

Health Letter

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September 2004 ♦ VOL. 20, NO.9

Blood Safety

The following is excerpted from a testimony of Sidney M. Wolfe, M.D. at a meeting of HHS Advisory Committee on Blood Safety and Availability in January 2004.

The risks to patients from government-regulated products really depend on the balance of power between the government, industry, and patients. This risk relationship is often naively portrayed as an equilateral triangle, but it really is not. Sometimes the government is much closer, appropriately so, to the corner of the patients. More often, unfortunately, it is closer to the corner of industry. In these circumstances we have tried, with some success over the years, to get drugs or other products that are too dangerous off the market, or to warn people about hazards of various products, mostly FDA-regulated, despite resistance from the FDA-industry alliance not to do so.

The regulation of blood is an example of a situation in which we believe the government has, more recently, properly aligned itself with patients and has taken on the industry. In this case, it is the industry of blood and blood products and blood collection. These were the findings from an FDA inspection of the American Red Cross (ARC) Headquarters completed almost four years ago [in 2000]: deficient quarantine system to prevent release of unsuitable products; improper release of CMV-(cytomegalovirus)

positive blood products; donors being associated with incorrect histories; inadequate oversight of system problems; failure to follow manufacturer's test kit for an HIV antigen test; lack of timeliness in addressing problems.

In the case of blood or blood supply, timeliness is a very, very important element. The history of these serious problems goes back 15 or more years when the FDA was regularly finding the Red Cross not to be complying with Federal laws and regulations concerning blood. Eventually, a consent decree was signed in 1993 between the FDA and the Red Cross, but it was being regularly violated by the Red Cross. Finally, about two years ago, the FDA asked for the Red Cross to be held in

contempt of court for violating this consent decree. It must be stated that there are a large number of other companies or organizations such as ARC who have at one point in the last 10 years been involved in consent decrees with the FDA. In many cases these consent decrees have been very helpful in terms of resolving problems. That is not the case with the Red Cross. About a year and a half ago, inspection of ARC Headquarters found that the Red Cross had failed to do an adequate investigation following the death from hepatitis B of a patient who had received two units of red blood cells manufactured by ARC. A total of 134 suspected post-transfusion hepatitis cases across all of the Red Cross

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regions were not investigated because the hepatitis cases involved the use of blood products arising from more than 10 donors. The idea behind this nonsensical Red Cross policy was that if there were more than 10 donors it was too complicated to go back and figure out which one had been infected. It is, of course, more complicated, but many of problems discussed this morning are far more complicated but probably have less risk than this.

The Quality Assurance Officer in the [Red Cross] National Testing Laboratory stated there was a culture to hide problems. This is an organization that supplies half of the blood in this country. Another employee "reported fearing retaliation if she was seen reporting the problem to the supervisor." Staff interviewed "verified they found documents which were changed and their initials had been forged in the changed documents."

More recently, a few months ago, is a letter from Lee Bowers, who's been heavily involved in this ARC investigation because the Baltimore District FDA Office, of which he is the Director, is the office that inspects the national ARC headquarters. The 1993 consent decree requires that ARC investigate, correct and prevent all problems. Yet ARC's standard operating procedure clearly ignored that requirement, instead only requiring investigation of certain problems. This is from Bowers' letter. "Because of the egregious failure to comply

The negligence is primarily on the part of the companies that continued selling these contaminated products, but FDA allowed this to happen and tried to keep it quiet.

with the decree, FDA is assessing [ARC] an \$8,500 per diem fine for the period June 6, 2003 through August." Total amount of the fine was \$518,000.

The following problem has to do with the safety of the process of donating blood. This is a case, very recently adjudicated, involving a 32-year-old Virginia blood donor who suffered an ulnar nerve injury and permanent pain because of negligence by a blood technician. It turned out that this blood technician had been recently hired by the Red Cross. The Red Cross had known that this technician had been fired from a previous job that involved phlebotomy [drawing blood from people] because of "inability to follow procedures." This is not the kind of back-

ground that should lead to the hiring of someone as a blood technician who is going to draw blood.

Shifting over to another consent decree involving other products, this is with Abbott in 1999, and it concerned 300 diagnostic products that Abbott manufactures, ranging from tests used to ensure the safety of donated blood to tests that detect heart attacks. The consent decree to settle the issue was undertaken because Abbott did not correct the problems, very similar to the familiar over a long period of time of the Red Cross, despite 6 years of government inspections and warnings. There was a \$100 million fine.

Here now is the risk triangle shifted in a dangerous direction, in which the industry and the government were, at least in our view, acting too close to one another. It had to do with the shipment of a large amount of Factor VIII [a blood clotting factor administered to people with hemophilia to prevent them from bleeding] that was contaminated with HIV [from infected donors] back in the 1980s. This is a statement attributed to former FDA official, Dr. Harry Meyer, who was then head of the Bureau of Biologics, the predecessor agency to FDA's CBER [Center for Biologics Evaluation and Research — the regulator of blood and blood products]. The memo, written 15 months after the U.S. approval of Cutter's safe heat-treated Factor VIII, safe because the heat killed HIV and other infectious agents, stated Meyer

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THE PUBLIC CITIZEN HEALTH RESEARCH GROUP

Health Letter

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Published Monthly by
Public Citizen Health Research Group
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The Health Research Group was co-founded in 1971 by Ralph Nader and Sidney Wolfe in Washington, D.C. to fight for the public's health, and to give consumers more control over decisions that affect their health.

