

DRUGS, DEVICES AND PREEMPTION

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I. PRESCRIPTION DRUGS

Prescription drugs are big business. Spending surged for the fourth consecutive year in 2001, climbing 17.1% as sales of a relatively small number of expensive drugs boosted sales. Outpatient prescription drug spending totaled \$154.5 billion last year, up from \$131.9 billion in 2000, according to a study conducted by the National Institutes of Health. The study found that just 50 drugs out of 9,482 of the retail market were responsible for 62.3% of the \$22.5 billion increase in spending last year. Leading the list of drugs contributing to the increase were cholesterol treatments Lipitor and Zocor, arthritis drugs Vioxx and Celebrex, pain reliever OxyContin and antidepressant Celexa. The study also found that the drugs that led the list were the ones most advertised by their manufacturers to consumers and doctors. Analysts predict huge growth in pharmaceutical sales as the nation's enormous baby boomer generation ages.

But how safe are those drugs? It is estimated that over 100,000 Americans die each year as a result of an adverse drug reaction. This means that adverse drug reactions would be between the fourth and sixth leading cause of death in the U.S., behind only heart disease, cancer, stroke and pulmonary diseases. Since the FDA does not "test" proposed new drugs, it relies almost exclusively on the safety and efficacy data provided to it by the drug sponsor. At the same time, the FDA is increasingly understaffed, only having a full time staff of 52 to monitor the safety of 5,000 medications. The Division of Pharmacovigilance and Epidemiology has only eight M.D.s and one Ph.D. in epidemiology. The FDA Medwatch Office only has four employees. To compound the problem, in the past ten years there has been increased pressure from Congress and industry to approve drugs at an accelerated rate. All too often we hear of drugs which have been approved by the FDA only to be withdrawn a short time later due to significant safety concerns. Although the FDA has stated that the number of drug withdrawals demonstrates that the system "works," the facts are to the contrary. In fact, the added pressure to approve new drugs at a faster and faster rate and the lack of adequate resources appears to have affected the FDA's ability to protect the public health.

A. Baycol (cerivastatin sodium)

1. History of the Drug:

Baycol (marketed as Lipobay outside the United States) was manufactured by Bayer AG and co-marketed by GlaxoSmithKline. It was approved by the FDA in 1997. Baycol is one of a number of drugs that are part of a class known as statins, which are prescribed for the treatment of high total and LDL cholesterol levels. Statins are taken by eight million people and, as a group, are the fastest-growing segment of the drug industry, with sales expected to hit \$20-\$25 billion by 2005. Statins reduce cholesterol by blocking an enzyme called HMG-CoA reductase that is involved in the formation of cholesterol. Baycol was distinguished from the other statins (other than Lescol, fluvastatin), because of the way it is metabolized. While a portion of all the statins are metabolized through the cytochrome P450 pathway and the isoenzyme 3A4, Baycol also utilizes the isoenzymes 2C8 and 2A6.

A big selling point for Baycol, particularly with HMOs, was that it was the cheapest of the statins. In its advertising, Bayer listed price comparisons between Baycol and its competitor statins, claiming that there were savings of 30% compared to Lipitor, 37% for Zocor and 63% for Pravachol.

On August 8, 2001, Bayer A.G. voluntarily recalled Baycol from all world markets except Japan, when it was withdrawn on August 23, 2001. A chronology of significant events is attached as Appendix A. At the time of the recall, Baycol was being marketed in 63 countries. The recall, endorsed by the FDA, came after 52 deaths were linked to Baycol. Months later, Bayer admitted to more than 100 Baycol related deaths. Baycol was the 12th prescription drug taken off the U.S. market for dangerous side effects since 1997.

Prior to its withdrawal from the market, Baycol accounted for about 7% of prescriptions filled and refilled for cholesterol-lowering drugs. More than 700,000 people filled 10.6 million prescriptions for Baycol. In 2000, Baycol generated \$554 million in sales and Bayer had predicted that sales would top \$800 million in 2001. Bayer's shares plunged nearly 17% immediately following the recall.

Baycol was not a needed drug -- except for Bayer's bottom line. There were already a number of statins available to physicians for prescription, and Baycol just did not work that well at the lower dosages. Bayer knew this and kept upping the dosage levels -- finally up to 0.8 mg., which led to continuing escalating adverse reactions, whether the exceedingly potent drug was prescribed alone or in combination with other drugs.

2. **Problems Caused by the Drug:**

All of the deaths associated with the use of Baycol were reportedly the result of rhabdomyolysis, a severe muscle disorder caused when muscle cells break down and are released into the blood stream, which can lead to renal failure and death. Rhabdomyolysis is characterized by the following symptoms:

- muscle pain, weakness and/or tenderness
- abnormal urine color -- usually dark red or brownish, caused by the release of muscle contents into the blood stream
- fever
- nausea
- vomiting
- general fatigue, malaise

The significant lab values to consider in a Baycol case are as follows: [Normal values vary depending on the clinical lab used by the physician]

	<u>Normal</u>
Serum creatinine kinase (CK) _	(35 - 170 mg/dL)
Blood urea nitrogen (BUN) _	(7 - 20 mg/dL)
Myoglobin in urine	none
Potassium (K) _	(3.5 - 5.0 mg/dL)
AST (SGOT) _	(0 - 45 IU/L)
ALT (SGPT) _	(0 - 50 IU/L)
Creatinine _	(0.8 - 1.4 mg/dL)
CK-MM (CK in muscle)	(96 - 100%)

Treatment for rhabdomyolysis: early and aggressive hydration may prevent complications by rapidly eliminating the myoglobin out of the kidneys. The hydration needs with muscle necrosis may approximate the massive fluid volume needs of a severely burned patient. This may involve intravenous administration of several liters of fluid until the condition stabilizes. Diuretic medications such as mannitol or furosemide may aid in flushing the pigment out of the kidneys. If the urine output is sufficient, bicarbonate may be given to maintain an alkaline

urine state. This helps to prevent the dissociation of myoglobin into toxic compounds.

NOTE: A study which came out in the May issue of *Neurology* reports that polyneuropathy is a rare side effect of the statins. The Danish study reported that doctors should be alert to the possibility of nerve damage among patients on statins.

B. Celebrex (celecoxib) and Vioxx (rofecoxib)

1. History of the Drugs:

Both Celebrex and Vioxx are used in the treatment of rheumatoid and osteoarthritis. They are both NSAIDs that block production of prostaglandins, but they differ from traditional NSAIDs by inhibiting the enzyme COX-2, but not enzyme COX-1. Most NSAIDs inhibit both COX-1 and COX-2 isoenzymes. COX-1 is involved in the maintenance of the integrity of the gastrointestinal mucosa and platelet aggregation. COX-2 is induced to mediate or reduce inflammation and pain. Therefore, Celebrex and Vioxx were designed to selectively inhibit COX-2 which would give pain relief, without the concurrent gastrointestinal problems of other NSAIDs.

Celebrex is manufactured by G.D. Searle, which was the pharmaceutical branch of Monsanto. In April of 2000, Pharmacia, Upjohn and Monsanto merged to form Pharmacia Corporation. Celebrex was approved by the FDA on December 31, 1998 for the treatment of rheumatoid arthritis and osteoarthritis and on December 23, 1999 as a drug treatment aimed at reducing the number of intestinal polyps in patients with a rare genetic disorder called familial adenomatous polyposis (FAP). In May 1999, Searle sent a Dear Health Care Provider letter warning of bleeding events in the elderly when Celebrex was taken with Warfarin. In December of 2000, Searle amended the label with respect to teratogenic effects of the drug. The FDA has warned Searle on several occasions about misrepresentations in advertisements. Pharmacia and its predecessor have consistently downplayed the danger of Celebrex used with Warfarin in an effort to distinguish its product from Vioxx. An article published in August, 2001 in JAMA (Journal of the American Medical Association) raised concerns over the possible impact on cardiovascular health.

In September 2001 the American Heart Association, the National Stroke Association and the Arthritis Foundation asked Pharmacia and Merck to test whether Celebrex and Vioxx increase the risk of heart attack and stroke.

Vioxx is manufactured by Merck & Co., Inc., the nation's second largest drug maker, and was approved by the FDA on May 20, 1999 for the treatment of osteoarthritis, menstrual pain and for the management of acute pain in adults. Since that time, over 52 million Vioxx prescriptions have been written in the U.S. At the heart of the controversy is the VIGOR (Vioxx Gastrointestinal Outcomes Research) study, which was paid for by Merck. The study was organized to examine whether Vioxx had a lower association with gastrointestinal events than COX-1 and COX-2 inhibitors like naproxen. The study reported a lower risk of such events with Vioxx. The study also concluded that the difference in the rate of myocardial infarction between rofecoxib and naproxen was "not significant." However, the fallacy of the VIGOR study regarding the risk of cardiovascular events was revealed in August 2001. First, it was pointed out that the VIGOR study had excluded all patients requiring aspirin for cardiac reasons, so the baseline characteristics between groups were similar. Second, if all serious cardiovascular events in the subjects were included, 111 patients in the rofecoxib

group and only 50 patients in the naproxen group suffered severe cardiovascular events during the study. Therefore, the risk of a serious cardiovascular event was 2.2 times higher in the rofecoxib group, which is a significant number. The FDA issued a Warning Letter to Merck on September 17, 2001, that Merck had misrepresented the "favorable cardiovascular safety profile" of Vioxx:

- Merck's claim that Vioxx has a "favorable cardiovascular safety profile," is "simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen. The implication that Vioxx's cardiovascular profile is superior to other NSAIDs is misleading; in fact, serious cardiovascular events were twice as frequent in the VIOXX treatment group as in the naproxen treatment group in the VIGOR study."
- Merck's claim that "Vioxx can be used safely with warfarin," is "troublesome because Merck was aware of this potentially dangerous drug interaction in 1999."
- Merck failed to point out that VIOXX may have pro-thrombotic properties.

