

Health Letter

SIDNEY M. WOLFE, M.D., EDITOR

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Documentary Shows Problems In Pharmaceutical Industry, FDA

On November 13th, PBS's *Frontline* aired a one-hour documentary entitled "Dangerous Prescription," highlighting serious problems in the pharmaceutical industry and within the FDA that had allowed dangerous drugs to be approved and had delayed the banning of other drugs, resulting in many avoidable deaths and injuries. Health Letter Editor Dr. Sidney Wolfe was interviewed for the documentary. The web site for the program is:

<http://www.pbs.org/wgbh/pages/frontline/shows/prescription/>

It includes the transcript of the program and a video version.

Below, we reprint excerpts from "Dangerous Prescription," written, produced and directed by Andy Liebman, to give readers an idea of the power of its message.

Back in 2000, an unusual number of [adverse drug reaction] reports started coming in about people like Angus McLean, a retired Naval Intelligence expert. While raking leaves one weekend, Angus suddenly felt intense muscle pain all over his body — a severe reaction to a new "statin" drug he was taking to lower his cholesterol.

When his symptoms became severe, his wife rushed him to the

hospital, where he was diagnosed with a life-threatening, muscle wasting condition called rhabdomyolysis. It's a rare side-effect that can cause a person to lose vast numbers of muscle cells, which then have to be eliminated from the body. Angus required emergency kidney dialysis. For an entire week, he hovered on the edge of death — drifting in and out of consciousness.

The drug that caused Angus' problem — Baycol — had recently been approved by the FDA.

WOOSLEY: I think Americans need to recognize that every time they put a pill in their mouth, especially a new pill that they've never taken before, it's an experiment. When a drug goes on the market, only about 3000 patients have ever been

given that drug.

Dr. Raymond Woosley runs a national center to study the side effects of drugs at the University of Arizona College of Medicine. He worries that most people don't understand how much about new drugs is unknown.

Two years after approving Baycol, the FDA okayed a higher dose — .4. Sales started to rise.... But soon Bayer began getting a troubling number of reports that patients were developing that muscle wasting condition, rhabdomyolysis.

PETROFF (attorney representing people injured by Baycol) : When Bayer realized that they were getting increased numbers of reports, what they wanted to

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do was try to compare it to the other statins to see if the other statins had just as high an incidence.

To do that, the company asked the FDA for copies of all Medwatch reports associated with Baycol and its competitors.

While Bayer was waiting for the information, ... a company memo shows there was growing concern among some doctors that Bayer wasn't being honest about what was going on. After some rhabdomyolysis patients died, another company memo shows that Bayer was worried about the news getting out.

In the Spring of 2000, Bayer received and analyzed the Medwatch Reports it had requested from the FDA. Company officials compared Baycol with the industry leader Lipitor and got discouraging results. For every 100,000 prescriptions given without other cholesterol drugs, Baycol had 20 times more reports of rhabdomyolysis than Lipitor — also known by its chemical name atorvastatin.

With the FDA in the dark about Bayer's Medwatch Report analysis, in the summer of 2000 the agency approved sales of Baycol .8 — an even higher dose that Bayer needed to compete effectively against Lipitor.

David Archer was one of many patients put on the new Baycol .8 dosage. He was also switched over from Lipitor.....and his wife Lucy

remembers that her husband was in excellent health until he began taking Baycol.

LUCY ARCHER: David was always very active. He would chop trees. He would do a lot of things. But then as he was taking the Baycol, I noticed as we walked especially, he would complain about his toes, then he would complain about the calf, his legs, and his muscles, his back. Finally it got so that he just couldn't seem to bend over to put his socks on and shoes. And no way had I ever thought that this Baycol was doing this. He took it October, November, and December he was gone. He should have never, never died.

Lucy Archer's husband died more than five months after Bayer had strong indications their drug might be less safe than Lipitor. Bayer declined Frontline's request for an interview to explain why the company continued selling Baycol despite the safety concerns.

Under pressure from the FDA, Bayer voluntarily took Baycol off the market in August 2001 — two years after first getting reports there might be problems with the drug.