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Annual subscription price is \$18.00 (12 issues). Mail subscriptions and address changes to Health Letter, Circulation Department, 1600 20th St., NW, Washington, D.C., 20009. Our Web site address is www.citizen.org/hrg.

Product Recalls

July 17 — August 16, 2004

This chart includes recalls from the Food and Drug Administration (FDA) Enforcement Report for drugs and dietary supplements, and Consumer Product Safety Commission (CPSC) recalls of consumer products.

DRUGS AND DIETARY SUPPLEMENTS

The recalls noted here reflect actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request or by FDA order under statutory authority. A Class I recall is a situation in which there is a probability that the use of or exposure to the product will cause serious adverse health consequences or death. Class II recalls may cause temporary or medically reversible adverse health consequences. A Class III situation is not likely to cause adverse health effects. If you have any of the drugs noted here, label them "Do Not Use" and put them in a secure place until you can return them to the place of purchase for a full refund. You can also contact the manufacturer. If you want to report an adverse drug reaction to the FDA, call (800) FDA-1088. The FDA web site is www.fda.gov.

Name of Drug or Supplement; Class of Recall; Problem

Aspirin, Enteric Coated Tablets, 81 mg, 120 count bottles, Adult Low Strength Pain Reliever, BROOKS brand. Also sold under the following brand names: GOOD SENSE; Longs; Perfect Choice; SAFEWAY; Shop Rite; Equate; FOOD LION; Brite-Life; Good Neighbor Pharmacy; Valu-Rite; Family Pharmacy; Leader; Class III. Dissolution failure; Enteric coating.

Children's Motrin Tablets (ibuprofen) 50 mg, 24 count bottles, Grape-Flavored Chewable Tablets, Pain Reliever/Fever Reducer, Class I. Mislabelled; bottles labeled as Children's Motrin Chewable Tablets actually contain Tylenol 8 Hour Geltabs.

Enalapril Maleate Tablets USP, 5 mg, 100 and 1000 count bottles, Rx only, Class II. Subpotent; 18 month stability.

Levoxyl Tablets, (Levothyroxine Sodium Tablets, USP), 25mcg, 100 and 1000 count bottles, Rx only; Class II. Stability, inability to maintain stability through labeled expiration.

Lot #; Quantity and Distribution; Manufacturer

Lot Nos. 2DE0148 and 2DE0584; Exp. 01/05; 99,252 bottles distributed nationwide; Perrigo Co.; Allegan, MI

Lot No. JAM108, Exp. 01/06; 73,248 bottles distributed nationwide; McNeil Consumer & Specialty Pharmaceuticals, Division of McNeil-PPC, Inc.; Fort Washington, PA

Lot Nos. 108684VA 10/2004; 108684VB; Exp. 10/04; 19,125 bottles distributed nationwide; IVAX Pharmaceuticals, Miami, FL

Numerous lots; 992,428 bottles distributed nationwide; King Pharmaceuticals, Inc.; Bristol, TN

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had said that "Although the FDA could revoke these [approval of non heat treated factor VIII] he [Meyer] did not want any attention paid to the fact that the FDA had allowed this situation to continue for so long, and would like the issue quietly solved without alerting the Congress, the medical community and the public" In the absence of those kinds of alerts that would have followed a ban of non-heat-treated Factor VIII, lots of non heat-treated Factor VIII, contaminated with HIV in many cases, were shipped to a number of

countries in Asia or South America. The actual number is not known. Probably between 50 and 100 at least cases of HIV occurred. A negligent FDA action. The negligence is primarily on the part of the companies that continued selling these contaminated products, but FDA allowed this to happen and tried to keep it quiet.

These are, finally, my recommendations. FDA must continue to lead, on behalf of patients, in the area of blood and blood product safety. I think it has done a very good job. I would not say the same thing about the FDA's performance in the area of

prescription drugs or medical devices. Because of a dangerous closeness between those parts of the FDA and the pharmaceutical and device industries, we have had to push for many prescription drugs and some devices to be taken off the market. But in this area, the FDA has to continue to lead — which it has — the effort towards evidence-based trust in the collection, processing, storing and distribution of blood and blood components. The need for government regulation over both the not-for-profit and for-profit sectors of this industry has never been greater.

DRUGS AND DIETARY SUPPLEMENTS *cont.*

Name of Drug or Supplement; Class of Recall; Problem

Nu-IronÆ V, Polysaccharide-Iron Complex, 10mg; Calcium Carbonate 312mg, 10 x 10 count blister packs (PVC/Foil), Rx only, Class III; Sub-potent (Calcium Carbonate).

Twice-a-Day 12 Hour Nasal Spray (oxymetazoline hydrochloride 0.05%), sold in 1/2 fl. oz. (14.8mL) and 1 fl. oz. (30mL) bottles, major brand, Regular, nasal decongestant, also sold under other name brand as: DU brand Nasal Spray Atomizador, Maximum Strength, Nasal Decongestant Spray; Class I. Microbial contamination; Burkholderia cepacia.