As a result of the FDA's findings, Merck was required to make extensive changes to its labeling in May 2002. Merck's second-quarter profit fell 3.6% as costs rose faster than sales. Although net income fell to \$1.75 billion, or 77 cents a share, revenue rose 7.7% to \$12.8 billion.

2. Problems Caused by the Drugs:

The problems caused by these medications are thrombotic or clotting problems, including thrombotic strokes, myocardial infarctions, nephrotoxicity and acute renal failure, pulmonary edema and death. Merck added a "geriatric use" precaution in 2002: "As with other NSAID's including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients."

In the 2001 and 2002 PDR, Merck also added aseptic meningitis under adverse reactions. From May 1999 through February 2001, there were seven meningitis cases reported to the FDA of Vioxx users. Patients developed symptoms of headache, stiff neck, eye pain, fever and chills up to 12 days after starting the drug. Through March of this year, another five cases had been reported. Celebrex has been linked to six cases of meningitis. Both companies deny a causal relationship.

C. Fen-Phen (fenfluramine-phentermine)

1. History of the Drug:

The Fen-Phen "cocktail" and Redux were prescribed for the treatment of obesity. Both Redux (dexfenfluramine) and Pondimin (fenfluramine) were manufactured by American Home Products. The drugs were removed from the market in September 1997 after having been taken by an estimated 5.8 million Americans. In September 2000, U.S. District Judge Louis C. Bechtel in Philadelphia approved the Nationwide Class Action Settlement Program. Important dates in that settlement program are as follows:

- January 3, 2002: all appeals were exhausted, making the settlement final. Several deadlines are triggered by this final judicial approval.

- August 1, 2002: to get a free echocardiogram from the settlement, refund of diet drug purchases, reimbursement for privately obtained echo, and/or a hardship echo, a blue form must have been filed.
- January 3, 2003: the screening period lasts for twelve months after final judicial approval, unless extended by the federal District Court. This means that, by this date, anyone hoping to obtain matrix level payments or exercise an opt-out right, must have an echo which shows FDA-positive injuries [defined as having at least mild aortic regurgitation or moderate or greater mitral regurgitation] or mild mitral regurgitation.
- Anyone qualifying for an intermediate or back end opt-out right by this date, must file the opt-out form (Orange #2 for intermediate or Orange #3 for back-end) by January 3, 2003.
- Those who qualify for an intermediate or back end opt-out right *after* January 3, 2003, must file the opt-out form within 120 days of qualifying for opt-out right and bring their opt-out lawsuit within one year of exercising their opt-out right.
- May 3, 2002: Anyone hoping to obtain matrix level payments must file a blue form by this date and must file a green form at the time they are diagnosed with a matrix level injury.

Fund A of the settlement covers persons who have not yet been diagnosed with serious heart injury caused by the drugs and provides compensation by reimbursement for the cost of the drug and associated medical services (if applicable). Fund A eligibility:

- Those who used Pondimin and/or Redux, whether or not diagnosed as FDA positive by September 30, 1999, are eligible for a refund in the amount of \$30 per month of use for Pondimin and \$60 per month of use for Redux, plus the cost of the prescriber (assuming funds are available after all medical testing is complete).
- Those who used Pondimin and/or Redux for more than 60 days but were not diagnosed FDA positive as of September 30, 1999, are eligible for one echocardiogram and an associated interpretive physician visit. If the echocardiogram indicates FDA positive, then the person is entitled to receive either \$10,000 in valve-related diagnostic medical services or \$6,000 in cash plus possible compensation benefits from Fund B, depending upon the severity of the injury.
- Those who used Pondimin and/or Redux 60 days or less who obtain an FDA positive echocardiogram, will be reimbursed the cost of the echocardiogram and a physician visit and entitled to receive either \$5,000 in valve-related diagnostic medical services or \$3,000 in cash. Depending on their financial circumstances, they may be entitled to an echocardiogram plus possible compensation benefits from Fund B, depending upon the severity of the injury.

Fund B is designed to compensate those who have been diagnosed (or who become diagnosed) FDA positive per the Claims Matrix below, in an amount defined for that matrix level. Compensation is between \$7,389 and \$1,485,000, depending on age and severity level, for those who used Pondimin and/or Redux over 60 days. Compensation is between \$7,389 and \$297,000, depending on age and severity level, for those who used Pondimin and/or Redux 60 days or less.

2. Claims Matrix

Level I	Severe asymptomatic valvular heart dysfunction or heart infection
Level II	Moderate to severe valvular heart dysfunction with signs of heart injury
Level III	Repair or replacement surgery performed or recommended
Level IV	Serious complications of valvular heart dysfunction or surgery such as stroke
Level V	Very serious complications such as transplant or death

Persons eligible for Fund B will be reimbursed for medical screening costs and drugs if:

- they are diagnosed as FDA positive or as having mild mitral regurgitation prior to the end of the screening period and have registered in Fund B by March 30, 2000; or
- develop thickening of the arteries (endocardial fibrosis), regardless of whether they have valvular regurgitation; or
- are a derivative or representative claimant of someone with the above injuries.

3. Problems Caused by the Drug:

Shortness of breath, chest pain, swelling of feet, fainting, heart murmur, heart valve insufficiency and primary pulmonary hypertension (PPH).

D. Meridia (sibutramine)

1. History of the Drug:

Meridia was launched in the U.S. in March 1998 by Abbott Laboratories to treat obesity. More than 8.5 million patients in more than 70 countries have used the drug. Public Citizen has linked Meridia to 29 U.S. deaths (32 deaths worldwide) and, on March 19, 2002, requested that the FDA recall the drug. Meridia is also under fire by health officials in Europe, who linked the anti-obesity drug to two deaths and adverse side effects in hundreds of people. On May 22, 2002, Public Citizen called on the U.S. government to bring criminal charges against Abbott Laboratories, claiming the company withheld from the FDA crucial information about adverse events and eight patient deaths. The group's allegations were based on an FDA inspection of an Abbott manufacturing plant in Illinois conducted on March 21 through April 3, 2002.

For the second time in three months the FDA has sent a warning letter to Abbott regarding Abbott's violations of federal reporting rules. The FDA found that Abbott failed to report one death and submitted inaccurate information in regard to three other deaths, and that the company failed to submit serious and unexpected adverse drug experience reports within 15 days of learning of the reactions.

Prior to its approval in 1997, an FDA advisory committee voted five to four that the benefits of Meridia did not outweigh the risks. The FDA medical officer who reviewed the drug wrote that Meridia "has an unsatisfactory risk-benefit ratio and therefore this Reviewer recommends non-approval of the original submission." The concern of both the advisory committee and the FDA medical officer was based on evidence that Meridia significantly increases blood pressure and heart rate in patients. The PDR for Meridia lists 86 reported adverse events associated with the use of Meridia.

In the wake of all this, Abbott sent out a "Dear Patient" letter on June 28, 2002 "to assure you of the safety, effectiveness and continued availability of Meridia." The letter states that, because Meridia "substantially increases blood pressure in some patients," patients should receive regular monitoring of blood pressure and pulse rate. The letter also lists the following contraindications: Meridia should not be used in patients with uncontrolled or poorly controlled hypertension; patients with a history of coronary artery disease, arrhythmias, congestive heart failure or stroke; patients with severe liver or kidney disease; patients taking other medications that regulate the neurotransmitter serotonin in the brain (ex: Prozac, Zoloft, Effexor, Luvox, Paxil or Zyban); women who are breast feeding, pregnant or plan to become pregnant; used with caution in patients with narrow-angle glaucoma or history of seizures.

Abbott's total sales in 2001 were \$16.2 billion, with Meridia making up \$200 million of that amount. Abbott's shares have recently fallen about 6% on the NYSE.

2. Problems Caused by the Drug:

Meridia has been linked to elevated blood pressure and abnormal heart rhythms.

E. OxyContin (oxycodone)

1. History of the Drug:

OxyContin, approved by the FDA in 1995, is manufactured by Purdue Pharma L.P. and co-marketed by Abbott Laboratories. It is the best selling pain medication in the U.S., bringing in approximately \$1 billion in revenue per year. OxyContin is a synthetic drug that converts to morphine in the system. It is a time released version of oxycodone, which carries several brand names, such as Percodan and Tylox. OxyContin is covered in a protective coating that dissolves slowly, making the drug longer-lasting. Each tablet of OxyContin contains 2-10 times the dose of oxycodone.

The manufacturer has been criticized for not properly informing doctors and patients of the high potential of OxyContin addiction. Abuse of the drug, dubbed as "Hillbilly Heroin," has run rampant and occurs when the pill is chewed, crushed, snorted or injected. OxyContin addiction is as severe as heroin addiction because they are both derived from opium. Opioids like OxyContin and heroin block pain messengers to the brain and central nervous system. They also increase the amount of dopamine in the brain which causes increased feelings of pleasure and euphoria. Tolerance develops and the individual soon needs more and more OxyContin to get the same pleasurable feelings. OxyContin addiction creeps up on the individual until acquiring the drug becomes a full time obsession. One county in West Virginia reported that one-quarter of its entire population sought treatment for addiction to the drug.

A boxed warning concerning addiction was not added until July of 2001. The abuse of the drug has made doctors increasingly unwilling to prescribe it, even after the drug company issued tamperproof prescription pads. At least nine states have limited Medicaid patients' access to the drug. Purdue Pharma has stopped distribution of the drug in 160 mg tablets, its highest-strength dosage, and has recently hired Rudy Giuliani to advise the company on solutions aimed at preventing prescription drug abuse. Reports of deaths linked to OxyContin vary but are in the hundreds nationwide.

2. Problems Caused by the Drug:

Addiction.