Although Bayer has won a few jury trials in cases where it was unclear that Baycol caused damage, the company has settled more than 1200 lawsuits and paid over 430 million dollars to victims.

Beyond the harm done to individuals, though, the Baycol story reveals how dependent the FDA is on information supplied by drug companies.

[In 1992] Congress passed the Prescription Drug Users Fee Act — or PDUFA — a law that requires companies to pay up to a 500,000 dollar fee with each new drug application to help the FDA hire more reviewers and get drugs onto market quicker. Today over half the FDA's drug reviewers are paid with industry money — and the approval time for many drugs has gone from over 2 years to less than six months.

SIDNEY WOLFE: The culture at the FDA has become "please the industry, avoid conflict, look upon our role as getting out as many drugs as possible."

Sidney Wolfe of Public Citizen's Health Research Group in Washington believes industry-funding has created an FDA that's reluctant to challenge company claims about safety and effectiveness.

WOLFE: This system has created a very unhealthy relationship between the industry and the FDA, where the FDA says, "We have to be nice to these people because they are paying our bills."

Michael Elashoff thinks this new relationship partly explains what happened to him at the FDA three

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years ago when he opposed the approval of a new anti-flu drug called Relenza.

ELASHOFF: Simply stated, Relenza just didn't work in the United States clinical trials. It really had no effect at all on the symptoms of influenza. It had no effect at all on influenza complications. It maybe knocked half a day or less off the duration, and even that wasn't established statistically. So, it was pretty much no different from placebo as far as efficacy.

What also bothered Elashoff was a life-threatening side-effect that caused some users to have trouble breathing.

ELASHOFF: One of the concerns during the review, was that Relenza had the potential to cause bronchospasm or constriction of the airways, and it was observed in several patients in the clinical trials.

To sort things out, the FDA called an advisory committee meeting. Elashoff told the panel of 17 experts that Relenza had little benefit and real risk.

ELASHOFF: Ultimately they decided that it was not worth approving and voted 13 to 4 to reject the drug. The next day after the advisory committee, several people in FDA management told me that they blamed me for the drug getting turned down at the advisory committee, that I wouldn't be allowed to present at the advisory committee meetings in the future for any other drugs.

Elashoff still had to write up a formal review of Relenza — and here he says he got reined in again.

ELASHOFF: I was told very explicitly, don't write in your review that you're recommending against approval. Write that the data is unclear, you could go either way. So it was, it was quite explicit.

In the end, the FDA approved Relenza after the manufacturer — Glaxo — sent the agency a strong letter complaining that Elashoff was judging their drug by stricter standards than what had been agreed upon before the review began. Nine months later, the FDA forced Glaxo to put a new warning on the Relenza label saying that deaths and injuries can occur from bronchospasm, the very thing that worried Elashoff.

By then, Elashoff had left the agency after working there 5 years. He says his experience wasn't an isolated example of an FDA scientist being asked to brush aside bad news about a drug.

ELASHOFF: In nearly all the cases that I was familiar with, both that I worked on and other people in my division worked on, there would be a pressure to approve those drugs, or soften the language in the review, soften the language in the labels, so that they could have a more easy justification for why they were approving. So I would say it was very common.

Frontline asked the FDA's Steven Galson about Elashoff's charge.

GALSON: We're certainly not proud to hear that there's anybody that has opinions like that but we just don't think that it's average or even reflective of what most people think. We wouldn't condone anyone being asked to change their review. I think the idea of forcing someone to change something that they've written or

something that they've analyzed, is highly unusual.

ELASHOFF: That's a joke! I mean it happens all the time. I guess the only reason it doesn't happen as frequently as it might otherwise is people start censoring themselves. That they say, OK after the first time I've noted a problem and it's been glossed over, well, you know, why bother the second time?

An investigation by Sidney Wolfe's Heath Research Group revealed that charges like Elashoff's are common at the FDA.