Trispec-PE Pediatric Drops, 25 mg, 1 fl oz. bottles, Grape Flavor, Sugar Free, Dye Free; Class III. Superpotent; (18 month stability).

Urimax, Urinary Antiseptic Tablets, 100 count bottles, Rx only, Class III; Disintegration failure.

Lot #; Quantity and Distribution; Manufacturer

Lot No. R0401, Exp. 06-05; 1,187 boxes distributed nationwide; Merz Pharmaceuticals; Greensboro, NC

Numerous lots; 416,677 bottles distributed nationwide; Propharma, Inc.; Miami, FL

Lot No. 2K143; Exp. 10/04; 11,450 distributed in Puerto Rico; Deliz Pharmaceutical Corp.; Carolina, PR

Lot No. 312032, Exp. 02/05 & Lot No. 401071, Exp. 01/05; 7,561 bottles of 100 tablets distributed nationwide; Xanodyne Pharmaceuticals, Inc.; Florence, KY

CONSUMER PRODUCTS

Contact the Consumer Product Safety Commission (CPSC) for specific instructions or return the item to the place of purchase for a refund. For additional information from the Consumer Product Safety Commission, call their hotline at (800) 638-2772. The CPSC web site is www.cpsc.gov.

Name of Product; Problem

Bicycle Helmets. The helmets may not meet CPSC safety regulations for helmets, which poses a risk of a rider sustaining a serious head injury if he/she falls from a bicycle.

Blower Blades. The ends of the blades on these Country Clipper riding mowers can break off and become projectiles, leaving the mower deck at a high rate of speed. The recalled blades can break because "slots" in the blade cause metal fatigue.

Bunk Beds. These bunk beds have gaps between parts of the upper bunk end structure that violate the federal safety standard because they pose entrapment or strangulation hazards to children.

Children's Toy Balls. The wooden rings on the holes of the product may crack, allowing the small wooden heads to fall out and pose a choking hazard to young children.

Chrome Dumbbells. Because they do not fit together properly, the weights can fall off the handles of these dumbbells and strike the user.

Lot #; Quantity and Distribution; Manufacturer

DBX Engage (VT-3), DBX Ravage (FX-2), and Geartec ESPY bicycle helmets; 4,600 sold nationwide from June 2003 through June 2004; Mackarl Enterprises Inc.; City of Industry, CA and KHS Bicycles Inc.; Rancho Dominguez, CA; (866) 432-7832 Ext. 195

Country Clipper Jazee and Jazee One Grass Collection System Blower Blades; 125 grass collection units sold nationwide from September 2003 through May 14, 2004; Shivers Manufacturing; Corydon, IO; (800) 344-8237

Wooden bunk beds: Twin/Twin, Twin/Double, and Loft Bunk (manufacturer's label is located on the inside of the upper bunk's end structure); 337 sold in Portland and Hillsboro, Oregon, between June 1, 2000, and February 29, 2004; PJ Sleep Shop; Portland, OR; (888) 232-5225

Peek-a-Boo Balls, blue wooden ball with six holes located equally around the ball, each hole contains a small wooden head with smiling face; about 22,500 sold exclusively through HearthSong's catalog and Web site from October 2001 through March 2004; HearthSong Inc., Madison, VA; (888) 623-6557; www.hearthsong.com

Reebok and NordicTrack Chrome Dumbbells, between 2 and 50 pounds; about 1.2 million sold nationwide from June 2000 through May 14, 2004; Jumpking Inc.; Mesquite, TX; (800) 322-2211; www.jumpking.com

CONSUMER PRODUCTS *cont.*

Name of Product; Problem

Ceiling Fans. These ceiling fans were assembled without the proper wire insulation sleeving, which could result in exposed wiring. Consumers could receive an electrical shock during installation or removal.

Combination TVs/VCRs. The TV/VCR cabinets can break when lifted by the ventilation holes in the top rear of the cabinet, permitting the TV/VCR to fall and injure hands and feet.

Corningware Slow Cookers. The heating element can drop to the bottom of the unit and melt through the plastic outer shell posing burn and fire hazards.

Decorative Light Bulbs. The glass bulb can separate from its base and break during use. The broken glass can present a laceration injury to consumers, the hot broken bulb can present a burn injury to consumers, and an exposed bulb filament can present a shock hazard if handled while power remains applied to the fixture.

Eyelash Curlers. The plastic handles can detach and cause consumers to lose their grip, resulting in injuries to the eyes and face.

Lawn Tractors and Riding Mowers. A safety switch under the seat of these lawn tractors and riding mowers is designed to stop the mower blade turning within 5 seconds of the operator leaving the tractor seat. The recalled mowers' blades can continue to turn longer than 5 seconds after the operator leaves the seat, posing a laceration and amputation hazard.

Light Boxes. Overheating around the socket (where the bulb fits into the light box) can result in melted plastic and smoke, posing a possible fire and burn hazard.

Plush Frog Stuffed Animals. The seams in the toy can tear open and expose small plastic pellets, posing a choking or aspiration hazard to young children who mouth the pellets.

Pokémon Plush Toys. Tips of sewing needles have been found in the stuffing posing a puncture hazard.

