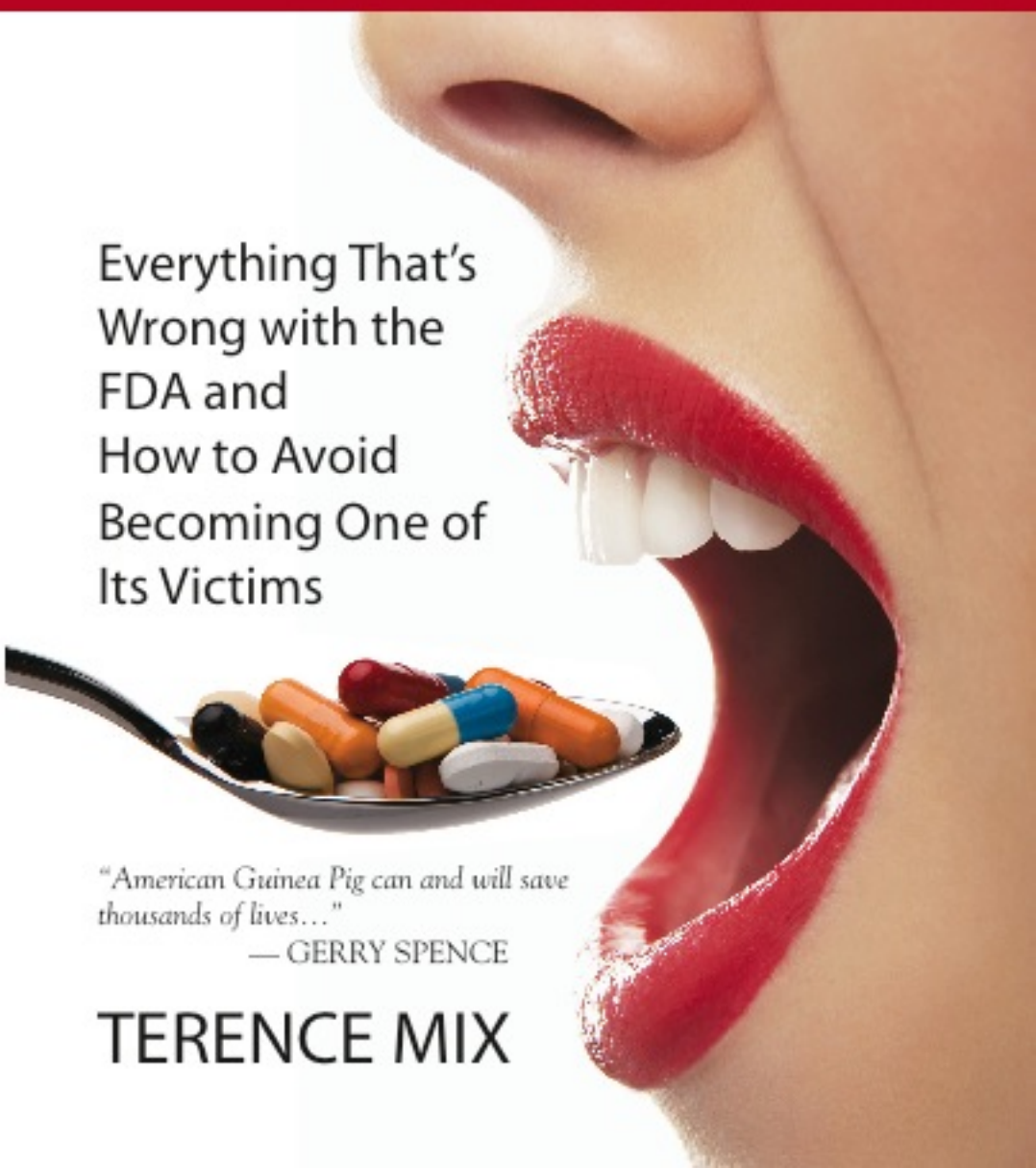
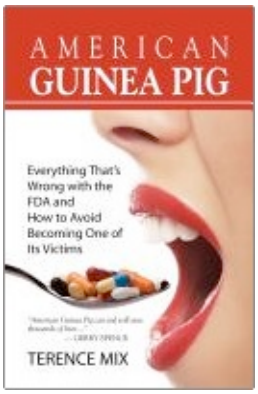
AMERICAN GUINEA PIG

Everything That's Wrong with the FDA and How to Avoid Becoming One of Its Victims



"American Guinea Pig can and will save thousands of lives…"
— GERRY SPENCE

TERENCE MIX



American Guinea Pig *explores how and why the FDA and the drug industry contribute to 230,000 deaths and 2.3 million hospital-stays per year - and the changes that are needed to solve the multiple problems. Also offered are practical and effective steps that consumers of drug products can take to significantly reduce the risk of taking a trip to the hospital or morgue and becoming another statistic of the system.*

American Guinea Pig

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INTRODUCTION

What did Michael Jackson, Heath Ledger and Anna Nicole Smith have in common?

They all died as a result of an adverse reaction to a combination of prescription drugs—a drug cocktail, you might say. But these were the ones who got attention. There were actually many more—hundreds of thousands more—who lacked celebrity, but experienced a similar fate.

Every year about 230,000 Americans die as a result of an adverse reaction to one or more prescription and nonprescription drugs.[1] You read that right—*230,000 Americans die every single year as a consequence of the use of legally purchased drugs,* the vast majority either prescribed or recommended by the victim's treating physician. In five years they kill in excess of *one million Americans*. It is the third leading cause of death in the United States, behind only heart disease and cancer. To put this in perspective, it would be comparable to every man, woman and child in the city of Orlando dying within a 12-month period—leaving a ghost town right next to Disney World.

And here's the scary part. Of that number, almost half—105,000—are taking the drug exactly as specified by the pharmaceutical company that manufactured the drug.[2] Bottom line: *prescription and over-the-counter drugs can kill you*—even when everything is done right.