F. Paxil (paroxetine)

1. History of the Drug:

Paxil, manufactured by GlaxoSmithKline plc (GSK), was introduced into the U.S. market on December 29, 1992. Paxil belongs to a newer class of antidepressants called selective serotonin reuptake inhibitors (SSRI), along with Celexa, Luvox, Prozac and Zoloft. Paxil is the country's second-largest selling anti-depressant and accounted for more than \$2 billion in sales in 2001. Litigation claims are that the drug is addictive and induces physical and physiological dependency. Withdrawal symptoms are reported to occur in up to 30% of patients who abruptly discontinue SSRIs.

On August 16, 2002, a California federal judge, Mariana R. Pfaelzer, issued a preliminary injunction enjoining GSK from airing television commercials after September 1, 2002, which state that Paxil is non-habit forming. The ruling came in a class action lawsuit (*In Re: Paxil Litigation*, No. 01-7937, C.D. Calif.) filed a year ago on behalf of 35 patients who said they suffered severe withdrawal symptoms once they discontinued the drug. Even though GSK changed its label on December 14, 2001, indicating that some patients will suffer serious effects if they are taken off the drug too quickly, it continued to run commercials and distribute brochures saying Paxil "may cause mild, usually temporary side effects in some individuals." Judge Pfaelzer said that the ads' claims may "create confusion in the patient-doctor relationship if a physician's diagnosis is at odds with what the patient has been led to believe based on the ads." The judge also noted that Paxil's label in other countries warns of adverse withdrawal actions.

The Justice Department has asked Judge Pfaelzer to reconsider her order. The FDA has also protested the ruling, issuing a statement arguing that the ad ban was "improvidently entered" and contrary to the agency's regulatory role. Likewise, the Justice Department argued that the FDA had the regulatory responsibility to police drug advertisements and said Pfaelzer's ruling sets up a potential conflict between the FDA and federal courts over who can regulate drug advertising. Judge Pfaelzer wrote that the FDA's "acquiescence" to the ads "may have been based on incomplete information, a lack of attention to the specific issue, or any other number of factors."

Surging U.S. sales of Paxil and the asthma drug Advair led a 15% increase in second-quarter profits for GSK. Global sales of Paxil grew 29%.

2. Problems Caused by the Drug:

Addiction and severe withdrawal symptoms, including nausea, fever and other flu-like symptoms, gastrointestinal and somatic complaints, sleep disturbances, movement disorders and psychological symptoms.

G. PPA (phenylpropanolamine)

1. History of the Drug:

PPA is a common derivative of amphetamine that was used as an appetite suppressant and a cold and cough remedy. For decades the safety of PPA was questioned by the FDA and industry literature. Concerns regarding PPA were confirmed in the fall of 2000 with the publication of a Yale University School of Medicine study entitled "Phenylpropanolamine & Risk of Hemorrhagic Stroke:

Final Report of the Hemorrhagic Stroke Project." The study was a five-year case control study to determine whether there was an association between PPA and hemorrhagic stroke. At the conclusion of the study, the Yale scientists reported that taking PPA increased the risk of hemorrhagic stroke (bleeding into the brain or into tissue surrounding the brain). The FDA's Nonprescription Drugs Advisory Committee reviewed the Yale study and confirmed the association between PPA and hemorrhagic stroke. On November 6, 2000, the FDA issued a warning, alerting consumers of the risks associated with PPA and asking companies to voluntarily discontinue marketing products containing PPA.

The Yale study suggests that women, age 18-49, were at almost 16 times greater risk of hemorrhagic stroke within the first three days of taking appetite suppressants containing PPA than those who did not take PPA. The study also suggests that overall, hemorrhagic stroke victims were about 50% more likely to have ingested PPA within the three days prior to the stroke than the control subjects.

At least 22 over-the-counter medications contained PPA. They include AcuTrim Diet Gum Appetite Suppressant, AcuTrim Maximum Strength, Alka-Seltzer Plus Cold Medicine, Alka Seltzer Plus Children's Cold Medicine, BC Allergy Sinus Cold Powder, BC Sinus Cold Powder, Comtrex Flu Therapy & Fever Relief, Contac 12-hour Cold Capsules, Contac 12-hour Cold Caplets, Coricidin "D" Cold, Flu and Sinus, Dexatrim Gelcaps, Dimetapp Cold and Allergy Chewable Tablets, Dimetapp LiquiGels, Dimetapp DM Cold and Cough Elixir, Naldecon Pediatric Drops, Permathene Mega-16, Robitussin Allergy Cough, Robitussin CF, Tavist-D 12-Hour Relief, Triaminic DM Cough Relief, Triaminic Expectorant and Triaminic Syrup.

2. Problems Caused by the Drug:

PPA mimics the effect of adrenaline causing vasoconstriction and cardiac stimulation. The vasoconstriction of blood vessels in the brain can lead to a hemorrhagic stroke, especially in young women.

H. Prempro

1. History of the Drug:

Prempro is a hormone replacement therapy (HRT) combining estrogen and progestin. The drug is manufactured by Wyeth Inc. and was first sold in 1995. The company spent \$40 million marketing the drug to consumers and heavily relied on television, magazine and newspaper ads. About three million women in America are taking Prempro to help them fight the symptoms of menopause, to strengthen their hearts, and to guard against osteoporosis.

On July 9, 2002, the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH), stopped a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer. The trial was begun in 1997 and included over 16,000 women ages 50 to 79 who were divided into two groups, one given the drug and the other a placebo. The trial, a component of the Women's Health Initiative (WHI), also found increases in coronary heart disease (CHD), stroke and pulmonary embolism. Although there were benefits found, including fewer cases of hip fractures and colon cancer, the risks were felt to outweigh the benefits. The study was scheduled to run until 2005 but was stopped after 5.2 years. The trial predicts that one in 100 women will have a bad outcome from long-term Prempro use.

The researchers found that the frequency of some of the top killers of women went up even further with the estrogen/progestin combination. Among the women on HRT, the chance of having heart disease went up 29%, breast cancer rose 26%, strokes increased by 41% and blood clots by 113%. Of note, the study tested only postmenopausal women with an intact uterus taking only one drug regimen. The results do not necessarily apply to lower dosages of these drugs, to other formulation of oral estrogens and progestins (birth control pills) or to estrogens and progestins administered through the transdermal route. Importantly, the trial could not distinguish the effects of estrogen from those of progestin.

Researchers concluded that women should not start or continue taking this combination of hormone replacement therapy for the prevention of heart disease or osteoporosis. The AMA recommends that clinicians stop prescribing the combination for long-term use, such as to prevent CHD and osteoporosis.

The FDA recently announced that they have begun a major reassessment of the risks and benefits of all combination hormone products containing estrogen used by post-menopausal women. Several public forums are scheduled for this fall sponsored by the NIH, the FDA and the Agency for Healthcare Research and Quality.

2. Problems Caused by the Drug:

Increased risk of heart disease, stroke, blood clots and breast cancer.

I. Propulsid (cisapride monohydrate)

1. History of the Drug:

Propulsid was manufactured and distributed by Janssen Pharmaceutica, Inc., a Johnson & Johnson Co. subsidiary. The drug was originally approved December 11, 1993, for the treatment of severe nighttime heartburn for patients with gastroesophageal reflux disease (GERD), which occurs when the acidic contents of the stomach back up into the esophagus. Propulsid was also used off-label by physicians to treat premature babies.

Janssen has changed its warnings several times and sent out more than one Dear Healthcare Provider letter warning of problems. The first was a labeling guidance from the FDA in September of 1997, where potential drug interactions were described in a warning box. On June 26, 1998, Janssen sent a Dear Healthcare Provider letter wherein it admitted that patients had experienced arrhythmias even without taking contraindicated medications. The manufacturer described a list of patient conditions which would eliminate patients as appropriate candidates for Propulsid, such as patients with congestive heart failure, multiple organ failure, chronic obstructive pulmonary disease which causes serious respiratory problems and advanced cancer.

On June 1, 1999, Janssen sent another letter, revised the warning giving specific number of deaths and recommended that ECGs be performed prior to administration of Propulsid. As of December 31, 1999, use of Propulsid had been associated with 341 reports of heart rhythm abnormalities including 80 reports of death. Propulsid had \$950 million in sales in 1999.

Another Dear Healthcare Provider letter was sent on January 24, 2000, calling attention to the Boxed Warning on the Propulsid labeling. On March 23, 2000, Janssen announced that it would stop marketing the drug in the United States as

of July 4, 2000. The delay was supposedly to allow physicians and patients time to find alternative medications. The drug has been linked to 111 deaths and nearly 400 cases of heart abnormalities.

Propulsid was given to many children and babies for treatment of gastric reflux and has been linked with the development of Sudden Infant Death Syndrome (SIDS). Labeling changes advising of infant deaths were requested by the FDA in August of 1997 but were not agreed to by the company until June of 1998. The revised label did acknowledge "several pediatric deaths" but stated that "causality has not been established."

2. Problems Caused by the Drug:

Propulsid use has been linked to serious cardiac arrhythmias and death. The rhythm disturbances include ventricular tachycardia (fast heart beat), ventricular fibrillation (quivering heart beat), torsades de pointes and QT prolongation. The rhythm disturbances have been linked to interactions between Propulsid and other medications being taken by the patient, including certain antibiotics, some anti-depressants, certain anti-fungals, and protease inhibitors. All of these drugs inhibit the liver isoenzyme known as P450, 3A4.

J. Rezulin (troglitazone)

1. History of the Drug:

Rezulin was manufactured and distributed by Parke-Davis, a division of Warner Lambert. In February of 2000, Warner Lambert was acquired by Pfizer, and on June 19, 2000, Warner Lambert became a wholly owned subsidiary of Pfizer, the largest U.S. drug maker. Rezulin was approved for treatment of adult onset Type II diabetes on January 30, 1997 and was launched in March 1997. The warning label that accompanied the drug had no warning of liver toxicity and further represented that adverse effects were no worse than those which were seen with placebo. The Rezulin launch was accompanied by an unprecedented media blitz, including direct to consumer advertising.