SIDNEY WOLFE: In the context of the large number of drugs that had come off the market in the late 90s, we did a study of physicians at the FDA who are in the drug approval division. And found that between them, they had identified 27 drugs that they thought were too dangerous to come on the market. But those drugs were approved over their objection. They eventually signed off on the drugs. But they told us, anonymously in a survey, that they thought the drugs should not be on the market.

In late 2000, soon after the Health Research Group survey was published, the FDA completed its own survey about morale at the agency. Frontline obtained the results of this internal study. Among those who responded, a number said their reports were edited and they had been asked to change negative opinions about pharmaceuticals. ONE THIRD said they feared being stigmatized if they recommended that a drug not be approved. And a third also said they were uncomfortable expressing differing scientific opinions.

Product Recalls

October 16, 2003 — November 14, 2003

This chart includes recalls from the Food and Drug Administration (FDA) Enforcement Report for drugs, dietary supplements and medical devices, 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

Estrace tablets (estradiol tablets, USP) 0.5mg, 1mg, and 2mg; physician samples, 7 and 21 count boxes, Rx only, Not an oral contraceptive; Class II; Dissolution failure.

Indomethacin capsules, 25 MG, 60 capsule plastic bottles, RX only; Class II; Label Mix-up: bottles labeled as containing 25 mg strength capsules actually contain 50 mg capsules.

Kaletra capsules (lopinavir/ritonavir); Each soft gelatin capsule contains: Lopinavir 133.3mg, Ritonavir 33.3mg, 180 capsule bottles, Rx only; Class II; Counterfeit: bottles labeled as containing Kaletra capsules may contain Kaletra capsules and/or Agenerase capsules or a mix of both, as well as, bottles of Kaletra capsules have been repackaged/re-labeled by an unknown source with an extended expiration date/counterfeit lot number.

Kaletra capsules (ritonavir/lopinavir 33.3mg/133.3mg), 180 capsule bottles, Rx only; Class II; Counterfeit: An unknown number of bottles bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Kaletra capsules (lopinavir/ritonavir), 133.3/33.3mg, 180 capsule bottles, Rx only; Class II; Counterfeit: An unknown number of bottles bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Levoxyl tablets, (Levothyroxine, Sodium Tablets, USP), 25mcg, 100 count bottles, Rx only; Class III; Subpotency: Stability failure (18 month CRT-controlled room temperature)

Lot #: Quantity and Distribution; Manufacturer

Lot No. 64-GCA07; 106,871 blisters distributed nationwide; Bristol-Myers Squibb Company, Princeton, NJ

Lot No. 213981BB Exp. 7/04; 400 bottles distributed nationwide; Direct Dispensing, Inc.; Miami, FL

Lot No. 852072E25; 71 bottles distributed nationwide; The Harvard Drug Group, Livonia, MI

Lot No. 852002E21, Exp. 1 FEB 2004; 71 bottles distributed nationwide; Mid Atlantic Csc, Perryman, MD

Lot No. 852072E25 (Exp. 1JUN2004) and Lot No. 852002E21 (Exp. 12/03 or 02/04); 387 bottles distributed nationwide; Midwest Drug Supply LLC

Lot No. 7478, Exp. 11/03; 24,872 units distributed nationwide; King Pharmaceuticals, Inc., Bristol, TN

Name of Drug or Supplement; Class of Recall; Problem

Lipitor tablets (Atorvastatin Calcium), 10 mg, Rx only, 5000 tablets; Important — This package for pharmacy stock use; Class II; Counterfeit: An unknown number of units bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Mentax(r) cream (butenafine HCL), 1%, Topical Antifungal Cream 1%, 12.2 gram tubes, Physician Sample, Rx only, For topical Dermatologic Use Only; Class III; Stability failure, sodium benzoate (18 month test point)

Morphine-Sulfate Extended-Release Tablets; 15 mg, 100 tablets, Rx only, Class III; Mis-labeling: some tablets are not imprinted with an identification number, bearing the number "15" on each side. (Each tablet should be imprinted with the number "15" on one side and with the identification code "E652" on the other side).