Pool Pump Water Guns. The cone-shaped nozzle can unexpectedly come off the water gun and be propelled causing injury.

Portable Electric Heaters. A faulty electrical connection can cause the heater to overheat and stop working, posing a fire hazard to consumers.

Lot #; Quantity and Distribution; Manufacturer

Ceiling Fans with Light, Model number 355-6645; 1,200 sold at Menard stores nationwide between January 2002 and May 2002; Vaxcel International Co. Ltd., Glendale Heights, IL; (800) 482-9235

Panasonic, Quasar, RCA, and JCPenney Combination TV/VCRs; about 500,000 sold nationwide from January 1995 through December 1996; Matsushita Electric Corporation of America; Secaucus, New Jersey; (800) 833-9626; www.Panasonic.com

Corningware 4 Quart Slow Cooker (QVC item number K2585); about 39,000 units sold on QVC television nationwide from January 2004 through April 2004; Select Brands Inc.; Lenexa, KA; (800) 677-1291

60 watt B10 Décor Light Bulbs; 5.6 million sold nationwide from September 2002 through June 2004; Osram Sylvania Products Inc.; Danvers, MA; (877) 423-3772

"Frosted Grip" eyelash curlers; 220,000 sold nationwide from September 2003 through June 2004; The W.E. Bassett Company; of Shelton, CN; (877) 929-1933; www.trim.com

Lawn Tractors and Riding Mowers include Regent/500/2500 Series lawn tractors, Coronet/2400 Series riding mowers, and Lancer/4400 Series riding mowers; 5,900 sold nationwide from June 2003 through May 2004; Simplicity Manufacturing Inc.; Port Washington, WI; (800) 357-8244; www.simplicitymfg.com

"10,000 Lux Light Box;" 226 sold nationwide from November 2002 through June 2004; OTT-LITE Technology; Tampa, Florida; (866) 421-5181; www.ott-lite.com

11 1/2 inch purple stuffed frog with a green chin, belly, hands and feet; 90,000 sold at Kohl's Department Stores nationwide throughout July 2004; Determined Productions Inc.; Larkspur, CA; (877) 925-0660; www.kohls.com

Pokémon plush dolls, beanbags, and key chains; about 7,400 sold nationwide from January 2004 through August 2004; Pokémon Center NY of New York, NY; (800) 691-8055

15-inch-long water guns, shaped like giant syringes; about 38,600 sold at Kmart stores nationwide from January 2004 through June 2004; Kmart Corporation; Troy, MI; (866) KMART4U

Portable electric whole room heaters having model numbers 180VH(r), VH(r), Intellitemp(r), EVH(r), and DVH(r); 1 million sold nationwide from July 1991 through January 2004; Vornado Air Circulation Systems Inc.; Andover, KA; (888) 221-5431; www.vornado.com

Why is the U.S. So Far Behind on Prescription Drug Price Controls?

Largely because there are more pharmaceutical industry lobbyists in Washington than there are members of congress, the idea of having price controls in the Medicare prescription drug benefit law that just was passed — so that the drugs could actually be affordable — was quickly killed.

But in other countries such as Germany and, for that matter, almost all developed countries, price controls are a fact of life. Nevertheless, the pharmaceutical industry never tires in its efforts to undermine such controls.

In the March 27th issue of the British Medical Journal, the latest defeat for the pharmaceutical industry is discussed:

“The European Court of Justice has ruled that Germany’s state health insurance associations are entitled to set the maximum price that they will pay for drugs. Europe’s highest court, which is based in Luxembourg, said that Germany’s system, in which state health insurance associations can determine a price ceiling for drugs, does not break EU laws on competition. This is because such associations cannot be considered to be companies operating in the free market but rather are government agencies that act as guardians of the public health.

“Groups of health insurance funds,

such as the German Health Insurance Fund Association, do not constitute enterprises or associations of enterprises as understood under EU competition rules,” the court said.

Germany’s health insurance associations welcomed the court’s decision. A spokesman for Berlin’s health insurance associations said that the practice of setting ceilings on the price of drugs had proved to be the most effective way to control the rising cost of medicines. He said that the associations expected to save as much as 2.5bn euros (£1.7bn; \$3.1bn) in 2004 because of it.

The Social Democrat health minister, Ulla Schmidt, also had strong praise for the court’s ruling, saying that it provided a “sound foundation” for the continuation of the German system. She said that the ruling had shown “beyond all doubt” that EU antitrust laws cannot be applied to the 350 state health insurance associations in Germany.

Germany introduced legislation in 1989 obliging the associations to agree on the maximum prices they would pay for drugs in a bid to keep down healthcare costs. The associations, which provide health insurance to more than 90% of the German population, reimburse patients for the costs of drugs. Patients who spend

more on a drug than the upper limit specified by the associations have to pay the difference themselves.

The case came to the European Court of Justice after drug companies challenged the German system. The companies had argued that the system kept drug prices too low and so cut into the profits available to them for drug research and development.