The other 125,000 deaths occur as a result of a *mistake*. Either the prescribing doctor did not follow the directions specified by the drug company, or a nurse did not properly administer the drug, or the patient did not follow the instructions given by the physician and/or the pharmacy, or the pharmacy filled the prescription improperly. And yes, doctors and other medical care providers do make mistakes. According to the Institute of Medicine, there are approximately

1,500,000 *preventable* medication errors every year, most of which are caused by physicians and nurses.[3] Indeed, the majority of medication errors leading to deaths or a serious adverse drug reaction (ADR) occur in a hospital setting, where the patient has little opportunity to make a mistake with ordered medications. No less than 770,000 of these ADRs are serious enough to actually extend the hospital stay.[4]

Thus, pharmaceutical products do more than kill us—they also put us in the hospital. Every year 1,500,000 Americans are hospitalized as a result of a serious ADR.[5] Combined with in-hospital events, this equates to 2,270,000 annual victims spending time in the hospital as a direct consequence of using one or more prescription and/or nonprescription drugs. Although we never quite make it into a hospital, over 4,000,000 more of us seek medical care at physician offices and hospital outpatient departments and emergency rooms.[6]

Unfortunately, these tragedies are not limited to prescription drugs. Over-the-counter (OTC) drugs also take their toll. For example, according to statistics recently released by the FDA, 56,000 patients annually seek emergency room treatment as a result of liver failure caused by the use of acetaminophen, with most of the cases involving inadvertent overdosing.[7]

Acetaminophen overdoses are the leading cause of acute liver failure in the United States, Great Britain and most of Europe; and of the 56,000 related emergency room visits in the U.S., 2,600 of these patients are hospitalized and nearly 500 die annually.[8] But even keeping your use at recommended doses may not afford protection. Researchers have also found that taking acetaminophen at regular doses can cause liver damage.[9] For those of you who rarely read the labeling on OTCs, one brand of acetaminophen is *Tylenol*.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of pharmaceuticals that also wreak havoc on this country. And although the most dangerous NSAIDs are prescription drugs, others such as ibuprofen (i.e., *Advil* and *Motrin*) also take their toll. Even taken at recommended doses (up to 1200 mgs/day), ibuprofen has been known to cause hospitalization and death, especially when used with aspirin. Since ibuprofen has anti-inflammatory benefits, it is often taken by patients with arthritis. However, if combined with aspirin, it can be deadly. It has been reported that patients taking both aspirin and ibuprofen have a 73 percent increased risk of death from heart disease.[10]

This national crisis goes beyond the tragedy of hundreds of thousands of preventable deaths and the avoidable suffering of millions. It also has an impact on our pocketbooks. It has been calculated that the total annual health care costs as a consequence of adverse drug reactions equals $177.4 billion.[11] And that was in 2000 prices. The current number *easily exceeds a staggering $200 billion.* That is one trillion dollars over five years. It is thus a major contributor to the health care calamity that is consuming this country and holding us hostage in the results of a recession that will be felt for years to come.

Those are the numbers and they are as frightening as they are shocking.

They have also driven me to write this book. As a trial attorney who spent a major part of his career litigating against pharmaceutical companies, I had an intimate knowledge of what went on behind the scenes in the drug industry and its unhealthy relationship with the Federal Food and Drug Administration (FDA) that purportedly was its regulatory overseer. I thus was quite familiar with the multitude of problems in the system and why so many of my clients were suffering severe side effects from drugs that were never the subject of a

warning, either by their doctor or the pharmaceutical company. What I lacked was an appreciation of the *scope* of the problem.

Since 1975, I have had numerous exchanges and dealings with the FDA, ranging from requests for records under the Freedom of Information Act, to multiple pieces of correspondence and e-mails, to testifying in front of an FDA advisory committee,[12] to the filing of a formal citizen petition demanding that the agency order studies and warnings on fertility drugs. I have seen confidential corporate memoranda prepared by drug companies containing the content of discussions with FDA personnel at meetings and during telephone conversations. I have read numerous papers and books written by members of both the medical and legal professions, dissecting all of the problems associated with the testing and monitoring of drugs in the United States. I have literally reviewed over 1,000 peer-reviewed published studies assessing the effectiveness and risks associated with the use of pharmaceuticals. I have examined and cross-examined medical experts in the fields of pharmacology and toxicology, epidemiology, pathology and the standards of care for drug companies, including a former commissioner of the FDA. In the recent past, I spent no less than three and a half years researching and writing a nonfiction book[13] which followed the 48-year history of the fertility drug, Clomid, exposing all of the concealment, deception and failures not only of its manufacturer but also the manufacturer's counterpart in Rockville, Maryland.

You might say that my education has not only been extensive but historical. I have had the benefit of seeing how the FDA has dealt with adverse reaction issues in the 1970s, 1980s, 1990s and currently. Over those decades, of course, there have been changes, both procedural and substantive. Some have represented an improvement. But in my opinion the most significant ones have been enacted to

accommodate the interests of the drug industry, all to the detriment of the American consumer of drug products.

This view is shared not only by many members of the medical profession but even some holding important positions with the FDA itself. When Dr. David Graham testified before the Senate Finance Committee on November 18, 2004, he really opened some eyes. Not only did he recite the tragic history of Vioxx,[14] he also painted a graphic picture of inefficiency that then existed at the FDA. At the time of his testimony, Dr. Graham had worked for the agency for 20 years and was the associate director for science and medicine of the Office of Drug Safety (ODS).[15] As an insider, he spoke from a position of knowledge and experience. His words had the conviction of a concerned scientist who wanted to right the ship. What was portrayed to Senator Grassley (R-Iowa) and his committee was not pretty.

> The problem you are confronting today is immense in scope. Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless. It is important that this Committee and the American people understand that what has happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, FDA and its Center for Drug Evaluation and Research[16] are broken. . . . The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division [Office of New Drugs] approves a new drug, it is also saying the drug is 'safe and effective.' When a serious safety issue arises post-marketing, their immediate reaction is

> almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. *The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest.* At the same time, The Office of Drug Safety [ODS] has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs. (Emphasis added.)