The labeling was revised on August 4, 1997, incorporating a new indication as a monotherapy or in combination with sulfonylureas in the treatment of Type II diabetes. On October 28, 1997, Parke-Davis sent a Dear Healthcare Provider letter to provide additional information concerning the incidence of "idiosyncratic" hepatocellular damage to patients taking Rezulin. The company referred to the reports as rare and noted 35 cases as of October 21, 1997. The letter also recommended liver function test during the first one to two months of therapy and periodically thereafter. Parke-Davis changed the label for Rezulin in accordance with its letter on November 19, 1997.

On December 1, 1997, after only a month on the market, Glaxo Wellcome temporarily suspended its marketing of Romozin, the equivalent of Rezulin, in the U.K. pending analysis of liver problems associated with the drug. Only 5,000 patients had taken the medication in the U.K. At the time of withdrawal, Glaxo indicated six deaths had reportedly been associated with the drug, four in Japan and two in the U.S. At the same time, sources in the U.K. reported over 130 cases worldwide of hepatic reactions to troglitazone.

Also on December 1, 1997, Parke-Davis sent another Dear Healthcare Provider letter commenting on Glaxo's withdrawal of Romozin and the fact that its original healthcare provider letter had "as expected" increased reports of hepatic dysfunction. Parke-Davis also stated that everyone should be relieved to know

that the additional reports "do not indicate a greater frequency" of liver damage than previously estimated. Even so, the letter recommended more aggressive monitoring of liver enzymes. On the same day, the FDA released a "Talk Paper" which related that it now had 150 reported adverse events. Even so, the FDA leadership (which had just overseen the embarrassing withdrawal of the diet drugs Pondimin and Redux in September) reaffirmed its commitment to Rezulin.

On December 15, 1997, Parke-Davis came out with new labeling, which for the first time, included a "black box" warning concerning hepatic damage. On June 5, 1998, the National Institutes of Health decided to discontinue Rezulin treatments in its diabetes prevention clinical trials in response to the death of a patient from liver failure. Investigators have since looked into the fact that Dr. Richard C. Eastman, a senior researcher at NIH, served as a paid consultant to Warner-Lambert at the same time he oversaw the selection of Rezulin for use in a \$150 million government clinical trial.

On July 28, 1998, Parke-Davis sent another Dear Healthcare Provider letter setting more stringent liver enzyme monitoring and narrowing the scope of potential patients by lowering the threshold liver enzyme value. On March 23, 1999, the Endocrinology and Metabolic Drugs Advisory Committee met to evaluate the risks and benefits of Rezulin. At that time, some presenters recommended that the product be removed from the market. The FDA allowed the product to continue in the U.S. market. Also in March of 1999, regulators in the U.K. denied Glaxo Wellcome's attempt to start marketing Romozin again. In June of 1999, Parke-Davis dropped the usage of Rezulin as a monotherapy as one of the indicated usages for the product.

On March 21, 2000, the FDA asked Parke-Davis to withdraw Rezulin from the market. At that time, the FDA was aware of 90 liver failures, including 63 deaths and seven nonfatal organ transplants. This number represents a fraction of the total number of fatalities and injuries. Approximately one million patients used Rezulin.

2. "Fast Track " Approval:

Rezulin was the first drug to be granted "fast track" status under the Food and Drug Administration Modernization Act of 1997, 21 U.S.C. §301. This designation limited the time of FDA's consideration of the NDA to six months. Thus the Rezulin NDA was submitted in June of 1996 and approval was granted in a record six months, by January of 1997. The first FDA medical officer to examine Rezulin, Dr. John L. Gueriguian, a twenty year veteran of the FDA, opposed granting a fast-track review to the drug at an internal meeting in August 1996. In October 1996, he recommended that Rezulin be kept off the market, citing the drug's potential harm to the liver and the heart. For his efforts, he was kicked off the FDA's team looking into approval of Rezulin at the request of Warner Lambert.

3. Problems Caused by the Drug:

The reported problems associated with Rezulin include an elevation in liver enzymes (ALTs and ASTs). Symptoms include nausea, vomiting, abdominal pain, fatigue, anorexia and dark urine. Hepatic reactions include severe hepatocellular damage, hepatic necrosis and hepatic failure. The average time to the onset of the reaction was three months (range two weeks to eight months).

K. Serzone (nefazodone hydrochloride)

1. History of the Drug:

Serzone, manufactured by Bristol-Myers Squibb Co., is used to treat depression. Worldwide sales of Serzone were \$409 million in 2001. Serzone acts as a selective 5-HT₂-receptor antagonist and inhibits the presynaptic uptake of serotonin and norepinephrine. These pharmacologic characteristics differentiate Serzone from other antidepressants.

On December 7, 2001, the FDA informed Bristol-Myers Squibb that it must include a "black-box" warning after the drug was linked to hepatic failure leading to death or the necessity of a liver transplant. On January 9, 2002, Bristol-Myers Squibb issued a manufacturer's warning advising health care providers that "cases of life-threatening liver failure have been reported in patients treated with Serzone." The warning stated that the rate of liver failure associated with its use is "about 3-4 times the estimated background rate of liver failure" and that this "is an underestimate because of under reporting and the true risk could be considerably greater than this." Cases involving liver failure resulting in death or transplant generally ranged from two weeks to six months of Serzone therapy.

Serzone should be discontinued if there are any clinical signs or symptoms suggesting liver failure. Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels three times the upper limit of normal should be withdrawn from the drug.

2. Problems Caused by the Drug:

Liver dysfunction, such as jaundice, dark colored urine, loss of appetite, nausea, gastrointestinal complaints and malaise. Hepatic failure resulting in death or liver transplant. There have also been reports of rhabdomyolysis involving patients receiving the combination of Serzone and either simvastatin (Zocor) or lovastatin (Mevacor).

L. Thimerosal

1. History of the Drug:

Thimerosal is an antifungal packaging additive used to make multi-dose vials of childhood vaccines free of bacterial and fungal growth once the sterility of the bottle has been breached by the first needle puncture. Thimerosal contains roughly 50% by weight of ethyl mercury, a known neurotoxin, and has been linked to the explosion in the rates of autism and other serious neurological problems among children. Autism is a neurological disorder that usually manifests itself in the first two years of life and is characterized by sensory, neurological and behavioral problems. Autism used to be a rare condition, but the incidence of autism in boys and girls increased steadily through the 1990s, and its prevalence cuts across geographical, racial and economic lines.

The most dramatic increases have been in a form of autism known variously as late-onset, regressive or disintegrative autism. Children suffering from this form of the disease develop normally from birth and hit most of their developmental milestones through the first 16-18 months of life, but then experience a fairly sudden and often dramatic loss of their language, social, cognitive and fine motor skills. There has also been a rise in reports of Asperger Syndrome (also known as Asperger's Disorder) and Pervasive Developmental Disorder (PDD), two less severe forms of autistic behavior.

Research into causes of the epidemic of disintegrative autism looked at the possible role of childhood vaccines, for two primary reasons. First, the steep rise in autism rates through the 1990s coincided with an increasingly aggressive pediatric vaccine schedule, as more vaccines were added to the recommended childhood immunization schedule and the vaccines were given earlier and earlier in an infant's life. In addition, pediatric vaccines are given on a generally consistent schedule throughout the country and are essentially mandatory for children attending public/private schools, which might account for the increase of autism across geographic, economic and racial lines. In 1999 the recommended pediatric immunization schedule included as many as 17 different vaccine shots and boosters by a child's second birthday, with a child typically getting 3-4 shots at each visit to the pediatrician. Of those 17 shots, as many as 11 of them likely contained thimerosal, with each dose of thimerosal containing between 12.5 and 25 micrograms (ug.) of ethyl mercury. The EPA has established a safety threshold for mercury of 0.1 ug per kilogram of body weight per day. The cumulative dose of mercury based on the typical vaccine schedule is in excess of 200 ug. But most significantly, the typical infant born in this country between 1990 and 2001 received 187.5 micrograms or more by the age of six months, when the brain is going through rapid, complex and critical development.

In October 2001, the Institute of Medicine (IOM) released a report concluding that there is a statistically significant relationship between thimerosal exposure and a list of neurodevelopmental delays, that the correlation was dose-related, and that the causal relationship between childhood thimerosal exposure and autism is "biologically plausible." Thimerosal is no longer being used in new vaccines but old stores of vaccines may still contain the preservative.

The litigation focuses on the fact that it was always feasible for the drug companies to eliminate thimerosal from vaccines by packaging them in single dose vials or syringes. The only issue was the extra cost of such individual packaging, and thus the lower profits such safer packaging would entail.

2. Problems Caused by the Drug:

Organic mercury crosses the blood-brain barrier, which is not completely formed in infants, and mercury interferes with normal neurological development at a crucial stage in the child's life. The developing brain structure of an infant can be profoundly affected by this environmental insult. In addition to the immediate neurological damage, mercury poisoning is associated with a host of other health problems, including immune system suppression, gastrointestinal dysfunction and cardiovascular irregularities.

M. Zyban (bupropion hydrochloride)

1. History of the Drug:

Many drug companies are looking for alternative uses of their drugs as a way to provide a cushion for future lost sales to generics. One such drug is Zyban, sold by GlaxoSmithKline since 2000 as an anti-smoking drug. Zyban is the exact same drug as GSK's Wellbutrin, approved as an antidepressant in 1996. Wellbutrin sales in 2001 were \$905 million, while Zyban kicked in another \$78 million.

Zyban has been linked with 57 deaths in Britain, according to the Medicines Control Agency. An estimated 500,000 people so far have taken the drug in Britain and, as of January 10, 2002, the MCA had received 6,975 reports of suspected adverse reactions to Zyban, with 168 reports of seizures. GSK's

response is that "there is currently no reason to believe that patients taking Zyban have an increased risk of death. The medicine is used in patients who are already at risk because of smoking."