Sounds familiar, does it not? Whereas Germany has rejected the idea that the pharmaceutical industry, with its extraordinarily high profit margin, does not have enough money to develop drugs even with controls on prices, we are far behind in the U.S. One crucial difference is the power of the drug lobby in Washington. In 2003, according to Public Citizen’s Congress Watch, the drug industry spent a record \$108.6 million on federal lobbying activities and hired 824 individual lobbyists — both all-time highs. In 2002, based on a more narrowly defined survey, the drug industry spent \$91.4 million and hired 675 lobbyists. Add to this tens of millions of dollars a year in campaign contributions from the pharmaceutical industry to members of Congress and it is quite apparent how and why our “democratic” system is under the influence. It is time for a major change!

CONSUMER PRODUCTS *cont.*

Name of Product; Problem

Range Hoods. These range hoods could have the blower motor installed with a screw that might penetrate the motor housing, posing an electric shock hazard to consumers.

Rival Slow Cookers. The handles on the base of the slow cookers can break, posing a risk of burns from hot contents spilling onto consumers.

Rugs. The recalled rugs violate the federal Flammable Fabrics Act and could ignite, presenting a risk of burn injuries.

Lot #; Quantity and Distribution; Manufacturer

“Bosch” Range Hoods; about 43 sold nationwide from September 2003 through April 2004; BSH Home Appliances Corp.; Huntington Beach, CA; (800) 758-1001

Rival Crock-Pot(r) slow cookers; 1.8 million sold nationwide from January 1999 through May 2002; The Holmes Group Inc.; Milford, MA; (800) 299-1284; www.rivalrecall.com

Pottery Barn Bailey Chenille Rugs; about 960 sold nationwide from November 11, 2002 to August 27, 2003; Classic Concepts; Los Angeles, CA and Williams Sonoma/Pottery Barn; San Francisco, CA; (800) 254-1927; www.potterybarn.com

DO NOT USE!

Lawsuit Reveals Serious Safety Problems With The Nonsteroidal Anti-inflammatory Drug (NSAID) Valdecoxib (BEXTRA)

Public Citizen filed suit in the District Court for the District of Columbia on February 25, 2004 against the Food and Drug Administration (FDA) asking that they make public complete copies of the agency's scientific reviews of the nonsteroidal anti-inflammatory drug (NSAID) valdecoxib (BEXTRA). As a result of this litigation, documentation from these FDA reviews has come to light associating valdecoxib and its injectable counterpart, paracoxib, with serious safety problems.

Valdecoxib was approved by the FDA in November 2001 for the management of dysmenorrhea (painful menses) and osteo- and rheumatoid arthritis, but failed to gain approval for the management of acute pain. The FDA reviews reveal that safety, not effectiveness, was the reason the drug was not approved for acute pain.

Valdecoxib, along with the NSAIDs celecoxib (CELEBREX) and rofecoxib (VIOXX), are called COX-2 inhibitors. In theory, they selectively inhibit the enzyme cyclooxygenase-2 (hence the shorthand name COX-2), and thereby relieve the symptoms of pain and osteo- and rheumatoid arthritis, without causing the perforations, ulcers, and bleeding that are such serious adverse effects of the NSAIDs. In fact, all of the NSAIDs, including the COX-2 NSAIDs, carry essentially the same FDA-required warning about the risk of perforations, ulcers, and bleeding that is in the box above.

The drug is co-marketed by Pfizer and Pharmacia & Upjohn in the U.S. Approximately 8 million prescriptions were dispensed for the drug in 2003 in this country, with sales total-

<p style="text-align: center;">WARNING</p> <p style="text-align: center;">Nonsteroidal Anti-inflammatory Drug- (NSAID) Induced Gastrointestinal Toxicity</p> <hr/> <p>All members of the NSAID family of drugs can cause gastrointestinal toxicity that can lead to gastrointestinal bleeding and hospitalization or death. The risk of gastrointestinal toxicity from these drugs increases with increasing doses and the length of treatment.</p> <p>If the following symptoms develop while you are taking an NSAID, stop the drug immediately and contact your doctor: severe abdominal or stomach pain, cramping, or burning, severe and continuing nausea, heartburn, or indigestion, bloody or black, tarry stools, vomiting blood or material that looks like coffee grounds, or spitting up blood.</p>

ing more than \$900 million.

We listed valdecoxib as a DO NOT USE drug in the 2002 *Companion* to the 1999 edition of *Worst Pills, Best Pills*. Our initial supposition, without having access to the complete FDA reviews, was that valdecoxib failed to receive approval for acute pain because of lack of effectiveness. We thought this because celecoxib (CELEBREX), another top selling NSAID, initially was not granted FDA approval for the management of acute pain on the grounds that it lacked effectiveness. Celecoxib subsequently has been approved for acute pain.

Since 1998 the FDA has made a practice of posting a complete set of reviews for a new drug on the Internet without the public having to make a formal request (using the Freedom of Information Act) for this information. We routinely study these publicly available reviews. When the FDA posted the documents for valdecoxib, they removed (redacted) all of the agency's analyses regarding acute pain. The FDA's explanation for this information's removal was that it is considered to be confidential commercial information and not disclosable to the public under the

Freedom of Information Act. We complained to the FDA that the information about acute pain could not be considered confidential information, as the manufacturer had announced in a press release in March 2001 that it was seeking approval for valdecoxib for this use. The agency was sympathetic but still did not give us the information we wanted.