Dr. Graham's views seem to be shared by Dr. Janet Woodcock, Deputy Commissioner of Operations for the FDA and the director of the Center for Drug Evaluation and Research (CDER)—at least back in 2005. When Dr. Woodcock appeared before a medical advisory panel to the Institute of Medicine on June 8, 2005, her comments seemed to echo the views of her FDA colleague.[17] The FDA's drug safety program had "pretty much broken down," she reported. And when it came to discovering the dangers of drugs already on the market, there was room for a "lot of improvement."

Some might argue that those problems were fixed when Congress passed the Food and Drug Administration Amendments Act of 2007 in the fall of that year, which certainly granted post market powers to the FDA that it lacked prior to its enactment. But, as will be explained later, until such time that the FDA demonstrates a willingness to efficiently *use* those powers, this might be another example of the horse unwilling to drink the water. For as currently structured, it is the

partnership between industry and regulator that has a stranglehold on the rank and file of the FDA, many of whom are committed to public safety. That legislation, unfortunately, addressed neither the conflict referred to by Dr. Graham nor the two major *premarket* problems that, in my view, are largely responsible for using the general public to discover most of the serious ADRs that are killing and sending us to hospitals—that have effectively made us unwitting guinea pigs for the pharmaceutical industry.

More than 50 percent of approved drugs have serious adverse reactions not detected prior to approval—they are discovered only *after* they are marketed.[18] What makes this statistic particularly terrifying is that the study upon which it is based used statistics compiled from 1976 to 1985, prior to the enactment of the Prescription Drug User Fee Act (PDUFA) in 1992. As is explained in Chapter 2, the PDUFA and its renewals every five years have created an environment at the FDA in which drugs are literally rushed to market. This percentage is thus unquestionably higher, as corroborated by a study published in 2007[19] in which they found a 2.6-fold increase in serious ADRs reported to the FDA between 1998 and 2005, 87.6 percent of which were new and serious drug reactions *not included in the product labeling*.

If an adverse reaction occurs only once in 100,000 users—or even once in every 10,000—then this might be understandable. But when the incidence is less than 1/1000, this is not only unacceptable, it is inexcusable. When evidence of a serious and fatal drug reaction surfaces only *three months* after the drug was introduced on the market—as it did with the cholesterol-reducing drug, Baycol—something is horribly wrong with our premarket testing system. The Baycol story will be discussed, along with a number of other drug debacles, and the multiple reasons why they occurred and continue to occur at an alarming rate.

To solve any problem, it is necessary to recognize that it does in fact exist and look at why it is occurring. Part I of this book will explore in depth what is and has been occurring, with special emphasis on the past decade. The use of example is a great educational tool; and you will read about several different drugs, some of which have received considerable notoriety and others you may not have heard about. All will demonstrate the problems with the current system of testing and monitoring of drugs.

Part 2 will propose important solutions to those problems, which can only come about by an act of Congress. In fact, as you will learn, Congress played a major role in establishing laws which virtually mandate pushing new drugs onto the market without an adequate opportunity to assess their safety. This first occurred in 1992, when agency and industry approached members of Congress and encouraged them to enact the Prescription Drug User Fee Act—which they renewed with minor revisions in 1997, 2002 and 2007.

The current system by which the FDA evaluates the safety and effectiveness of drugs is inefficient and responsible for a large proportion of our country's annual health care costs. Not only does the FDA lack accountability and transparency, the *premarket* testing of drugs is archaic—in need of a major overhaul—and the FDA's *postmarket* monitoring system lacks any reasonable measure of urgency to promptly respond to established dangers arising out of the general public's use of prescription and nonprescription drugs. Addressing and fixing these problems could result in an annual savings of at least $100 billion in health care costs—a savings of one trillion dollars over ten years. Part 2 of this book proposes ways to do just that—and so save 100,000 lives a year and immeasurable suffering in the process.

All drugs have side effects, including those which you can purchase at your local pharmacy or supermarket without a prescription. However, to reach the marketplace, they must go through an assessment by the FDA to determine whether their *benefits outweigh their risks.* This is a process referred to at the FDA as *risk evaluation and mitigation strategies*. If a drug cannot meet this minimum standard, it is either not approved for marketing or removed from circulation if it has already been sanctioned for sale. Thus, if a drug has only negligible or minimal effectiveness, the presence of even mild to moderate adverse reactions will likely keep it off the market—at least in theory. But if it has been shown to be effective at treating a serious or potentially fatal disease or condition, even severe side effects will not preclude its use. In such instances, it is dealt with by requiring *adequate warnings* of those risks. The strongest cautions about a serious ADR are contained within a *black box warning*.

Warnings serve two primary purposes. First, they allow the user of the drug to make an *informed choice* on whether or not to use the drug. What are the odds of developing a serious side effect? Can it be permanent or fatal? Is it worse than the condition I am trying to treat? Is there an alternative form of treatment available, including another drug with less severe adverse reactions? This is the ideal analysis a patient should make before agreeing to take a drug or, for that matter, even before it is purchased.

Second, they provide patients with an *early detection system* to educate them about what to be on the lookout for before the drug reaction becomes so severe and advanced that it is beyond any form of effective treatment. What are the initial warning signs? How quickly do they develop? Are they too far advanced by the time the clinical symptoms are manifested? If so, are there laboratory studies available that can monitor your vital organs and expose the ADR

when it is still subclinical? This is the desired education every patient should seek before ingesting the pill or receiving the injection.

But what do you do when the ADR is never mentioned by the prescribing doctor or listed in the product labeling that accompanies the drug or is handed out by the pharmacy? How can you protect yourself when neither the doctor nor the pharmacy is aware of the ADR? Part 3 of this book arms you with the tools needed to protect yourself and your family as a last line of defense—to access available information about the dangers of the drug that has yet to be distributed to the medical profession at large. Much too often, the FDA has received incriminating evidence that it is sitting on, *sometimes for months and years*, before acting to mandate warnings or to order removal of the drug from the market. Part 3 will educate you on –methods and means available to discover and understand the results of cutting edge studies about the potential risks of drugs currently on the market. It will become your handbook for each step to take before using *any* drug in the future.