2. **Problems Caused by the Drug:**

The most common problems associated with Zyban include nausea, nervousness, breathlessness, dizziness, dry mouth, anxiety and irritability, trouble sleeping or insomnia, convulsions and seizures.

II. **MEDICAL DEVICES**

Twenty-five million Americans -- nearly one in ten -- have one sort of medical implant or another, including artificial heart valves, pacemakers, hip and knee joints, dental implants, stents, orthopedic plates and screws, or breast implants. The multimillion-dollar medical device implant industry is supposed to be overseen by the FDA which is, in fact, so laxly regulated that devices often reach the market without clinical testing and with little oversight afterward.

During the past ten years, 573 recall notices covering more than 2 million implants were issued for lapses such as mislabeling, structural failure or manufacturing defect. Of the 3,500 proposed medical devices, including implants, reviewed by the FDA last year, 98% were approved for sale under an expedited process that requires no clinical testing (*see* Pre-Market Notification Process in III.(A)(2) below). Recalls have more than doubled in recent years while the number of implants on the market has remained roughly the same.

The FDA relies on an honor system among manufacturers for reports of problems but admits not all of them comply. In case after case, implant manufacturers were slow to respond to surgeon's warnings of problems with their products. In many cases, companies were reluctant to issue recalls and continued to sell the product just days before they announced the recall.

Under federal law, the FDA is required to inspect medical device manufacturing plants every two years. But because of budget constraints, it actually visits U.S. plants on average once every five years and overseas plants once every 13 years. There has been a shrinking number of field investigators: 1,128 in 1997 to 1,023 in 2001, even though its budget has grown from \$148 million in 1997 to nearly \$180 million this year.

As the FDA's resources have dwindled, the number of recalls has climbed. Recall data over a ten year period shows that from 1992 through 1998, the average number of implanted medical devices withdrawn per year was 40. That number jumped to 96 in 1999, 79 in 2000 and 117 in 2001.

A. Artery Implants - Medtronic, Inc. and Guidant Corporation

1. ***AneuRx Stent Graft System***, manufactured by Medtronic, Inc. of Minneapolis since September 1999, is a device to treat abdominal aortic aneurysms. A stent is inserted into the aorta through a small incision near the patient's groin. It is then positioned within the aneurysm to channel blood flow. If an abdominal aortic aneurysm bursts, it is almost always fatal. On average, 15,000 Americans die that way each year. \$260 million a year is spent on implants to treat aneurysms.

In a May 2000 letter to Medtronic, the FDA said it had received notice of only two ruptures during clinical trials. It approved the device; a month later, the company informed the FDA that five more ruptures had taken place. Medtronic later confirmed in a letter to doctors that three more unreported ruptures had occurred during the clinical trials, bringing the total number of aneurysm ruptures -- the very type of event the device was designed to prevent -- to ten. Almost a year later, the FDA sent its own letter to doctors, citing evidence by then of 25

aneurysm ruptures and other medical complications, such as migration of the stent. In response, Medtronic issued a statement that it "regrets" the situation and has worked to improve its reporting and monitoring systems. The company added some new warnings to the product, including lifetime monitoring and imaging tests every three to six months.

About 22,000 of the AneuRx devices, costing \$12,000 each, have been implanted in patients worldwide. Through June 2002, there have been 591 adverse events involving AneuRx reported to the FDA, including 361 injuries to patients and 58 deaths.

2. ***Ancure Endograft System***, manufactured by Guidant Corporation of Indianapolis, was also approved in September 1999. Like AneuRx, Ancure is inserted through an incision in the groin. It is a patch with metal hooks that grab onto a healthy section of the aorta and forms a kind of sleeve that provides a stronger path for the blood flow. Guidant admitted that following approval of the device by the FDA, the company made manufacturing changes without FDA approval. They further admit that about 520 blood vessel injuries went unreported once the product was approved and on the market. The device was recalled March 16, 2001. However, the company made changes to the device and reintroduced it to the marketplace last August. The company reportedly lost \$15 million during that time period. Through June of this year, 1,092 adverse events regarding Ancure were reported to the FDA, including reports of 734 patient injuries and 48 deaths. The number of adverse events has dwindled since the device was changed.

B. Bronchoscopes - Olympus America, Inc.

Olympus America, Inc., of Melville, New York sent out recall letters on November 30, 2001, saying that its bronchoscopes, flexible tubes with a small light and camera used to inspect a patient's lungs and to take tissue samples, had a loose valve that could trap bacteria. Olympus is a U.S. subsidiary of the Japanese company Olympus Optical Co., Ltd. The recall applies to 14,000 devices sold worldwide, including to more than 2,000 hospitals in the U.S. In addition to the U.S., the defective bronchoscopes were distributed to Canada, Mexico, Dominican Republic, Argentina, Brazil, Panama, Chile, Peru, Ecuador, Columbia, Venezuela, Paraguay, Uruguay, Costa Rica and El Salvador between June 5, 1997 and December 10, 2001.

The Centers for Disease Control and Prevention said that Olympus learned of the problem on September 17, 2001, when they were notified by Skylark Hospital in Tennessee that an unusually high number of tests on lung fluids drawn with the faulty bronchoscopes were positive for Pseudomonas bacteria. Pseudomonas bacteria can cause pneumonia and be life-threatening in patients already suffering from critical illnesses. Although they learned of the problem in September, Olympus waited two months to send recall letters to hospitals and did not inform the FDA of the defect until December 2001.

Physicians at Johns Hopkins Hospital said the recall was "so quiet" that they did not learn about it until early February of this year. In the meantime, Hopkins physicians noted a two-to-three fold increase in the number of patients infected with Pseudomonas in December. By early February, they realized the device was the culprit. However, Johns Hopkins waited another month before alerting 415 patients that they may have received the dangerous lung infection from the devices. One hundred of those patients have tested positive for Pseudomonas bacteria and two have died. The patients underwent a diagnostic procedure called bronchoalveolar lavage (BAL) between June 2, 2001 and February 4, 2002. The hospital offered free evaluations and testing to the patients and asked them to call their doctors if they experience symptoms such as fever, coughing, phlegm or shortness of breath.

Dr. William Jarvis of the CDC has said he is "perplexed" that neither the FDA nor Olympus posted the recall notice on their Web sites. Olympus has issued a statement saying the company "initiated an immediate and vigorous investigation resulting in a prompt recall" and that notices had been sent to 2,361 health-care institutions. However, the company has admitted that fewer than 40% of the recalled bronchoscopes had been sent back to the company for inspection and repair. On February 27, 2002, Olympus issued a second recall notification letter to facilities that did not respond to their first letter. About 460,000 patients undergo bronchoscopies every year in the U.S.

C. Heart Valves - St. Jude Medical, Inc.

On January 21, 2000, St. Jude Medical, Inc. instituted a worldwide recall of all field inventory of heart valve replacement and repair products incorporating its proprietary Silzone® coating on the sewing cuff fabric. The company did not recommend explants of these products unless individual patient monitoring detected complications. The silzone technology was first introduced in 1997 and purportedly had the potential to reduce the incidence of endocarditis in valve procedures. The silzone valves were distributed in March 1998. St. Jude's estimates there have been approximately 36,000 implants of the silver-coated valves worldwide, including 12,000 in the U.S. The publicly traded company took a \$26 million special charge after the recall.

After distribution of the valves, St. Jude conducted a clinical follow-up to determine the effect of the silzone coating on the incidence of valve endocarditis. The study examined one group consisting of patients implanted with the standard St. Jude heart valve, and a second group implanted with the new silzone coated valves. The study indicated a higher incidence of paravalvular leakage with the silzone valve. A paravalvular leak is a flow of blood around the artificial valve usually between the valve sewing ring and the heart tissue to which the valve is attached. Of the 800 patients studied, only one out of 400 implanted with the standard St. Jude valve had a paravalvular leak; the 400 with the silzone valve had eight cases of paravalvular leak. According to St. Jude's own clinical study, at least two percent of those implanted with the silzone valve may have paravalvular leakage.

There is also a concern that persons implanted with silzone valves face higher risks of thrombus formation, thrombosis and stroke. A thrombus is a blood clot that can form upon the valve, affecting its operation or even rendering it inoperable. Thrombosis is a condition in which blood clots form and then move through the blood stream. These clots can ultimately cause a transient ischemic attack (TIA) or a stroke due to thromboembolism. In November of 1999, The Medical Device Agency in London issued an Advice entitled "Thromboembolic Complications involving Silzone® Mechanical Heart Valves." This bulletin reported a study in the United Kingdom of 51 patients implanted with silzone valves. Seven of these patients suffered a stroke. Upon reviewing the data, the Society of Cardiothoracic Surgeons of Great Britain and Ireland confirmed that there is a greater thromboembolic event rate associated with silzone valves compared to standard St. Jude mechanical heart valves.

Although St. Jude has settled some of the cases, it still faces more than 100 lawsuits. The litigation charges that the company did not adequately test the silver-coated valve before putting it on the market, relying on a small study of sheep and an "observational study" of 20 patients for two months. Further, the company failed to act quickly when presented with indications from surgeons and other doctors that the product was going bad.

D. Hip & Knee Implants - Sulzer Orthopedics, Inc.

On December 8, 2000, Sulzer Orthopedics, Inc. announced a recall of its Inter-Op acetabular shells used in hip implants and manufactured in Austin, Texas. Sulzer Orthopedics is a subsidiary of Swiss-based Sulzer Medica Ltd., renamed Centerpulse last

year when it was spun off to shareholders by former parent company Sulzer AG. The problem with the implants arose when Sulzer brought the manufacturing process in-house and changed that process to save money. As a result, a lubricant residue, which leaked from the milling machines during manufacturing, was left on the devices, preventing them from bonding to the pelvic bones. Several months after the hip implant recall, Sulzer announced that their Natural Knee II tibial baseplates, used in knee replacements, had been manufactured by the same process.