NuLYTELY, Powder for Reconstitution, (PEG 33350, Sodium Chloride, Sodium Bicarbonate and Potassium Chloride for Oral Solution), Rx only, disposable jug; unflavored, cherry, lemon-lime, and orange; Class II; Product overfill: double one ingredient (PEG-3350)

Oxygen, USP, Compressed, cylinders, sizes-H, E, D, C, ML 6 and M6, Rx.; Class II; Good Manufacturing Practice Deviations (GMPs); including but not limited to, failure to perform purity analysis.

Senokot-S tablets (Sennosides 8.6 mg and Docusate Sodium 50 mg) tablets, 30 count bottles; Class III; Subpotent (Sennosides)

Sterile Diluent for Humulin L, Humulin U and Lente Iletin, Lilly, 10 ml. vial. Warning: Use ONLY with insulins listed on side panel. PROFESSIONAL PACKAGE NOT TO BE SOLD; Class II; Particulates: vials exhibit white particulates/ white precipitate on vial wall which does not resuspend.

Tegretol tablets (Carbamazepine USP), 200 mg, 1000 tablet bottles. Rx only; Class II; Dissolution failure; stability (at 30-months).

Zyprexa tablets (Olanzapine), 5 mg, 10 mg, 15 mg and 20 mg 60-tablet bottles; Class II; Counterfeit: An unknown number of bottles are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Zyprexa tablets (Olanzapine), 10 mg and 15 mg 60-tablet bottles, Rx only; Class II; Counterfeit: An unknown number of bottles bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Lot #: Quantity and Distribution; Manufacturer

Lot No. 16092V Exp. 7/2004; 20 bottles distributed in Texas; QK Healthcare, Inc., Ronkonkoma, NY

Lot No. RBER, Exp. Jan-04; 506,736 units distributed nationwide; Bertek Pharmaceuticals, Inc., Durham, NC

Lot No. TP168A, Exp. 2/2006; 22,608 bottles distributed nationwide; Endo Pharmaceutical, Inc., Garden City, NY

Lot No. (unflavored) N3E005 Exp. Date: 5/06 ; (cherry) C3G020 Exp. Date: 7/05; (lemon-lime) L3F014 Exp Date: 6/05; (orange) R3G011 Exp. Date: 7/05 and R3E009, Exp. Date: 5/05; 69,744 bottles distributed nationwide; Braintree Laboratories, Inc., Braintree, MA

All Lots. Estimated 50 cylinders distributed in Michigan; Classic Medical Inc., St. Clair Shores, MI

Lot No. PB11; 45,420 bottles distributed nationwide; The Purdue Frederick Company, Stamford, CT

Lot No. 7RE39M and 7RT38M; 6,814 vials distributed nationwide, in Canada, and Japan; Eli Lilly and Company, Indianapolis, IN

Lot No.218D8264; 3,622 distributed nationwide; Novartis Pharmaceuticals, Corp., East Hanover, NJ

Numerous lots; 547 bottles distributed nationwide; Walsh Heartland, LLC, Paragould, AR

Lot Nos. 10 mg 6AH19A (Exp. 01/05), 7AA39A (Exp. 03/05), 7EA97A (Exp. 04/05); Lot numbers 15 mg 6AH35A (Exp. 01/05) and 6AG70A (Exp. 11/04); Unknown amount distributed nationwide; R&L Associates of Walled Lake, LLC, Walled Lake, MI

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DRUGS AND DIETARY SUPPLEMENTS *cont.*

Name of Drug or Supplement; Class of Recall; Problem

Zyprexa tablets (Olanzapine), 5 mg and 10 mg 60-tablet bottles, Rx only; Class II; Counterfeit: An unknown number of bottles bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Zyprexa tablets (Olanzapine), 5 mg and 10 mg 60-tablet bottles, Rx only; Class II; Counterfeit: An unknown number of bottles bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Zyprexa tablets (Olanzapine), 20 mg, 60 tablet bottles, Rx only; Class II; Counterfeit : An unknown number of bottles bearing these lot numbers are counterfeit, in that they have been repackaged, relabeled and/or may contain different strengths or mixed strength tablets differing from their labeled contents and/or bear extended expiration dates, as the source of the repacked and/or relabeled bottles is unknown.