We can never know with certainty that all true *rare* ADRs have been discovered until a drug has been on the market for years and consumed by millions. With proper use if this book, however, and implementation by Congress of its many proposals, there will no longer be a reason for each of us to be viewed by the drug industry and the FDA as an *American Guinea Pig*.

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[1] Smith, *American Pharmacy* NS29 (1) February 1989; Lazarou et al., JAMA 279 (15) April 1998: 1200–05.

[2] Lazarou et al., JAMA 279 (15) April 1998: 1200–05.

[3] "Preventing Medication Errors," Institute of Medicine Report Brief, July 2006.

[4] Classen et al., JAMA 277 (4) 1997: 301–06; Cullen et al., *Critical Care Medicine* 25 (8) 1997: 1289–97; Cullen et al., *Journal of Quality Improvement*, 21 (10) 1995: 541–48.

[5] Moore et al., JAMA 279 (15) April 1998: 1571–73.

[6] Zhan et al., *Jt Comm J Qual Patient Saf* 31 (7) July 2005: 372–78.

[7] Matthew Perrone, Associated Press article, June 30, 2009.

[8] Lee, *Hepatology Research* 38 (Suppl.1) 2008: S3–S8.

[9] Watkins et al., JAMA 296 (1) July 2006: 87–93.

[10] MacDonald and Wei, *The Lancet* 361 (9357) 2003: *cet*, 361, 573–74.

[11] Ernst et al., *J. Am. Pharm. Assoc*. 41 (2) March–April 2001: 192.

[12] The FDA currently has at its disposal 16 different advisory committees comprised of independent experts who provide the agency with the benefit of their opinions on a multitude of issues, including the necessity of warnings or whether a drug should be withdrawn from the market. The FDA, however, is not bound by the decision.

[13] *THE PRICE OF OVULATION: The Truth about Fertility Drugs and Birth Defects—and a Solution to the Problem* (Aurora, Colorado: Tendril Press, 2009).

[14] For the full story on Vioxx, see Chapter 8.

[15] The Office of Drug Safety is now the *Office of Surveillance and Epidemiology*, which is responsible for the monitoring of drugs after they are on the market.

[16] The Center for Drug Evaluation and Research (CDER) is the division of the FDA responsible for evaluating and monitoring the safety and effectiveness of drugs.

[17] "Drug Safety Problem's Broken, a Top FDA Official Says," *New York Times*, June 9, 2005.

[18] *FDA Drug Review: Postapproval Risks, 1976–1985* (Washington DC: US Government Accountability Office, April 26, 1990), GAO/PEMD-90-15.

[19] Moore et al., *Archives of Internal Medicine* 167 (16) September 10, 2007: 1752–59.

PART ONE

The Problems

CHAPTER 1:

PREMARKET - THE FOX-GUARDING-THE-HENHOUSE PROBLEM

After a drug company has completed its preliminary studies on a drug, in order to commence clinical (human) studies, it is necessary to file an Investigational New Drug (IND) application with the FDA. Included within the application are the results of all animal pharmacology and toxicology studies; the experience with humans, if available—generally from other countries; chemical and manufacturing information; and clinical protocols (guidelines) for the proposed studies, along with an investigator's brochure, the qualifications of the proposed clinical investigators and informed consent information for the patients to be treated. *Clinical investigators* are physicians who have been handpicked by the pharmaceutical company to administer the drug during the clinical trials. They are generally expert/specialists at treating the disease or condition that the drug is intended to cure or improve. These studies are referred to as *clinical investigations*.

This filing not only kicks off the procedures to commence the clinical investigations, it is at this stage that the FDA becomes involved for the first time in the overall process to evaluate the safety and effectiveness of drugs destined to be marketed throughout the nation.

Once the IND is approved by the FDA, the studies are conducted under the supervision and monitoring by the drug company in three phases: *PHASE I* usually involves between 20 and 100 subjects, and is conducted to determine the metabolic and pharmacological actions of the drug, the dose levels to be given and to detect any early side effects; *PHASE II* is primarily done to determine the effectiveness of

the drug, along with continuing to assess the risk of potential side effects, and normally involves 100–500 patients; and *PHASE III* clinical trials usually involve from 1,000 to 5,000 patients, and are designed to evaluate the overall safety and effectiveness of the drug, including its proper dosage, any and all adverse reactions and interactions with other drugs. PHASE I clinical trials last for about one year; PHASE II clinical trials about two years; and PHASE III clinical trials about three years.[1]

All such premarket clinical trials are designed, supervised, conducted and monitored by the drug manufacturer, which thereafter gathers all of the records from the studies, compiles the statistics, summarizes them and ultimately reports its findings and conclusions to the FDA, along with copies of the clinical investigators' records on the patients treated with the drug.

It is this submission of records from the *drug company* that are reviewed by medical officers within the Office of New Drugs (OND) at the FDA's Center for Drug Evaluation and Research (CDER) to determine whether or not the drug under study is safe and effective. Importantly, these records are not sent directly from the clinical investigators to the FDA—they first take a detour to a pharmaceutical company that stands to lose hundreds of millions of dollars should the drug be rejected by the FDA for marketing.

Drug Company Conflict of Interest

It is hard to imagine a more biased entity than a drug company under these circumstances. By the time a drug is approved for marketing, it will have been involved in drug discovery, research, development, testing and review for about 15 years and the manufacturer will have incurred hundreds of millions of dollars in costs. And it is not the cost of a single approved drug that is

important; it is the *entire cost* of the company's total program for research, development, testing and review.