Sulzer is a case study in how companies can take advantage of a lax federal regulatory system that allows them to skirt the rules at the expense of patient health. The company had known of problems in the field with their product for months prior to the December 8, 2000 recall. Yet Sulzer failed to file "adverse event" reports to the FDA until late November 2000. Under federal law, manufacturers are required to report all adverse events involving medical devices that result in death, serious injuries or malfunctions to the FDA within 30 days. Unfortunately, the reporting is based on an "honor system" which is often, as in this case, not honored by the company. Instead, Sulzer entered into a concerted cover-up and continued to promote the devices for implantation until five days before the recall.

In the class action settlement discussions in August 2001, Sulzer said they would pay \$37,500 to those requiring replacement of the defective product, threatening bankruptcy if the deal was not accepted. Following a \$15 million verdict for three women in Corpus Christi who had received the defective implant, Sulzer realized nobody would accept that deal. Through the efforts of a team of Texas lawyers, headed by Ed Blizzard and Tommy Jacks, the Sulzer companies finally agreed to a \$1 billion settlement, which was approved by Judge Kathleen O'Malley on May 8, 2002. The key terms of the settlement are as follows:

- I. Class members who have undergone a revision to remove the affected product, or who undergo a revision by June 5, 2003 for an affected shell, September 8, 2004 for a reprocessed shell or November 17, 2003 for a tibial baseplate:
 - \$160,000 to class members and \$1,600 to derivative claimants (spouses, significant others) of this group;
 - Attorney fees of 23% will be paid by the Fund; attorneys can enforce their individual contracts over and above that amount if they chose to;
 - Those who registered for the Guaranteed Payment Option (GPO) will receive \$40,000 around September 1, 2002 (no attorney fees will be deducted from this amount); \$48,000 in approximately January 2003; and the remaining \$72,000 in approximately August 2004.
 - Those who did not register for the GPO will receive \$88,000 in approximately January 2003 and the remaining \$72,000 in approximately August 2004.
- II. Class members who received a recalled product but who do not get a revision by the dates listed in I. above:
 - \$1,000 to class members and \$250 to derivative claimants of this group;
 - No attorneys fees will be paid by the Fund for this group.
- III. \$120,000 to class members whose doctors have told them they need a revision, but for medical reasons are unable to get one;
- IV. There is also an Extraordinary Injury Fund (EIF) which will pay additional amounts (up to a total of \$800,000 per individual) for problems resulting from a revision, including dislocations, pulmonary embolism, permanent nerve injury,

permanent vascular injury, heart attack, stroke or death. Derivative claimants will receive up to 1% of the total EIF benefit paid to a class member.

- V. Sulzer is paying subrogation claims of Medicare, health insurance companies and other third-party payors.

Deadlines for turning in claim forms are as follows: Blue Form (no revision): September 5, 2002; Orange Form (revision): November 4, 2002 [must be submitted by September 5, 2005 to sign up for the GPO]; Green Form (EIF Benefits): November 4, 2002; Yellow Form (Derivative Claimants): same dates as Blue and Orange Forms; Red Form (uninsured product recipients): November 4, 2002.

E. Human Tissue - CryoLife Corporation

On August 14, 2002, the FDA shut down a substantial part of CryoLife Inc., the nation's largest processor of donated human tissue, saying that the company could not adequately assure patients that its products were free of deadly bacteria and fungi. The agency said 27 people had developed serious infections after receiving tissue implants processed by the company and one of them had died. About 650,000 Americans have surgery involving soft-tissue implants each year, and CryoLife supplies about half of the market.

The FDA ordered the company to recall all soft tissues such as tendons, ligaments and cartilage processed since October 3, 2001, and to withhold from the market or destroy tissue processed after that date. The tissues, obtained from cadavers, are widely used in elective orthopedic surgery to repair worn-out knees and other joints. Last November, a 23 year old Minnesota man died of a rare bacterium, *clostridium sordelli*, four days after receiving CryoLife tissue in knee surgery. In December, the Center for Disease Control learned that the donor for the knee tissue had committed suicide and that the body was not refrigerated for 19 hours after being picked up by a tissue bank. CDC investigators then found two strains of deadly clostridia in the donor's other knee, which was still in CryoLife's warehouse. Ten other patients received grafts from the same donor. Of the 19 tissue samples not implanted, at least two had *clostridium sordelli* bacterium.

The FDA said it is considering a similar recall of heart valves processed by the company if they are found to pose similar contamination risks. A New Mexico girl died from a rare fungal infection, *arthrographis kalray*, after receiving a heart valve implant. The fungus is usually found in soil and rotting vegetation. CryoLife is the nation's largest supplier of heart valves obtained from human donors. It processes 70% of the nation's heart valves and 90% of vascular tissue. The FDA said that patients who become ill after receiving soft-tissue implants usually developed symptoms within days or a few weeks of their surgery, but that with the heart valves, it can take months for infections to produce symptoms.

The FDA inspected CryoLife's facilities in Kennesaw, Georgia for two weeks in March and April and reported that they found "significant violations" of regulations. The agency sent a warning letter to the company on June 17, 2002, and stated that the company has not responded in "ways that assure that their material is not bacterially contaminated."

At least nine families have filed lawsuits accusing CryoLife of killing or maiming patients due to contaminated tissue. A class action suit on behalf of investors in the company was filed July 16, 2002, saying that CryoLife issued false and misleading statements regarding quality control problems.

III. PREEMPTION

A. Regulatory History

Congress enacted the Food, Drug, and Cosmetics Act (FDCA) in 1938, delegating to the FDA authority to promulgate regulations to enforce the Act.¹ In 1976, Congress enacted the Medical Device Amendments (MDA) to the FDCA, granting the FDA comprehensive and exclusive regulatory authority over medical devices.² The broad regulatory powers granted by the Act to the FDA are based on three statutory classifications:

Class I devices: devices which generally pose little or no threat to public health and are subject only to general controls on manufacturing.³ Examples: tongue depressors and crutches.

Class II devices: devices which pose a slightly greater risk of injury to patients, and accordingly, the MDA subjects them to performance standards, post-market surveillance, guidelines for use and other appropriate controls.⁴ Examples: oxygen masks, tampons and bone-conduction hearing aids.

Class III devices: includes all devices which are to be implanted into people, which are used to sustain life, or which pose a potentially unreasonable risk of injury.⁵ Examples: pacemakers, artificial heart valves, pedicle screws, polymethylmethacrylate bone cement, contact lens solutions, anti-wrinkle injections, penile prostheses.

1. Pre-Market Approval Process

The FDA's Pre-Market Approval (PMA) process applies to new medical devices introduced after May 28, 1976, the date the MDAs were enacted. To obtain a PMA, the sponsor must submit "all information, published or known to or which should reasonably be known to the applicant, concerning investigations which have been made to show whether or not such device is safe and effective,"⁶ a statement of the intended use of the product, a description of the expected manufacturing processes for the device, and any other information requested by the FDA.⁷

Although as a general rule, a Class III device must obtain a Pre-Market Approval before it can be marketed to the public, that rule has two exceptions: (1) Class III devices that are found by the FDA to be "substantially equivalent" to devices on the market before the MDA became effective (May 28, 1976) are only required to undergo a less stringent Pre-Market Notification process unless or until the FDA issues a regulation specifying that the device undergo the PMA review process;⁸ and (2) Class III devices that obtain an investigational device

¹ 21 U.S.C. §371(a).

² 21 U.S.C. §§301-360.

³ *Id.* at §360c(a)(1)(A).

⁴ *Id.* at 360c(a)(1)(B).

⁵ *Id.* at §360c(a)(1)(C).

⁶ *Id.* at §360e(c)(1)(A).

⁷ *Id.* at §360e(c)(1)(B)-(G).

⁸ *Id.* at §360e(b)(1).

exemption (IDE) from the FDA may be clinically tested on human subjects without first obtaining a PMA.⁹

2. Pre-Market Notification Process

An exception to the PMA requirement exists for devices that were already on the market prior to the MDA's enactment in 1976. To obtain FDA approval under this procedure, the applicant must demonstrate that its device is "substantially equivalent" in design and function to a device on the market prior to May 28, 1976.¹⁰ In contrast to the FDA's PMA process, the Pre-Market Notification process is more abbreviated and involves less FDA oversight. A manufacturer that intends to market a medical device pursuant to the substantial equivalence process must submit a pre-market notification, a §510(k) notification, to the FDA at least 90 days before it proposes to introduce the device into interstate commerce for commercial distribution.¹¹ The §510(k) notification must contain an "adequate summary" regarding the safety and effectiveness of the device containing "detailed information regarding data concerning adverse health effects and shall be made available to the public by the [FDA] within 30 days of the issuance of a determination that such device is substantially equivalent to another device."¹² FDA regulations state that a finding of substantial equivalence "does not in any way denote official approval of the device."¹³

3. Investigational Device Exemption Regulations

In order to encourage innovation, the MDA authorizes the FDA to grant to promising experimental devices exemptions from the usual requirement of establishing the safety and efficacy of a medical device before it can be sold.¹⁴ Before it can be granted an IDE, the manufacturer must submit a detailed application describing the device and setting forth a plan for studying its use in human subjects ("clinical investigation") during the experimental period.¹⁵ The application must be reviewed by an institutional review committee as well as by the FDA before it can be approved.¹⁶ After approval, the committee has a duty to monitor the clinical investigation.¹⁷

B. Preemption of Class III Medical Devices

There has historically been a presumption against preemption in this country absent "the clear and manifest purpose of Congress."¹⁸ State action law may be preempted by (1) express language in a congressional enactment; (2) implication from the depth and breadth of a congressional scheme that occupies the legislative field; or (3) implication because of a conflict with a congressional enactment.