The oral form of valdecoxib was to be the second prong of a two-pronged marketing strategy that would begin with paracoxib, the injectable form of the drug, that breaks down rapidly in the body to valdecoxib. The plan was to have both an injectable and an oral painkiller so physicians could seamlessly prescribe the same drug prior to surgery and upon a patient's discharge from the hospital.

In October 2000, the manufacturer submitted its application for the approval of paracoxib for the management of acute pain to the FDA. The FDA informed the company in July 2001 that paracoxib was "not approvable." The company did not reveal why the application for

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paracoxib had been rejected.

FDA approval of specific uses, such as acute pain, are important for the economic success of new drugs because legally, a drug company can promote its products only for those uses which are FDA-approved. In this case, however, the manufacturer's failure to gain approval for acute pain from the FDA did not stop them from promoting valdecoxib for the management of acute pain. This promotion leaves in question whether or not the peer reviewed medical literature can always be relied upon as an objective source of drug information.

While we were unsuccessfully urging the FDA to release their safety and effectiveness reviews of valdecoxib for the treatment of acute pain, the drug's manufacturer was making an end run around the FDA's approval process. A press release was issued announcing the publication of studies in the May 2002 issue of the *Journal of the American Dental Association* (JADA) concluding effectiveness for valdecoxib in the treatment of acute pain associated with dental surgery. This was unusual in itself, as we could not ever recall seeing a press release announcing the publication of drug studies for dental pain in a dental journal.

The JADA publication was co-sponsored by Pfizer and Pharmacia & Upjohn. The studies were conducted by Scirex, a contract research organization, (CRO) which, at the time, was owned partly by Omnicom, one of the world's largest advertising companies.

Three of the five authors were employees of Pharmacia & Upjohn: the corporation's Director of Biostatistics, Director of Medical Development, and the Clinical Vice President of Medical Development. These three company officials certainly must have known that valdecoxib failed to gain FDA approval for acute pain, as the two studies published in JADA had been submitted to the FDA in the attempt to gain approval for the drug for acute pain.

No matter how it is sliced, this company-sponsored study was a misleading commercial communication — an advertisement — and a perversion of ethical scientific communication.

According to a *New York Times* investigation published November 22, 2002 the JADA study "... helped light a fire under Bextra." Sales of the drug were reported to have increased 60 percent in the three months following the publication of the article. No matter how it is sliced, this company-sponsored study was a misleading commercial communication — an advertisement — and a perversion of ethical scientific communication.

The New York Times also reported that editors at JADA said the Pfizer and Pharmacia & Upjohn article was reviewed by at least three scientists. One reviewer, an associate editor of the journal, said the study was "carefully designed and rigorously performed." But, he also said he would have recommended that the journal reject the paper had he known that valdecoxib was not approved for acute pain.

The Unredacted FDA Review Of Valdecoxib

The FDA had originally redacted all information in their reviews concerning valdecoxib and acute pain. In the course of our litigation, we received most of what we had requested in the lawsuit, including

the unredacted FDA Medical Officer's conclusions and recommendations about the use of the drug for acute pain.

In the unredacted review the Medical Officer recommended:

Nonapproval of the acute pain, including opioid-sparing and prevention of operative pain. The only substantial multidose safety database is found in the Coronary Artery Bypass Graft (CABG) Surgery study 035. This study demonstrated an excess of serious adverse events including death in association with the use of paracoxib and valdecoxib 40 mg bid [twice daily] when added to ad lib [as needed] parenteral [injectable] narcotic analgesia.... These finding[s] warrants further investigation before valdecoxib can be considered safe and effective for the treatment of pain, particularly multidose therapy in the perioperative setting.

In study 035, the CABG study, there was an excess of clinically relevant adverse events in patients receiving valdecoxib and its injectable form paracoxib. There were 80 clinically relevant adverse events occurring in the 311 patients receiving paracoxib and valdecoxib (25.7%), compared with 23 (15.2%) in the 151 patients receiving the placebo.

The results of study 035 were ultimately published in *The Journal of Thoracic and Cardiovascular Surgery* in June 2003. This was 19 months after the FDA Medical Officer's review was written. This study generated little fanfare in the general media, certainly nothing to match the coverage of the JADA article published in May 2002.

In the Summary of Clinical Findings section of his review the Medical Officer concluded:

e) No efficacy advantage was demonstrated or suggested for valdecoxib compared to:

i. *ibuprofen* [MOTRIN],

Even Moderate Amounts of Exercise Can Prevent Weight Gain

Although we are often at odds with the Food and Drug Administration because they are so heavily influenced by the industries they are supposed to be regulating, occasionally we agree. The following article is from the March/April 2004 issue of *FDA Consumer*, a magazine published by the agency.

Moderate amounts of exercise, such as walking 12 miles per week, may help prevent weight gain and can promote weight loss in non-dieting individuals, researchers say.

Results from the National Health and Nutrition Examination Survey 1999 indicate that an estimated 61 percent of U.S. adults are either overweight or obese, defined as having a body mass index (BMI) of 25 or more, according to the Centers for Disease Control and Prevention.