On average, for every 10,000 chemical compounds studied by a pharmaceutical company during the discovery stage, only 250 go through preclinical studies (e.g., animal pharmacology and toxicology studies, etc.); of the 250, only five compounds are selected to go through the three phases of clinical studies; and of those five, only *one* gets FDA approval for marketing.[2] It is thus this *one* drug that the manufacturer is relying upon to not only return hundreds of millions of dollars invested in its research and development program but to show a handsome profit to its stockholders. Another dynamic playing a role on this issue is that, over the years, while relative costs for research and development have been steadily *increasing*, the number of new drugs being approved have been generally *declining*.[3] With everything riding on this one drug, it is not difficult to imagine a company minimizing or "overlooking" a serious adverse reaction being reported by its clinical investigators—or even concealing it from the FDA—especially if it otherwise is demonstrating some level of effectiveness in treating the designated illness or condition.

Clinical Investigator Conflict of Interest

Although the clinical investigators are in *theory* impartial third parties, in *reality* they have been handpicked by the drug company, not just because of their level of expertise in the treatment of the subject illness or condition, but frequently because the company has developed a prior relationship with the investigator.

In many instances the company has previously provided grants that allow the investigators to conduct studies that not only expand on their expert knowledge in the field but also their reputation among peers and others in the medical profession. This, in turn, can lead to a

lucrative referral business. Many are also paid fees and retainers to be consultants for the company. Others are given fees and expense coverage for speaking engagements at medical symposiums and seminars at which the speaker might put in a good word about the company's drug.[4] Pharmaceutical companies are also famous for their generosity to physicians who might be prescribing their drugs—doctors who might later become investigators in clinical studies. Stories abound about kickbacks to physicians and hospitals; gifts of trips to luxurious golf and ski resorts; and "educational grants" to pay for cocktail parties, Christmas parties and travel.

The tentacles of the drug industry are long and ubiquitous. Such ties and conflicts of interest between investigators and drug companies even extend to the National Institutes of Health (NIH), where many clinical investigations involving pharmaceutical products are conducted. One assessment of conflicts at the NIH revealed that over a five-year period ending December 31, 2004, at least 530 NIH scientists had received fees, stocks and stock options from pharmaceutical companies.[5]

Thus, not even the National Institutes of Health are immune from this infestation. This is particularly disturbing. When a drug company conducts or sponsors a clinical study that becomes published, the medical profession is put on notice of this fact and can take it into consideration when deciding what weight and merit to give to the study. But the NIH is a part of the federal health care system and has the appearance of being objective and independent. Whenever the NIH oversees or funds a drug study, it is presumed that it has been conducted without bias and uninfluenced by the manufacturer of that drug.

The value of these perks was not inconsequential. During this period of time, a laboratory director from the National Cancer

Institute received $70,000 in consulting fees from a company developing an ovarian cancer test; the NIH's top blood transfusion expert accepted $240,200 in fees and 76,000 stock options from drug companies developing blood-related products; and a senior psychiatric researcher took in $508,050 from Pfizer, which at the time was marketing an Alzheimer's drug.

One of the biggest beneficiaries of corporate largess was Dr. H. Bryan Brewer Jr., head of the National Heart, Lung, and Blood Institute's molecular disease branch, and a top authority on cholesterol.[6] Between 2001 and 2003, he was paid $114,000 in consulting fees from four pharmaceutical companies developing or marketing cholesterol drugs, including $55,500 from Pfizer (Lipitor) and $31,000 from AstraZeneca (Crestor). Lipid Sciences, Inc., another company involved in addressing cholesterol problems, paid Brewer an additional $83,000 during the same period. In September 2003, his consulting contract was converted to an annual fee of $125,000, plus stock options. Through December 2004, Brewer held 411,927 stock options in the company. At the same time, Brewer pulled down an annual salary from the federal government of $187,305.

Was there a *quid pro quo* for all the consulting fees and stock options? Judge for yourself. In 2003, the psychiatric researcher publicly endorsed Pfizer's Alzheimer drug; a study of a competitor's ovarian cancer test was dropped by the National Cancer Institute; and the blood transfusion expert spoke and wrote about the benefits of the blood-related products he had been consulting on.

Here again, Brewer justifies special attention. In 2001, along with eight other experts, he proposed stricter guidelines for reducing cholesterol levels. These standard levels were further reduced in July 2004. As a consequence, the number of patients using cholesterol-reducing drugs—and the resultant sales volume—likely doubled.

Eight of the nine members on the panel, including Brewer, had financial ties with drug companies that stood to see financial gains from the new standards.

On August 21, 2003, an article written by Brewer appeared in the *American Journal of Cardiology,* extolling the advantages of Crestor over three other competing cholesterol drugs. The publication followed by a week the drug's approval for marketing. It prominently mentioned Brewer's position with the NIH, but *failed to reveal any of his financial ties with AstraZeneca*. Brewer concluded in the paper that the "benefit-risk profile (of Crestor) appears to be very favorable." He assured that there was no cause for concern about patients developing rhabdomyolysis, the same sometimes-deadly side effect for which Baycol had earlier been removed from the market. "No cases of rhabdomyolysis occurred in patients receiving (Crestor) at 10 to 40 (milligrams)," he wrote. Unmentioned were eight cases that were reported during the Crestor clinical studies, including one patient who had taken the low dose of 10 mgs. When asked why he had failed to mention the eight cases, he defended the omission by explaining that seven of the patients had been on doses that exceeded the recommended amount and "it was not possible to definitely conclude" that the low-dose case had been caused by the drug.

During its first year on the market, the FDA received 78 case reports of rhabdomyolysis in association with use of Crestor, two of them fatal.

The practice of highlighting positions with the NIH and omitting financial ties has likewise been followed by many of Brewer's colleagues. In fact, federal employees at the NIH have been quite reticent about revealing their secondary sources of income to anyone—even their boss. In a random sampling of outside payments to NIH scientists, a July 2004 report from the United States Office of

Government Ethics found that 40 percent had not been approved in advance or accounted for within the agency.[7]

On September 10, 2006, the *Los Angeles Times*[8] reported on an internal review by the NIH related to a Dr. Thomas J. Walsh, one of its top cancer researchers. It was discovered that Dr. Walsh had received "consulting fees" in excess of $100,000 from various drug companies, which were neither approved nor reported in violation of established NIH rules and procedures. It was also revealed that Dr. Walsh had even appeared on behalf of a drug company (Merck) to advocate approval of its drug to an FDA advisory committee, following a review of the company's data conducted by Walsh and other NIH staffers.