⁹ *Id.* at §360j(g).

¹⁰ 21 C.F.R. §807.87.

¹¹ *Id.* at §807.81.

¹² 21 U.S.C. §360c(i)(3)(B).

¹³ 21 C.F.R. §807.97.

¹⁴ *Id.* at §813.

¹⁵ *Id.* at §813.20.

¹⁶ *Id.*

¹⁷ *Id.* at §813.65

¹⁸ *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947).

The Medical Device Amendments contain the following express preemption language in 21 U.S.C. §360k(a):

Except as provided in subsection (b) of this section, no State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement (1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.¹⁹

The MDA authorizes the FDA to promulgate implementing regulations. The FDA has, subsequently, extended application of §360k(a) to any state requirement "having the force and effect of law (whether established by statute, ordinance, regulation or court decision)."²⁰ The FDA regulations state that "[s]tate or local requirements are preempted only when the Food and Drug Administration has established specific counterpart regulations or there are other specific requirements applicable to a particular device under the act, thereby making any existing divergent State or local requirements applicable to the device different from, or in addition to, the specific Food and Drug Administration requirements..."²¹

1. Preemption of "Substantially Equivalent" Devices: *Medtronic, Inc. v. Lohr*²²

Courts were divided in determining the preemptive effect of the Medical Device Amendments and waited for years for the Supreme Court to offer some guidance and clarity on the subject. Since the Court's decision in *Lohr*, the lower courts are still divided in interpreting the Court's fractured opinion.²³ It is important to note that the *Lohr* opinion dealt with the 501(k) process and not with a product that had been approved under the PMA process. In *Lohr*, the plaintiff sued the manufacturer of the pacemaker, a Class III device, because of a defective electrical lead in the device. The plaintiff alleged state common law negligence and strict liability claims for defective design, failure to warn and negligent manufacturing. The Eleventh Circuit held that, although a finding of "substantial equivalence" did not preempt plaintiff's negligent design claim or strict liability claim, it did preempt plaintiff's failure to warn and negligent manufacturing claims.²⁴ The Supreme Court reversed with respect to the preempted claims.

Although the Court concluded that the *Lohr*'s tort claims were not preempted, the majority split on the broader question of whether the duties enforced by common law actions could ever be "requirements" for the purpose of preemption. The plurality opinion by Justice Stevens, writing for himself and Justices Kennedy, Souter and Ginsburg, distinguishing the MDA from the statute at issue in *Cipollone v. Liggett Group, Inc.*,²⁵ found that general common law actions were

¹⁹ 21 U.S.C. §306k(a).

²⁰ 21 C.F.R. §808.1(b).

²¹ *Id.* at §808.1(d).

²² 518 U.S. 470, 116 S.Ct. 2240 (1996)

²³ Justice Stevens announced the judgment of the Court and delivered the opinion of the Court with respect to Parts I, II, III, V, and VII, in which Kennedy, Souter, Ginsburg and Breyer joined, and an opinion with respect to Parts IV and VI, in which Kennedy, Souter and Ginsburg joined. Breyer filed an opinion concurring in part and concurring in the judgment. O'Connor filed an opinion concurring in part and dissenting in part, in which Rehnquist, Scalia and Thomas joined.

²⁴ *Lohr v. Medtronic, Inc.*, 56 F.3d 1335 (11th Cir. 1995), *aff'd in part & rev'd in part*, 518 U.S. 470 (1996).

²⁵ 505 U.S. 504 (1992).

not the "requirements" that Congress was concerned about when it enacted the preemption provision. Justice Stevens concluded that "§360k(a) simply was not intended to pre-empt most, let alone all, general common-law duties enforced by damages actions."²⁶ He stated: "It will be rare indeed for a court hearing a common-law cause of action to issue a decree that has the effect of establishing a substantive requirement for a specific device."²⁷

A contrary view was expressed by Justice O'Connor, writing for herself and Justices Rehnquist, Scalia and Thomas. Relying on the §360k preemption language and not the FDA's regulations, O'Connor concluded that "state common-law damages actions do impose 'requirements' and are therefore preempted where such requirements would differ from those imposed by the FDCA."²⁸ While these Justices agreed that the Lohrs' claims of defective design and failure to comply with federal requirements were not preempted, they were of the opinion that "some, if not all" of the Lohrs' common-law claims regarding the manufacturing and labeling would compel Medtronic to comply with requirements "different from, or in addition to, those required by the FDA" and thus would be preempted.²⁹

Justice Breyer, in his concurring opinion, agreed with O'Connor that the MDA could in fact preempt state tort suits, reasoning that a state requirement that takes the form of a duty of care is essentially no different from a state statute or regulation.³⁰ However, he agreed with the plurality that, because the FDA requirements relating to design, manufacturing and labeling in the 501(k) notification process were "not 'specific' in any relevant sense," the FDA did not intend the 510(k) notification procedures to preempt state tort claims: "I can find no actual conflict between any federal requirement and any of the liability-creating premises of the plaintiffs' state-law tort suit."³¹

2. Preemption of PMA Devices

Although the device at issue in *Lohr* was a Class III device, it had not undergone the PMA process. The Court made clear that "[t]he §501(k) notification process is by no means comparable to the PMA process; in contrast to the 1,200 hours necessary to complete a PMA review, the §501(k) review is completed in an average of only 20 hours."³² The majority of courts dealing with Class III devices which have obtained PMA approval have found that such approval is a "requirement" applicable to the device, thus holding blanket preemption of state law tort claims. In *Stamps v. Collagen Corp.*, a 1993 Fifth Circuit opinion, the court found that the PMA approval process preempted plaintiff's defective design and manufacture, inadequate labeling and warnings and negligent failure-to-warn claims.³³

²⁶ *Lohr*, 518 U.S. at 491.

²⁷ *Id.* at 502.

²⁸ *Id.* at 509 (O'Connor, J., concurring in part, dissenting in part).

²⁹ *Id.* at 513 (O'Connor, J., concurring in part and dissenting in part).

³⁰ *Id.* at 504 (Breyer, J., concurring).

³¹ *Id.* at 507-08 (Breyer, J., concurring).

³² *Id.* at 478-79.

³³ *Stamps v. Collagen Corp.*, 984 F.2d 1416 (5th Cir. 1993), *cert. denied*, 114 S.Ct. 86 (1993).

In a recent Fifth Circuit case, *Martin v. Medtronic*,³⁴ the court once again addressed the question of whether PMA approval preempted the plaintiffs' Texas common law products liability tort claims. The court re-evaluated the earlier *Stamps* decision in light of the *Lohr* decision and found that "[b]ecause only parts of Justice Steven's opinion commanded a majority, extracting the final meaning of *Lohr* is no easy task."³⁵

Stating that "[o]f course, we are plainly bound to follow the majority opinion in *Lohr*,"³⁶ the court goes on to say:

We think it is important to read the portion of the majority opinion addressing specific state requirements narrowly to avoid adopting as controlling law the broadly worded plurality opinion. Using Justice Breyer's concurrence as a guide, we can conclude only that general duties of care can generate specific requirements that conflict with specific FDA requirements.³⁷

The court concluded that "reading the language in the majority opinion through the lens of Justice Breyer's concurrence, we cannot say that *Lohr* overruled the holding of *Stamps* that common law tort claims challenging the safety or effectiveness of a device create specific requirements under state law."³⁸

Noting that *Lohr* states that "[n]othing in §306k denies Florida the right to provide a traditional damages remedy for violations of common-law duties, when those duties parallel federal requirements,"³⁹ the Fifth Circuit, therefore, holds that, following *Lohr*, "tort suits based on a manufacturer's failure to follow the FDA's regulations and procedures are not preempted."⁴⁰

Finding only that the broad holding of *Stamps* was "narrowed by *Lohr*'s finding that preemption requires substantive requirements imposed by common law duties to threaten federal requirements,"⁴¹ the Fifth Circuit declared that *Stamps* remained "binding authority:"

We therefore reaffirm that a medical device manufacturer's compliance with the FDA's PMA process will preempt state tort law claims brought with respect to that approved device and relating to safety, effectiveness or other MDA requirements which the substantive requirements imposed by those claims potentially conflict with PMA approval. Thus, the plaintiffs' tort law claims relating to design, manufacturing process, and failure to warn are preempted by the MDA.⁴²

³⁴ 254 F.3d 573 (5th Cir. 2001), *cert. denied*, 122 S.Ct. 807 (2002).

³⁵ *Id.* at 579.

³⁶ *Id.* at 581.

³⁷ *Id.* at 582.

³⁸ *Id.* at 583.

³⁹ *Lohr* at 495.

⁴⁰ *Martin* at 583.

⁴¹ *Id.* at 584

⁴² *Id.* at 585.

Following similar reasoning as the Fifth Circuit in interpreting *Lohr*, the Sixth Circuit in *Kemp v. Medtronic*,⁴³ the Seventh Circuit in *Mitchell v. Collagen*,⁴⁴ and the Eight Circuit in *Brooks v. Howmedica, Inc.*⁴⁵ determined that the PMA process constitutes specific federal requirements that preempt state tort suits.

However, other courts have disagreed, finding that the PMA process does not provide blanket preemption. In *Goodlin v. Medtronic, Inc.*⁴⁶ the Eleventh Circuit found that plaintiff's claims for negligent design and strict product liability were not preempted, holding that the "FDA's approval of a medical device pursuant to the PMA process, standing alone, imposes no specific federal requirement applicable to a particular device and, therefore, has no preemptive effect under section 360k(a) of the MDA."⁴⁷ Likewise, the District of Columbia in *Webster v. Pacesetter, Inc.*⁴⁸ found that "the MDA does not impose substantive requirements on medical devices through the PMA"⁴⁹ and, thus, plaintiff's state law claims of strict liability, negligent warnings, design, manufacture, and follow-up evaluation and breach of warranty were not preempted.