Lot #: Quantity and Distribution; Manufacturer

Lot Nos. 6AA66A and 6AH19A; 45 bottles distributed nationwide; Houston Rx, Inc., Humble, TX

Lot Nos. 6AA66A; 6AH19A; 500 bottles distributed nationwide; Rochester Drug Cooperative Inc., Rochester, NY

Lot No. 7AA79A, Exp. 3/1/05; 12 bottles distributed nationwide; Rochester Drug Cooperative Inc, Rochester, NY

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

All-Terrain Vehicles (ATVs). Damage to the fuel tank grommet can cause a fuel leak, posing a serious fire hazard to consumers.

Audio Evacuation Units (AEUs). The AEU can enter a "sleep" mode where it does not communicate with the system. When this occurs, audible evacuation signals associated with the failed AEU will not operate and building occupants may not be warned of an emergency.

Audio Video Controller/Amplifiers. The Controller/Amplifiers can short circuit and overheat, posing a risk of injury to consumers.

Lot #: Quantity and Distribution; Manufacturer

Magnum, Trail Boss and ATP model ATVs; Model numbers A03CD32(AA)(AC), A04CD32(AA)(AB)(AC), A04CB32(AA)(FC), A04CA32(AA)(AB), A04JD32AA, and A04JD50(AA)(AB)(CA); 14,000 sold nationwide from February 2003 through October 2003; Polaris Industries Inc.; Minneapolis, MN; (800) POLARIS

Used in FireVac 7200 System Control Units, including all V5 versions below V5.2-008 and V6 versions below V6.0.14; 276 sold nationwide from January 1998 through April 11, 2003; Fire Control Instruments; Westwood, MS; (800) 633-1311

Russound CAV6.6 Controller/Amplifiers have serial numbers ranging between 03141500000000 and 03281500000500; 1,200 sold nationwide from May 2003 through September 2003; Russound Inc.; Newmarket, NH; (800) 638-8055; www.russound.com/cav.alert