The *Times* article identified yet another senior NIH researcher, likewise caught with his hand in the cookie jar—a Dr. P. Trey Sunderland III. Dr. Sunderland's area of expertise involved Alzheimer's research. His hand was caught with an even larger bundle of dough—$612,000 from Pfizer, to be exact. In June 2006, Dr. Sunderland refused to answer questions before a congressional subcommittee investigating abuses at the NIH, seeking refuge under the Fifth Amendment. On December 4, 2006, he was charged by federal prosecutors with criminal conflict of interest.

With the power to select its own investigators, a drug company many times can almost guarantee a "clean bill of health" at the conclusion of a study—even at the NIH.

Access to Clinical Records

Although clinical investigators maintain their own set of records created during a study, they usually transfer information onto forms supplied by the drug company, which are sent to the sponsor[9] of the study along with copies of the investigators' records. As the

pharmaceutical company gathers these medical charts, laboratory studies and forms of the patients treated with the drug under study, it begins compiling the data onto its computers, and later summarizes and submits it to the FDA along with its interpretation and conclusions.

It is during this compilation stage that the company is in a position to alter, destroy or discard records reporting on unfavorable adverse reactions that might stand in the way of approval or dictate a strong warning that could impact sales.

The alteration, destruction or discarding thus takes place *before* the records are forwarded to the FDA as part of the IND or New Drug Application (NDA). At this point adverse reaction reports are also easily excluded from the compilation of data and statistics. Should a company choose to discard or destroy such reports, there is no way an FDA medical review officer could detect such actions, short of securing records directly from each and every investigator—which virtually is never done.[10] Indeed, such cross-checking would be impossible with the Prescription Drug User Fee Act deadlines currently in place (see Chapter 2).

Making records from clinical and animal studies "disappear" has no doubt been going on for decades, although rarely is anyone caught. On occasion a whistleblower will come forward, usually at great risk. Not only is the employee faced with certain termination at the targeted drug company, he or she would likely be confronted with ostracism from the drug industry at large. But it does happen.

Back in 1960, the cholesterol-reducing drug, Triparanol, was introduced onto the market by its manufacturer, Richardson-Merrell, Inc. The full story is detailed in the California appellate decision of *Toole vs. Richardson-Merrell, Inc.*[11] The plaintiff in that case had developed cataracts in both eyes as a result of using the drug.

Between 1957 and October 1961, the Wm. S. Merrell Co. division of Richardson-Merrell conducted various animal studies on rats, monkeys and dogs to assess the potential side effects from Triparanol. During the tests by its Toxicology Department, it was discovered that all three species of animals began developing abnormal blood changes, then eye opacities, cataracts and in several instances blindness. One of the technicians was ordered to falsify some of the test results in her laboratory notes. Brochures to be used by physicians in human studies were also falsified. When the company filed its New Drug Application with the FDA, it submitted numerous false statements regarding the animal studies, including the falsified chart, omission of any reference to the abnormal blood changes and statements minimizing the side effects. Eye opacities were reported as mild inflammation of the eyes, and reference to blindness was eliminated from the reports. Triparanol was approved for marketing in April 1960.

When Merrell began receiving reports of human patients developing cataracts, it initially failed to report them to the FDA and withheld sending a warning to the medical profession. Finally, in April 1962, FDA officials made an unannounced visit to Merrell's laboratories and confiscated all of its records related to animal experiments. They had been tipped off by a whistleblower. Within a month Triparanol was removed from the market. In the short time it was on sale to the general public, at least 490 people developed cataracts as a result of using the drug. Three employees of Merrell were indicted related to the above conduct, including the vice president/director of research for the Wm. S. Merrell Co. That division and its parent, Richardson-Merrell, were both heavily fined.

Absent a morally-committed and strong-willed employee from inside the company, the only other means for exposing the alteration or destruction of records is through litigation against the company and

having access to records afforded by court orders. Even then it can be difficult to detect. Depending upon the thoroughness of the pharmaceutical company, it is next to impossible to know that certain records from patients have been removed or destroyed and then simply excluded from the formal set of statistics presented to the FDA. This is why it is so tempting and a further means of insuring that nothing unpleasant surfaces during the clinical investigations.

But on occasion one can get lucky, especially if he gets a little creative. Such was the case when I was heavily involved in litigating against the manufacturer of the fertility drug, Clomid (clomiphene citrate).[12] The defendant manufacturer was Richardson-Merrell, Inc.—yes, the same company—and my discovery occurred during a document inspection trip to its plant in 1977 and some follow-up medical research over the subsequent months. Our contention was that the drug caused birth defects in the offspring of women who used it to induce ovulation, and I was looking for any supporting evidence as I dug through the 80,000 pages of records being produced. My experience was an eye opener.

By chance I stumbled upon a record unlike any of the others I had been reviewing at the time. It was a summary prepared by a Dr. Gerhard Bettendorf from Hamburg, Germany. Bettendorf was only one out of 364 worldwide clinical investigators retained by the company. The document summarized the results of *40 pregnancies*, of which only 18 had been completed at the time. Of the18 concluded pregnancies, 12 had resulted in miscarriages. But when I searched for the "Analysis of Pregnancy" forms from the official records, I could locate only *two* of them for this investigator!

To verify that only the two (rather than 40) cases were included in the 2,635 pregnancies that represented the official total from the study, I referred to the computer printout I had previously acquired from Merrell entitled, "Clomid Pregnancy Data as of January, 1970."

The document included a wealth of (purported) information on each pregnancy from the study that had been stored in Merrell's computers. I had also obtained all of the necessary legends, codes and other documents needed for its interpretation.