Obesity is associated with a higher

risk for several health problems, including heart disease and diabetes. It is widely believed that diet combined with physical activity plays an important role in weight management, but the amount of activity needed to prevent weight gain is unknown, according to Cris A. Slentz, Ph.D., of the Duke University Medical Center, Durham, N.C., and colleagues.

The researchers investigated the effects of different amounts and intensities of exercise on weight. The results are published in the Jan. 12, 2004, issue of *Archives of Internal Medicine*.

The randomized, controlled trial included 182 sedentary overweight men and women, ages 40-65 years, who were assigned to one of several groups: high amount/vigorous intensity exercise (equivalent to jogging about 20 miles per week at 65

percent to 80 percent peak oxygen consumption); low amount/vigorous intensity exercise (equivalent to 12 miles of jogging per week at 65 percent to 80 percent peak oxygen consumption); or low amount/moderate intensity exercise (equivalent to 12 miles of walking per week at 40 percent to 55 percent peak oxygen consumption). A fourth group in the study, the control group, did not exercise.

The study lasted eight months and participants were asked not to change their diets during this time. Body weight and waist and hip circumference were measured. The researchers found that there was a clear relationship between the amount of physical activity and amount of weight loss, with the most weight loss seen in the high amount/vigorous intensity group, and the least in the low

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VALDECOXIB, from page 7
naproxen [ALEVE], and acetaminophen with oxycodone [TYLOX] in analgesic studies

ii. naproxen, ibuprofen or diclofenac [VOLTAREN] in osteoarthritis studies

iii. naproxen in rheumatoid arthritis studies

In summarizing the safety of valdecoxib the Medical Officer stated:

With two notable exceptions — edema [swelling] and hypertension — valdecoxib was comparable to the standard non-steroidal agents [ibuprofen, naproxen, diclofenac] used as active controls in the trials.... The finding of a greater incidence of edema and hypertension at doses

above 20 mg/day, almost uniformly in the databases and clearly when prospectively addressed in formal safety Trials 47 and 62, is of concern.... The excess of serious cardiovascular thromboembolic [blood clots] in the valdecoxib arm of the CABG [Coronary Artery Bypass Graft] trial is of note as the entire study population received prophylactic low dose aspirin as part of the standard of care in this setting to minimize just such events. Given the emerging concern over a possible pro-thrombotic action of certain agents in the COX2 class, these data are of concern.

Valdecoxib is no better, and in some respects more dangerous, than drugs already on the market, including ibuprofen and naproxen which are available over-the-counter in non-prescription strengths.

The amount of money being wasted on valdecoxib is extraordinary with the biggest burden falling on those patients who must pay out-of-pocket for their drugs.

A 20 milligram per day dose of valdecoxib was compared to naproxen given in a dose of 500 milligrams twice daily in osteoarthritis trials. Using prices posted on the Internet from a Washington, DC chain pharmacy, the cost of a 30 day supply of valdecoxib is \$98.99. For a 30 day supply of naproxen, a patient would pay only \$18.19. This is a difference of \$80.80 per month or \$969.60 per year.

What You Can Do

You should not use valdecoxib. It is no more effective than older NSAIDs such as naproxen, ibuprofen or diclofenac and it is much more expensive.

DO NOT USE!

Long-Term Treatment With The Alzheimer's Disease Drug Donepezil (ARICEPT) Ineffective

Almost 3.0 million prescriptions were dispensed for donepezil (ARICEPT) in U.S. pharmacies in 2003, amounting to retail sales of more than \$486 million. At the level of an individual Alzheimer's disease patient or family, the cost of a one-year supply of donepezil, at a dose of 10 milligrams per day, is \$1,872 at a Washington, DC chain pharmacy. Sadly, it appears that this money is wasted, according to a long-term study published in the June 26, 2004 issue of the journal *The Lancet*.

Donepezil belongs to the family of drugs known as acetylcholinesterase inhibitors that also includes rivastigmine (EXELON), galantamine (REMINYL), and tacrine (COGNEX). These drugs increase the level of acetylcholine, a brain transmitter, with the assumption that this might improve Alzheimer's-associated dementia. We have listed all of these drugs as DO NOT USE drugs because of their lack of clinically important efficacy and in some cases because of safety concerns.

The Lancet study, also known as

EXERCISE, from page 9

amount/moderate intensity group.

The control group gained weight over the study period. Compared with the control group, all exercise groups significantly decreased their waist and hip circumference measurements.

"These findings strongly suggest that, absent changes in diet, a higher amount of activity is necessary for weight maintenance and that the positive caloric imbalance observed in the overweight controls is small and can be reversed by a modest amount of exercise. Most individuals can accomplish this by walking 30 minutes every day," the authors wrote.

AD2000 (Alzheimer's Disease 2000), was conducted in the United Kingdom (UK) and was funded by the British government's National Health Service. This study was different from those that have been sponsored by the drug companies which manufacture Alzheimer's disease drugs in that the research subjects were typical patients referred from local clinics and managed by local physicians.

AD2000 involved 283 patients assigned randomly to take donepezil, in a dosage of either 5 or 10 milligrams per day, and 283 patients given a placebo. The main aims of the study were to determine whether donepezil produces worthwhile improvements in disability, dependency, behavioral and psychological symptoms, caregivers' psychological wellbeing, or delay in institutionalization. The study lasted three years and is the first study of its type, a randomized placebo controlled trial (the scientific gold standard), that looked at donepezil's effectiveness beyond one year.