<i>Name of Product; Problem</i>	<i>Lot #: Quantity and Distribution; Manufacturer</i>
Candleholders. The base of the candleholder can unexpectedly fall off and cause the glass bowl or base to break, and the broken glass can cause cuts.	Footed Glass Floater Bowl candleholder intended for use with floating candles; about 5 1/4 inches in height, with a 9 inch diameter bowl and a 2 1/2 inch diameter base. 65,800 sold nationwide from March 2002 through October 2003; Pier 1 Imports; Fort Worth, TX; (800) 245-4595; www.pier1.com
Candle Gift Sets. The candle gift set can exhibit a larger-than-normal flame height as the tealight candle burns to the end, posing a potential fire hazard.	Includes two candle lamps and eight tealight candles sold in three different fragrance combinations; 50,600 sold at BJ's Wholesale Clubs from August 24, 2003 through October 30, 2003; Polardreams International Ltd.; of Fairfield, IA; (800) 446-6541; www.bjs.com/news
Children's Activity Books. The hub of the pink dial embedded in the inside back cover can come off during use in some of these books, posing a choking hazard to young children.	"Amazing Baby(tm) Listen and Play" book has a multi-colored cover with a baby face on the front; 5,300 sold nationwide from May 2003 through October 2003; Advantage Publishers Group; San Diego, CA; (866) 748-3731; www.advantagebooksonline.com
Cigarette Lighters. The cigarette lighters do not have qualified child resistant mechanisms and pose a fire hazard to children.	Digital wristwatch with cigarette lighter incorporated into it; cigarette-shaped lighter designed to resemble a filter cigarette; 3,000 wristwatch and 5,000 cigarette-shaped lighters sold nationwide primarily through internet sales; Style Asia, Inc.; Moonachie, NJ; (800) 522-7465
Curling Irons. The electrical insulation in the curling irons may break down, resulting in a possible electric shock and injury to the user.	"Duet 2 in 1 Hair Styler with 1 1/2 inch barrel" curling irons, models 5266-500 and 5266-500B; 6,000 sold nationwide from May 2003 through August 2003; Wahl Clipper Corporation; Sterling, IL; (800) 334-4627; www.wahlclipper.com
Deep Fryers. The mesh filter in the cover of the deep fryer can allow moisture to build in the oil reservoir, causing the oil reservoir to boil over during or shortly after use. This poses a burn hazard to consumers.	NESCO brand, stainless steel deep fryers with a black plastic top and handles on either side; 47,000 sold nationwide from May 2001 through October 2003; The Metal Ware Corp.; Two Rivers, WI; (800) 726-4457; www.nesco.com
Electric Scooters and Mini Bikes. The motor control circuits can malfunction causing the scooters and mini bikes to continue to run after the power or throttle button is released, posing a risk of injury to children.	Lightning PAC Scooters and MX3 Mini Bikes, Models 73530 (Lightning PAC) or 73535 and B2222 (MX3 Mini Bike); 30,000 electric scooters sold nationwide from November 2001 through October 2003, and 55,000 electric mini bikes sold nationwide from May 2003 through September 2003; Fisher-Price, East Aurora, NY; Fisher-Price; (800) 528-7153; www.service.mattel.com
Fire Alarm Control Panels. A software problem can result in system devices unexpectedly changing their Type ID, making them appear to be photo detectors. This condition should result in several trouble signals. If the problem is not corrected, the system will not operate as programmed and will not provide the expected level of protection.	Notifier model AM2020 and AFP1010 fire alarm control panels with date codes from 0100 to 2003 and firmware version 3.0 and 3.01; 6,000 sold nationwide from January 2000 through May 2002; Notifier; Northford, CT; (800) 289-3473
Fish-Shaped Cigarette Lighters. The lighters lack the required child resistant mechanisms and can expose children to fire hazards.	Fish-shaped lighters have metallic plastic bodies and come in 18 different colors; 3,100 sold nationwide from 2,000 to 2003; Sarut Group; New York, NY; (800) 345-6404
Halloween Tealight Candleholders. Because of the lack of ventilation in these ceramic candleholders, the tealights can flare up, posing a risk of burns to consumers.	In the shape of pumpkins, gourds, witch hats and ghosts; 165,000 sold nationwide from July 2003 through October 2003; Michaels Stores, Inc.; Irving, TX; (877) 562-3816; www.Michaels.com

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FDA Issues Public Health Advisory On Antidepressants And Suicide Risk In Children

DO NOT ABRUPTLY DISCONTINUE ANY OF THE ANTIDEPRESSANTS MENTIONED BELOW — DISCONTINUATION OF THESE DRUGS SHOULD TAKE PLACE UNDER MEDICAL SUPERVISION

The Food and Drug Administration (FDA) issued a Public Health Advisory on October 27, 2003 about reports of suicidal thinking and suicide attempts in clinical trials of eight drugs in pediatric patients with major depressive disorder (MDD).

This advisory follows earlier warn-

ing about the antidepressants paroxetine (PAXIL) and venlafaxine (EFFEXOR, EFFEXOR XR).

On June 19, 2003, the FDA issued a public advisory concerning the safety of paroxetine (PAXIL), a member of the selective serotonin reuptake inhibitor (SSRI) family of antidepressants, in children or adolescents less than 18 years of age. The advisory is based on reports of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents under the age of 18 taking paroxetine for MDD.

The FDA's advisory followed a similar announcement nine days earlier, June 10, 2003, by the Committee on Safety of

Medicines, the British counterpart to the FDA.

The manufacturer of the antidepressant venlafaxine (EFFEXOR, EFFEXOR XR), Wyeth Pharmaceuticals, issued a Dear Health Care Professional letter on August 22, 2003 warning of increased reports of suicide-related adverse events such as suicidal ideation and self harm, in addition to hostility, with the use of this drug in children and adolescents.

The FDA's October 27th advisory indicated that the agency had completed a preliminary review of clinical trials involving children for eight drugs: citalopram (CELEXA),

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CONSUMER PRODUCTS *cont.*

Name of Product; Problem

Hedge Trimmers. The fuel cap on the hedge trimmer can leak, posing a fire and burn hazard.