The Texas Supreme Court has also had its say with regard to Class III devices which received approval through the PMA process. In *Worthy v. Collagen Corp.*,⁵⁰ the court held that plaintiff's DTPA claims were preempted. The plaintiff had also asserted claims for negligent design, manufacturing and failure to warn, strict liability and breach of express and implied warranties; however, the court found that the plaintiff had failed to preserve those claims on appeal.⁵¹

The court attempted to analyze *Medtronic v. Lohr*, admitting that "the Court's three opinions in *Medtronic* do not dispel all confusion."⁵² Not surprising, the court chose to "treat as authoritative the matters on which Justice Breyer and Justice O'Connor agree,"⁵³ rather than the opinion of Stevens' plurality. The court notes that Justice Stevens' view that "it will be rare indeed for a court hearing a common-law cause of action to issue a decree that has 'the effect of establishing a substantive requirement for a specific device'"⁵⁴ was "expressly rejected by a majority of the Supreme Court."⁵⁵ The court states that they believe it is the view of the majority of the Supreme Court "that a federal requirement concerning a device can preempt a suit in which the claim is that the device should have been made or marketed differently provided, as we have already observed, the federal requirement is sufficiently specific."⁵⁶

⁴³ 231 F.3d 216, 226-227 (6th Cir. 2000).

⁴⁴ 126 F.3d 902, 913 (7th Cir. 1997).

⁴⁵ 273 F.3d 785 (8th Cir. 2001), *cert. denied*, 122 S.Ct. 1914 (2002).

⁴⁶ 167 F.3d 1367 (11th Cir. 1999).

⁴⁷ *Id.* at 1382.

⁴⁸ 171 F.Supp.2d 1 (D.D.C. 2001).

⁴⁹ *Id.* at 13.

⁵⁰ 967 S.W.2d 360 (Tex.), *cert. denied*, 524 U.S. 954 (1998).

⁵¹ *Id.* at 366.

⁵² *Id.* at 367.

⁵³ *Id.* at 368.

⁵⁴ *Lohr*, 518 U.S. at 502-503.

⁵⁵ *Worthy*, 967 S.W.2d at 370.

⁵⁶ *Id.* at 371.

Noting that although the Worthy's DTPA claims are statutory claims, "they are similar to common law claims for negligence, breach of warranty, and products liability."⁵⁷ In order to prevail, Worthy must "prove that Zyderm as approved by the FDA is not safe. This contradicts not only the FDA's specific finding to the contrary but also the manufacturing, and labeling protocols approved by the FDA."⁵⁸ The court finds that claims like Worthy's "stand as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," and that "if an action like Worthy's is not preempted, then we are unsure what kind of action would ever be preempted."⁵⁹

3. Preemption of IDE Devices

Since *Lohr*, the courts that have considered whether the less rigorous, through still specific, investigational device exemption (IDE) process results in preemptive requirements have been divided. Among those giving IDE approval preemptive effect are *Chambers v. Osteonics Corp.*⁶⁰ (strict liability and breach of warranty claims were preempted; negligent manufacturing claims that manufacturer had not complied with FDA requirements were not preempted); *Martin v. Telectronics Pacing Sys., Inc.*⁶¹ (manufacturing defect, design defect, inadequate warning and breach of warranty claims were preempted); *Chmielewski v. Stryker Sales Corp.*,⁶² (negligent design, failure to warn and strict liability claims are preempted; negligent manufacturing claim not preempted); *Berish v. Richards Medical Co.*,⁶³ (negligence and strict liability claims were preempted, claim for negligent manufacturing was not preempted).

Other courts have held that IDE approval does not have preemptive effect. See *Oja v. Howmedica, Inc.*⁶⁴ (plaintiff's failure to warn claims are not preempted); *Shea v. Oscor Medical Corp.*⁶⁵ (strict liability claims for design defect are not preempted); *Niehoff v. Surgidev Corp.*⁶⁶ (state law negligence and strict liability claims are not preempted); *Connelly v. Iolab Corp.*⁶⁷ (state law negligence, strict liability and failure to warn claims not preempted); *Baird v. American Medical Optics*⁶⁸ (noting general agreement that design defect, manufacturing defect, breach of warranty and fraudulent misrepresentation claims are not preempted).

4. Fraud-on-the-FDA Claim

The U.S. Supreme Court has recently resolved the split among the Courts of Appeals and ruled that state law "fraud-on-the-FDA" claims "conflict with, and

⁵⁷ *Id.* at 376.

⁵⁸ *Id.*

⁵⁹ *Id.* at 377.

⁶⁰ 109 F.3d 1243, 1247-48 (7th Cir. 1997).

⁶¹ 105 F.3d 1090, 1097 (6th Cir. 1997), *cert. denied*, 522 U.S. 1075 (1998).

⁶² 966 F.Supp. 839, 843 (D.Minn. 1997).

⁶³ 937 F.Supp. 181 (N.D.N.Y. 1996).

⁶⁴ 111 F.3d 782 (10th Cir. 1997).

⁶⁵ 950 F.Supp. 246, (N.D. Ill. 1996).

⁶⁶ 950 S.W.2d 816, 818 (Ky. 1997), *cert. denied*, 523 U.S. 1005 (1998).

⁶⁷ 927 S.W.2d 848 (Mo. 1996), *cert. dismiss'd*, 520 U.S. 1260 (1997).

⁶⁸ 713 A.2d 1019 (N.J. 1998).

are therefore impliedly pre-empted by, federal law."⁶⁹ *Buckman* dealt with the orthopedic bone screw litigation where plaintiffs claimed that, in order to get the device approved under the 510(k) process, the manufacturer's application fraudulently sought clearance from the FDA to market the screws for use in the arm and leg bones, not the spine. The Court made clear that preemption applied in that context because "[p]olicing fraud against federal agencies [was] hardly `a field which the States have traditionally occupied.'"⁷⁰ Since the *Buckman* decision, manufacturer's have, not surprisingly, argued that any claims which are grounded on communications between the company and the FDA are preempted. Most courts have disagreed, limiting *Buckman* to its very specific holding.⁷¹

⁶⁹ *Buckman Co. v. Plaintiff's Legal Committee*, 531 U.S. 341, 348 (2001).

⁷⁰ *Id.* at 347 (citations omitted).

⁷¹ See *Globetti v. Sandoz Pharmaceutical Corp.*, 2001 WL 419160 (N.D.Ala.) ("Notwithstanding that information may have been misrepresented to or concealed from the FDA, once defendant undertook to misrepresent those facts to *plaintiff*, or to conceal from *plaintiff* facts it was bound to disclose, the plaintiff's claim no longer rests simply on the assertion that the agency was defrauded but on the additional fact that *she* was defrauded.")

APPENDIX A

Baycol Chronology of Significant Events

June 30, 1997: FDA clears Baycol for marketing. Recommended dose is 0.3mg1x daily

February 18, 1998: Bayer announces the launch of Baycol. Advises that myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of plasma creatine kinase (CK), and patients should be advised to report promptly any such symptoms. Recommended that liver function tests be performed before the initiation of therapy or elevation in dose and periodically thereafter.

May 26, 1999: FDA approves 0.4mg strength pill as the recommended dose.

October 25, 1999: HHS/FDA letter to Bayer, instructing to cease and desist in disseminating promotional material that is "false, lacking in fair balance, or otherwise misleading." (Ex: "Baycol proven significantly better than Pravachol.")

December 15, 1999: Bayer sent its first Dear Health Care Professional letter about Baycol, recommending to doctors that Baycol not be prescribed concurrently with gemfibrozil because of an increased risk of myopathy and rhabdomyolysis.

July 24, 2000: FDA approves the marketing of new 0.8mg dosage of Baycol. Press release indicates:

- 0.4mg is the recommended starting dose for Baycol; however, 0.8mg is going to be very valuable for 'hard to treat' patients who require additional LDL-C lowering;
- in one clinical study using Baycol 0.8mg as the starting dose, women over 65 years of age, especially those with low body weight, were observed to be at an increased risk of myopathy;
- the combined use of cerivastatin and gemfibrozil is contraindicated due to the risk for rhabdomyolysis.

May 21, 2001: Second Dear Health Care Professional letter to inform physicians that the "dosage and administration" section had been revised to highlight that 0.4mg is the starting dose for Baycol:

- beginning therapy above the 0.4mg starting dose increases the risk of myopathy and rhabdomyolysis;
- changes made because Bayer received reports of rhabdomyolysis "during the post-marketing period" which indicated that "a substantial number of these cases occurred in patients receiving Baycol in a manner inconsistent with product labeling: e.g., patients were treated with concurrent gemfibrozil therapy and/or received Baycol 0.8mg as a starting dose."
- "In December 1999, Bayer changed the Baycol prescribing information to include a contraindication with gemfibrozil. The combined use of cerivastatin and gemfibrozil is contraindicated due to a risk for rhabdomyolysis and concurrent use should not occur under any circumstance."

July 25, 2001: Bayer changed the Baycol prescribing information to include a contraindication with gemfibrozil. The combined use of cerivastatin and gemfibrozil is contraindicated due to a risk for rhabdomyolysis and concurrent use should not occur under any circumstances.

August 8, 2001: Baycol withdrawn from the market.

August 13, 2001: Address made to the Bayer AG board by Dr. David Ebsworth, head of the Pharmaceuticals Business Group, indicating that the responsibility for the problems with Baycol should be assigned to physicians for prescribing the drug concomitantly with Lopid or in too high a starting dose (0.8mg vs. 0.4mg).

August 23, 2001: Baycol withdrawn from Japanese market.

February 2002: Bayer revised its earlier statement that the number of Baycol-related deaths was 52, and now acknowledged 100 Baycol-related deaths.