cause it fails to cure the underlying disease.²⁶³ Added benefits include the increase in jobs and economic growth derived from collaboration between research, industry, and government.²⁶⁴

Although the Japanese government inadvertently stymied the development of the pharmaceutical industry through its protectionist policies in the past, Japan has adopted a new approach. After the government targeted the pharmaceutical industry for international growth, the Japanese applied a unified approach to correlate industry and government actions. The Japanese joint investment in research and development will be instrumental in the Japan's potential success in dominating the pharmaceutical industry.

In summary, critical elements for the success of US pharmaceutical companies include the support of research for new compounds, the reduction of product liability suits and a more supportive and interactive relationship with the FDA. We must remember that cost savings of millions or even billions of dollars by decreasing basic research pale in comparison with the trillions that could be saved by developing breakthrough drug therapy.²⁶⁵

V. US CAN LEARN FROM THE JAPANESE

The US and Japan have historically taken different approaches to corporate development. The US can learn from the Japanese approach and integrate successful features of Japanese cooperation and funding of research and development into the US approach to the pharmaceutical industry.

A. Japanese Cooperative Approach

The Japanese government classically takes an interactive approach to integrate the government, regulatory bodies and industry in a cooperative effort to promote certain industries through administrative guidance.²⁶⁶ Through a comprehensive approach integrating industry, trade unions and the government, the Japanese government determines which industries it will target for growth and development.²⁶⁷

The trade association in the pharmaceutical field, the JPMA, has recently outlined the goals and concerns of the pharmaceutical industry in Japan. Despite the current rising profits in the pharmaceutical industry, the JPMA is concerned about a lower growth rate for drug development as compared to

²⁶³Tom Strong, *Porter, Biotech Broker, engineers NIH Funding Increase*, ASSOCIATES PRESS POL. SERV., July 30, 1995.

²⁶⁴*Id.*

²⁶⁵Everhart, *supra* note 259, at 2.

²⁶⁶ROBERT BALLON & IWAO TOMITA, *THE FINANCIAL BEHAVIOR OF JAPANESE CORPORATIONS*, 26-31 (1988).

²⁶⁷*See generally*, Michael Young, *Judicial Review of Administrative Guidance: Governmentally Encouraged Consensual Dispute Resolution in Japan*, 84 COLUM. L. REV. 923, 926-32 (1984).

other countries. Additional concerns include potential price reductions for drugs due to anticipated health care costs as the Japanese population ages.²⁶⁸ The JPMA plans to work with the Ministry of Health and Welfare's Pharmaceutical Safety Assurance and Safety Measures Study Group to improve the safety of new products and to increase the efficiency of the approval process. The JPMA is also dedicated to strengthening interactions with the US and the EC through the international activities with WHO, the PMA,²⁶⁹ and European groups. A major effort at interaction includes work through the Third International Conference on Harmonization in 1995 in Yokohama.²⁷⁰

In contrast, the US has historically taken a market force approach, holding that competition provides the most efficient method to market products.²⁷¹ The US pharmaceutical industry, the FDA and the government have come to see each other as opponents rather than as allies, making cooperation and the establishment of national goals significantly more difficult than in Japan. An effort to define common goals and to institute cooperation between industry, research and government would help promote the US pharmaceutical industry. Rather than diverting resources to hostile in-fighting by attacking FDA, cooperation would increase resources and efficiency.

User fees provide a good example of the mutual gain achieved by cooperation between industry and government. The industry benefits from decreased approval times for new drugs while the public profits from a greater accessibility to safe new drugs. Additionally, government resources should be used for research and education in the US to promote further technological innovation.²⁷²

US public policy, to protect individual rights, has proven stronger than the market force philosophy. Congress gave the FDA significant authority to regulate the approval of pharmaceutical drugs both because of the inherent dangers of pharmaceutical drugs and the inability of the market to protect the public from dangerous and/or ineffective drugs. This policy should be continued to enhance cooperation between government and industry.

B. Japanese Approach to Litigation

In Japan, unlike the US, the government passed the Drug Side-Effects Injuries Relief and Research Promotion Fund Act to avoid lengthy litigation and to aid those suffering from disease, disablement or death caused by the proper use of drugs.²⁷³ This Act provides benefits²⁷⁴ for injured patients but

²⁶⁸Issues facing Japan's Drug Industry in 1995, MARKETLETTER, Sept. 18, 1995, at 1.

²⁶⁹The US equivalent of the JMPA.

²⁷⁰See *supra* § III.B.6.a. on harmonization.