Lawn Mowers. A loose blade bolt could cause the blade to come loose or the blade adapter to crack, resulting in the blade falling off. Should this condition occur, the operator or a bystander could be injured.

Multicolored Sidewalk Chalk. The multicolored sidewalk chalk contains high levels of lead, posing a risk of poisoning to young children.

Pumpkin Tealight Candleholders. The beads on the candleholders can ignite, posing a fire hazard.

Toy Drums. The three rubber feet, which are screwed into the bottom of the drum, could be removed in some cases, posing a choking hazard to young children.

Utility Vehicles. Brass gear in the steering sector can break, causing consumers to lose steering capabilities.

Lot #: Quantity and Distribution; Manufacturer

Hedge trimmers have red engine covers, a red fuel cap and a label on the recoil starter that reads "Professional Shindaiwa," includes all model DH 230/231 and HT 230/231 with serial numbers up to 3080000; 59,200 sold nationwide from August 1997 to August 2003; Shindaiwa Inc.; Tualatin, OR; (800) 521-7733

Husqvarna Royal 53S or ROY53INTEK Walk-Behind Lawn Mowers with serial numbers between 24600001 and 31000205; 9,900 sold nationwide from December 2002 through August 2003; Husqvarna Forest and Garden Company; Charlotte, NC; (800) 448-7543 Ext. 3

Packaged in plastic that is molded to five sticks of chalk and a cardboard backing that is labeled "Double Dipp'n Fun;" 26,000 packages sold nationwide at Target stores from March 2003 through July 2003; Agglo Corporation, Hong Kong and imported by Target Corporation, Minneapolis, MN; (800) 440-0680; www.target.com

Colors of Autumn Beaded Pumpkin Tea Light Holders item number 642146; 5,000 sold nationwide from September 2003 to October 2003; Walgreen Co.; Deerfield, IL; (866) 778-6546; www.walgreens.com

Plan Toys Solid Drum is natural wood with blue and red triangles painted on the side; 2,100 sold nationwide from March 2003 through September 2003; BRIO(r) Corp.; Germantown, WI; (888) 274-6869; www.Briotoy.com

Raptor 1000M off-road utility vehicles, two-wheel drive with two seats and a back bed; 350 sold nationwide from June 2001 through August 2003; Koyker Manufacturing Company; Lennox, SD; (800) 456-1108

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fluoxetine (PROZAC), fluvoxamine (LUVOX), mirtazapine (REMERON), nefazodone (SERZONE), paroxetine (PAXIL), sertraline (ZOLOFT), and venlafaxine (EFFEXOR). At this time fluvoxamine is not approved for depression in the U.S.

Only fluoxetine was found effective in pediatric MDD patients and it is approved in the U.S. to treat children ages eight to less than 13 and adolescents 13 to 18 years of age. In the 20 controlled clinical trials reviewed by the FDA for these eight drugs, involving over 4,100 pediatric patients, there have been no reports of completed suicides.

The FDA urged that these drugs be used with caution and reminded prescribers of the following statement that is present in the professional product labeling or package insert for all antidepressant drugs:

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant

remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Drug X should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

We would add that in addition to close supervision during initial treatment with one of these drugs and only purchasing small prescriptions, that a physician qualified in treating serious mental illness in children make the diagnosis of MDD in pediatric patients. None of these drugs should be used for mild situational depression; they are approved to

treat MDD, a serious mental illness.

Nefazodone (see Outrage, p.12) is of special concern because of its association with the development of liver toxicity that has led to deaths. We have petitioned the FDA on two occasions to remove this dangerous drug from the market. The only two countries in which this drug is still being sold are the U.S. and Australia.

What You Can Do

Parents whose children are using any of the drugs mentioned above should consult the prescribing physician immediately.

DO NOT stop treatment with any of these drugs immediately. Discontinuation requires medical supervision.

OUTRAGE, from page 12

protect patients' health.

Nefazodone was listed by HRG as a Do Not Use drug in February 2002 after the Food and Drug Administration (FDA) required a black box warning in the drug's professional product labeling or package insert about its liver toxicity. A black box warning is the strongest type of warning that the FDA can require on a drug's labeling.