The comparison validated that *Merrell had excluded 38 of Bettendorf's 40 pregnancies from its official data on the clinical studies*. But what was particularly bothersome was that out of those 40 conceptions, *at least* 12 of them (30.0 percent) had resulted in miscarriages—and 11 of the 12 had been excluded from the already high statistics (20.4 percent) on the miscarriage rate.

In one fashion or another, 38 of Bettendorf's clinical records had not found their way into the official set of documents of either the IND or NDA. Had they been pulled and destroyed? Set aside in some dusty boxes in a basement storage room? Sent back to Bettendorf? Never received from the German doctor to begin with? The last question would not seem to be a likely scenario. Why send the records on two, but withhold the balance of the remaining 38? Why send a summary of all 40 if you haven't sent the records on all or, at least, a majority of them? It just didn't make sense.

For further assurance, I checked the literature upon my return from the inspection trip. And there it was. Bettendorf had published a summary of an earlier stage of his Clomid investigations.[13] His brief summary verified my earlier discovery. Among other things it stated, "There were a total 29 pregnancies, 14 have delivered, 8 aborted and 7 are still pregnant."

How many other records had been discarded? Could I find them even if they had? Probably not. I had searched through more than 1,500 pages of records and had found this summary just by chance. It was also too easy to remove undesired reports and medical charts from the official documents—or never file them to begin with. After all, it was Merrell that was preparing the summaries of the

investigations, not the investigators. It would also not be the first time that Merrell had falsified official FDA records.[14]

After locating the Bettendorf publication following my return to California, I also did a random check on a number of other investigators who had published the results of their premarket studies. My search was limited to papers reporting on pregnancies that could only have occurred prior to the date of initial marketing on May 15, 1967, and thus were not part of an independent postmarket study. The effort was rewarding.

One paper had been published by a Karow and Payne.[15] Dr. Sheldon Payne was also a Merrell clinical investigator. His publication reported on 180 pregnancies, including 140 on which the outcome was known at the time the paper was submitted for publication (1966). However, Merrell only reported on a total of 136 pregnancies for Dr. Payne.[16] Whatever happened to the other 44 pregnancies? Why were they missing?

A second publication was by Kempers, Decker and Lee.[17] Dr. David Decker was yet another Merrell clinical investigator. This publication reported on 15 pregnancies. "Nine of the 15 pregnancies [were] still in various stages of gestation. Of the remaining 6, five [had] ended in delivery of a single infant at term; 4 infants were normal and 1 had meningomyelocele and hydrocephalus [birth defect]. The sixth pregnancy ended in abortion at 6 weeks." Merrell only reported on 11 pregnancies.[18] Why were four missing?

Dr. Nathan Kase was from New Haven, Connecticut, and another Merrell investigator. His articles reported on 23 pregnancies,[19] but Merrell selected only eight to include in its composite list submitted to the FDA.[20] What happened to the other 15?

Yet another publication was authored by E. Rabau et al., from Tel-Hashomer, Israel.[21] Dr. Rabau reported on 34 pregnancies, which resulted in a spontaneous abortion rate of 20.6 percent. But *none* of

the pregnancies were included in Merrell's official list of 2,635 reported to the FDA.[22] Why they were selectively excluded?

Then it got really interesting.

Dr. Naotaka Ishizuka was a Clomid investigator from Nagoya, Japan. I was able to secure a translated copy of a published study by Ishizuka et al. that reported on the results of their premarket clinical investigations.[23] They detailed their then-current findings on 16 pregnancies. At the time, only seven had delivered; two resulted in spontaneous abortions, and one female of a set of twins "had a visceral protrusion with umbilical hernia and died on the second day." The twins were delivered after 33 weeks of gestation and conception occurred during a treatment cycle with clomiphene: *The investigators acknowledged a possible causal relationship between the birth defect and clomiphene.* "It may be presumptive to conclude that there was a cause-effect relationship with clomiphene administration in this case, but a possible effect of clomiphene in such a development must be taken into consideration in the future studies." Merrell included only one of the 16 pregnancies in its compilation, which, of course, *did not include the birth defect*.[24]

The final paper I located was authored by Curchod and Weihs.[25] Curchod was an investigator located in Lausanne, Switzerland. Their article summarized the results of five pregnancies. One resulted in a spontaneous abortion. Of the remaining four, one was delivered at 20 weeks, following six months of treatment, with "fetal malformations: evisceration of liver, intestine and stomach." This anomaly, also referred to as *exomphalos*, involves the described organs protruding in a sac outside of the body cavity. Merrell did not include any of these five pregnancies within its clinical investigational data—and again, *another birth defect was excluded*.[26]

Stimulated by these disparities, I pursued yet another means of verifying the incompleteness of the premarket clinical data. Clinical

investigator Edward Tyler, MD had testified during my 1974 Clomid trial that his clinic had reported on approximately 200 pregnancies induced by the drug.[27] Yet the official records at Merrell summarized only 87 of the some 200 pregnancies reported by Tyler.[28] Had Tyler exaggerated or mis-recollected the number of Clomid pregnancies? As a means of determining which number was the correct one, I secured the official correspondence file on Tyler that had been maintained by the pharmaceutical company. My effort again paid off. On December 11, 1967, Tyler had sent a telegram to A. H. MacGregor of the William S. Merrell Company in Cincinnati. The relevant language states, "Kindly send analysis of ovulation and pregnancies in 202 completed triplicates that you have as soon as possible." Tyler had previously sent pregnancy reports to Merrell in "triplicate forms." He now wanted Merrell's analysis of those reports to assist him in writing a paper for publication. So whatever happened to the other 115 pregnancies?

And how would Merrell Dow[29] reconcile the discrepancy between its official set of records and the numbers from its clinical investigators? During the 1994 Gandy trial,[30] it was provided with such an opportunity. One of Merrell's expert witnesses was a James Goddard, MD, the Commissioner of the FDA between January 11, 1966, and June 30, 1968, which included the year Clomid was initially marketed (1967). Now, 27 years later, he was coming to Merrell's rescue.[31] During my cross-examination, he was confronted with a number of these discrepancies. His half-hearted reply: "(Merrell) may have excluded others, because they didn't fulfill the criteria."[32] But what criteria and in what way was it not fulfilled? Certainly the investigators felt the cases qualified. In fact, they even chose to publish papers on them. Not only did Goddard fail to expand on this explanation, the subject was not even touched by Merrell's

counsel on redirect examination. Bottom line: Merrell *had* no explanation.