The main outcomes of the study, called the primary endpoints, were entry to institutional care and progression of disability, defined by loss of either two of four basic, or six of 11 instrumental, activities on the Bristol activities of daily living scale (BADLS). The BADLS is designed to reveal the everyday ability of people who have memory difficulties from various causes. It asks important questions relating to function such as is the individual able to wash regularly and independently; eat appropriately using the correct utensils; and select appropriate clothing and dress without assistance.

No significant difference was seen among patients receiving donepezil and placebo in the rate of entry to

institutional care. After one year, nine percent of the donepezil patients and 14 percent of patients given placebo were institutionalized. This was not a statistically significant difference. At the end of the three-year study, 42 percent of patients taking donepezil and 44 percent of those on placebo had been institutionalized.

The results for progression of disability using the BADLS found no statistically significant difference between donepezil and placebo at one year. There were 13 percent of donepezil users and 19 percent of those taking placebo classified as having their disability progress during this time period. At the end of the three-year study, 55 percent of patients taking donepezil and 53 percent of those on placebo were classified as having their disability progress.

Donepezil was found to be statistically better than placebo on a commonly used survey known as the mini-mental state examination (MUSE). The MUSE is a measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. Donepezil was 0.8 points better on average than placebo on this 30 point survey.

There was no statistical difference between donepezil and the placebo in behavioral and psychological symptoms, carer psychopathology, cost of care, unpaid caregiver time, adverse effects or deaths.

The AD2000 authors concluded that:

Donepezil is not cost effective, with benefits below minimally

relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.

The editorial accompanying *The Lancet* study from the Department of Psychiatry and the Behavioral Sciences, Department of Neurology at the University of Southern California said:

Results are incompatible with many drug-company-sponsored observational studies and advertisements claiming remarkable effects for cholinesterase inhibitors. For example, claims that donepezil stabilizes cognitive decline, or delays nursing-home placement by 2-5 years now can be seen as implausible in the light of AD2000.

We first listed donepezil as a DO NOT USE drug in the 1999 edition of our book *Worst Pills, Best Pills*. The basis for this classification was from several sources including the highly respected *Medical Letter on Drugs and Therapeutics* and the English language French publication *Prescrire International*.

The Medical Letter editors in their June 6, 1997 review of donepezil said:

"There is no evidence that use of either donepezil or tacrine [a drug we also listed as DO NOT USE] leads to substantial functional improvement or prevents the progression of the disease."

Prescrire International's October 1998 review of donepezil found that:

"... the effects of donepezil are moderate and visible only on psychometric scales [surveys]; the possible clinical benefit is unknown. In the long term, donepezil only delays cognitive deterioration by a few months."

Later research strengthened our original designation for this drug. A

statistical summary of clinical trials known as a meta-analysis, conducted by the prestigious Cochrane Collaboration in 2003, found in selected patients with mild or moderate Alzheimer's disease treated for periods of 12, 24 or 52 weeks that:

"... donepezil produced modest improvements in cognitive function and study clinicians rated global clinical state more positively in treated patients. No improvements were present on patient self-assessed quality of life and data on many important outcomes are not available. The practical importance of these changes to patients and carers [care givers] is unclear."

In the measures that are most important to patients and their families, the results of AD2000 show that

long-term treatment with donepezil has no effect on an Alzheimer's disease patient's chance of being institutionalized or the progression of their disability. Subjective survey's show only small changes on numerical scales in patients on donepezil that do not appear to translate to a change that can be recognized by either the patient or a family member.

Donepezil has been deceptively oversold to physicians and patients, perpetuating the exploitation of patients with Alzheimer's disease and their families.

What You Can Do

Donepezil should not be used because there is a lack of evidence that this drug provides any meaningful benefit to Alzheimer's disease patients.

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Weapons of Mass Destruction and Medicine

A physician from Australia in private practice, writing in the March 27th issue of the British Medical Journal, had one of the most cogent things to say about the much-discussed issue of weapons of mass destruction. He said that “when talking of weapons of mass destruction, we should give credit where credit is due.”

“Our real enemies are the powers that aim to make us dependent: the merchants who try to sell health care as a proactive entity rather than a reactive one. They offer free examinations, and they manipulate long established laboratory measurements, all in the name of more profit. They go hunting for potential new patients and persuade them that they need


“Weapons of mass destruction are hard to find in Iraq: in modern medicine they are abundant (if cosmetically enhanced).”

treatment or “preventive” measures. They deliver “health care” to the eager, brainwashed consumer like

the milkman delivers milk. But they often come empty handed. They do not owe you anything, but they promise much.”

“Weapons of mass destruction are hard to find in Iraq: in modern medicine they are abundant (if cosmetically enhanced).”

None of the above appears to be intended as an attack on real preventive measures such as better diet, more exercise and other lifestyle improvements. Rather, it seems to be an attack on those, including some physicians and many companies, selling medical alternatives—dietary supplements, drugs, surgical procedures, etc. — that may actually deter people from seriously engaging in healthier, truly preventive changes.

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