²⁷¹Fallows, *supra* note 236.

²⁷²See *supra* § IV.

²⁷³Tejima, *supra* note 237, at 732.

excludes many types of drugs such as blood products and treatment for cancer because the government assumes that patients must take some risk for their treatment.²⁷⁵ The Act also excludes cases where the pharmaceutical company (or doctor) is responsible for the adverse event.²⁷⁶ Thus, the Japanese Act protects pharmaceutical companies from excessive strict liability, provides compensation for unavoidable adverse events and still leaves manufacturers liable for negligence or fraud. A similar act in the US could both protect those injured by drugs and avoid many of the problems associated with strict liability for pharmaceutical drugs.²⁷⁷

C. US Research Opportunities in Japan

With innovative new compounds, US companies will have access to the Japanese market, the second largest user of prescription drugs. Recent changes in Japanese regulations have increased opportunities for US expansion in Japan.

Since 1984, foreign companies may go directly to the Konseisho (the Japanese equivalent of the FDA) for drug approval.²⁷⁸ Since 1986, the Ministry has accepted foreign preclinical studies and allowed foreign companies to apply directly to the Ministry for both approval and licensing without a Japanese partner.²⁷⁹

Thus, like the US, Japan has eased its previously stringent limitations on foreign drug investigations, approval and marketing. In response to the easing of restrictions against foreign pharmaceutical companies, well established US and European firms are expanding research and development facilities in Japan.²⁸⁰ These companies pose a significant long term threat to Japanese pharmaceutical companies.²⁸¹

US firms in Japan are also learning Japanese marketing strategy. For example, sales forces in Japan target doctors more than in the US because drugs

²⁷⁴*Id.* Provides medical expenses, medical allowance, personal damage pension, pension for upbringing managed children, bereaved family pensions, lump sum benefits for bereaved families and expenses for funerals.

²⁷⁵*Id.*

²⁷⁶*Id.* at 733.

²⁷⁷See *supra* § II.B.3.

²⁷⁸Mason, *supra* note 4, at 1. Before 1977, foreign companies had to apply through a Japanese company.

²⁷⁹Foreign data must be accompanied by a certificate of good laboratory practices from the applicable foreign government. Additionally, the Ministry requires Japanese data for some clinical tests including absorption, metabolism, exertion and dosage because of potential differences in populations. See Health Ministry, *supra* note 166 and Shirota, *supra* note 221.

²⁸⁰Rubinien, *supra* note 27, at 2.

²⁸¹Mason, *supra* note 4, at 2.

are sold by the physician to the patient, so that the physicians make a profit every time they sell a drug. Now US firms are not relying on the Japanese firms, but are marketing their own drugs.²⁸² Additionally, US companies are acquiring Japanese pharmaceutical companies.²⁸³ For example, Upjohn opened a large facility for 14 billion yen in June of 1988.²⁸⁴ Other examples of a US acquisitions in Japan include Merck's fifty-one percent share of Banyu, a Japanese company which has risen from the mid-twenties to the tenth or eleventh largest company in Japan, and Pfizer's wholly owned research facility in Japan.²⁸⁵ Such acquisitions will be far more profitable if the US develops new compounds to establish a competitive edge in foreign markets.

VI. CONCLUSIONS

The Japanese threat to dominate the US pharmaceutical industry within the next twenty years should not be ignored. The US must anticipate and defend against Japanese market offenses through support of the FDA to ensure safety and efficacy and to further research to develop new compounds.

To preserve the US role of leadership in the pharmaceutical industry as well as to protect our citizens, the FDA must preserve its standards for quality control and safety in the pharmaceutical market. Since Japan (and other countries) are eager to market their drugs in the US, and must comply with US laws, FDA regulation will protect not only US citizens, but potentially citizens worldwide.

Market forces and the legal system cannot adequately protect the public. Deregulation of the FDA would both hasten Japanese control of the US pharmaceutical industry and violate US public policy to protect individuals against undisclosed risks. Instead, the US needs to reform and improve the FDA and inject substantial resources into research and development to maintain our role as leaders in the world pharmaceutical market.

²⁸²Rubinfiem, *supra* note 27, at 2. Ciba-Giegy stopped relying on Takeda and Fujisawa; Eli Lilly now has independent sales force and is not so reliant on Shionogi.

²⁸³*Id.* For example, Merck & Co. acquired a major share of the family owned Banyu Pharmaceutical Co. in 1983.

²⁸⁴*Id.*

²⁸⁵Gerry, *supra* note 24.