Destruction or concealment of records might also be *inferred* from available evidence. Such may be the case with Baycol (cerivastatin), a cholesterol-reducing drug manufactured by Bayer. Just *three months* after Baycol was introduced onto the market in 1998, Bayer and the FDA were in receipt of reports on seven cases of rhabdomyolysis, a toxic muscle degeneration condition leading to kidney problems and death. [33] Baycol was pulled from the market in 2001 when it was determined that the cholesterol drug posed ten times the risk of causing rhabdomyolysis as other statin drugs, such as Lipitor, Pravachol and Zocor. When used in conjunction with a fibrate drug—to lower triglyceride fats—*10 percent* of the patients developed the muscle disorder. In six of the seven reported cases the patient had been taking a fibrate.

One might ask: Why would evidence of this serious adverse reaction surface only three months after marketing but escape detection during the premarket clinical studies? Phase III studies are supposed to include an assessment of the drug's potential interaction with other pharmaceuticals. Since one would expect that many patients on a cholesterol-reducing drug might also use a fibrate to reduce triglycerides, how could the premarket studies have missed a serious ADR (rhabdomyolysis) that would occur in one out of every ten users of both drugs? The full story of Baycol will be discussed in a later chapter.

In any event, every drug manufacturer/sponsor of a premarket clinical investigation has both the *motive* and *opportunity* to conceal, discard or alter the records produced during those studies; and it would be an act of extreme naivety to presume that none of them are taking advantage of it. Along with its ability to handpick its clinical

investigators, it is absolutely insane that for well over a half century we have continued to allow the fox to guard the henhouse.

[1] These times are only approximate, as the generally accepted time for all three phases combined is seven years.

[2] These statistics and most of the information and data in this chapter are taken from the US Government Accountability Office (GAO) report of November 17, 2006, to the Senate Committee on Health, Labor and Pensions and the House Committee on Government Reform.

[3] From 1993 to 2004, research and development expenses for the drug industry increased from nearly $16 billion to nearly $40 billion, a 147 percent increase, adjusted for inflation. In contrast, the number of NDAs submitted annually increased at only 38 percent and have generally declined over the past several years (a 21 percent decline from 1999 to 2004).

[4] I personally have seen correspondence authored by such a physician in which he threatened to make "negative comments" about a drug if the company cut back on his lecturing fees, as it had previously indicated it was going to do in the near future.

[5] To read the full story, see "The National Institutes of Health: Public Servant or Private Marketer?" *Los Angeles Times*, December 22, 2004.

[6] Ibid.

[7] Ibid.

[8] David Willman, "NIH Audit Criticizes Scientist's Dealings," *Los Angeles Times*, September 10, 2006, A1.

[9] The *sponsor* of a study is usually the pharmaceutical company that manufactured the drug.

[10] During the course of my review of the investigational records on the fertility drug Clomid, the fact that the investigators were from all over the world and across the United States created practical limitations on accessing their records. However, the fact that many of the 364 investigators *published the results of their studies* in peer review journals allowed me to discover numerous case histories that had been concealed from the FDA.

[11] *Toole v. Richardson-Merrell, Inc*. 251 Cal. App.2nd 689, 60 Cal. Rptr. 398 (1967).

[12] When I make reference to a brand name in this book, where relevant I also provide the generic of the drug in parentheses.

[13] 6th *Acta Endocr. Congr*. Suppl. 119 (1967) 224.

[14] See the reference to the Triparanol story at note 11 above.

[15] *Fertility and Sterility* 19, 1968: 351–62.

[16] Clomid Pregnancy Data printout of January 1970, pp. 28–34.

[17] *Obstet. Gynecol*. 30, 1967: 699–705.

[18] Clomid Pregnancy Data printout of January 1970, p. 114.

[19] *Conn. Med*. 31 October 1967: 695–97; *Amer. J. Obstet. Gynecol*. 98, August 15, 1967: 1037–42.

[20] Clomid Pregnancy Data printout of January 1970, pp. 75–76.

[21] *British Med. J.* 4, November 25, 1967: 446–49.

[22] Clomid Pregnancy Data printout of January 1970, p. 110.

[23] *Sanpu Chiryo* 17 (2) 1968: 185–98.

[24] Clomid Pregnancy Data printout of January 1970, p. 111.

[25] *Gynaecologia* (Basel) 165, 1968: 221–32.

[26] Clomid Pregnancy Data printout of January 1970, p. 113.

[27] Breimhorst partial trial transcript of April 2, 1974, pp. 26–27.

[28] Clomid Pregnancy Data printout of January 1970, pp. 51–55.

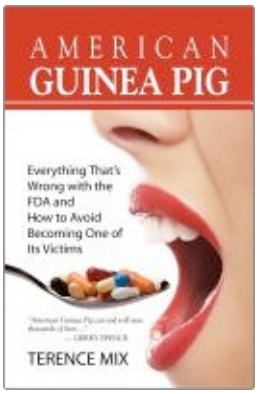
[29] Richardson-Merrell, Inc. changed its name to Merrell Dow Pharmaceuticals, Inc. on March 10, 1981.

[30] The *Gandy v. Merrell Dow Pharmaceuticals, Inc*. (LASC No. C703146) trial took place in Los Angeles, California, between May 2, 1994, and May 16, 1994. It settled just prior to closing arguments.

[31] For the handsome price of $28,800: Gandy trial transcript of May 13, 1994, pp. 972–73.

[32] Gandy trial transcript of May 13, 1994, pp. 1003–10.

[33] "Report: Bayer Held Back on Drug Dangers," *Los Angeles Times*, November 23, 2004.



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