The addition of the black box warning had only a modest effect on the prescribing of this dangerous drug. In 2001, over 4.5 million prescriptions for nefazodone were dispensed in U.S. pharmacies. The number dropped to approximately 2.8 million in 2002. Unfortunately, there is no requirement that patients see black box warnings before they receive a drug and the warning has not diminished the occurrence of life-threatening liver damage.

continued on page 10

Announcing

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OUTRAGE, from page 9

We warned readers again about the toxicity of the drug in March 2003 when Bristol-Myers Squibb halted the sale of nefazodone in all European countries after national drug regulatory authorities became concerned about its safety. Turkish authorities banned the drug in April 2003.

On March 6, 2003, we petitioned the FDA to immediately remove nefazodone from the market. At the time, our analysis based on adverse reaction reports to the FDA revealed that from 1994, when first marketed in the U.S., through the first quarter of 2002, nefazodone was associated with at least 53 cases of liver injury, including 21 cases of liver failure from which 11 people died.

A copy of this petition is available on our web site www.worstpills.org/public/petitions.cfm. Those without Internet access can write to us for a copy of the petition.

Because of the failure of the FDA to take action on our petition and the growing number of reports of liver toxicity associated with the use of nefazodone, we filed an amended petition with the FDA on October 29, 2003 again asking that the drug be immediately removed from the market. From April 1, 2002 through

May 12, 2003 there have been an additional nine deaths related to the use of nefazodone reported to the FDA. This brings the total to at least 20 deaths linked to the use of nefazodone.

This amended petition is also available on our web site at the Internet address given above.

The numbers of injuries and deaths reported to the FDA must be placed in their proper context. Because the safety reporting system is voluntary, the FDA estimates that only one in ten serious adverse drug reactions is ever reported.

Patients who are taking nefazodone who develop any of the following symptoms of serious liver problems should contact their prescribing physician immediately:

- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Nausea
- Abdominal (lower stomach) pain

The FDA's failure to ban this dangerous drug is incomprehensible. There are currently two dozen antidepressants, in at least four pharmacologic classes, available on the

market in the U.S. Not one of these drugs, including nefazodone, has been shown to be superior to another in the treatment of depression in controlled clinical trials. The best way to differentiate one from another, as is the case with most families of drugs which have similar efficacy, is on the basis of their known toxicities. Clearly, nefazodone possesses a known significant toxicity, the possibility of liver failure and death, and should be removed from the market immediately.

The Canadians have taken action before the FDA on several important drug safety issues and should be commended. However, the Canadian government's decision to allow Bristol-Myers Squibb to continue selling nefazodone until the end of November 2003 is dangerous and inexcusable.

What You Can Do

If you have never before been treated with an antidepressant, there is no medical reason why you should be started on nefazodone.

If you are currently taking nefazodone, discuss with your doctor switching to one of the numerous other, safer antidepressant drugs on the market.

How To Report Adverse Reactions To The FDA

Consumers can play an important public health role by reporting any adverse experiences with drugs, devices, or dietary and herbal supplements to the Food and Drug Administration (FDA). This can be done through the MedWatch program, the FDA's medical products reporting system. The FDA emphasizes that it is not necessary to prove that a medical product caused an adverse reaction — a suspected association is sufficient reason to make a report to the agency.

The FDA is particularly interested in suspected adverse events that led to the following outcomes:

- Death
- Life-threatening hazard
- Hospitalization
- Disability
- Birth defects, miscarriage, stillbirth, or birth with disease
- Needs intervention to avoid permanent damage

The FDA offers several ways for health professionals or consumers to submit MedWatch reports:

- *Online* — Go to the MedWatch Web site at www.fda.gov/medwatch/ and follow the instructions for submitting a report electronically
- *By mail* — Print out the form (see p. 11) from the Medwatch site and mail it to the address on the bottom of the form
- *By phone* — The toll-free number for reporting to the FDA is 1-800-FDA-1088
- *By fax* — You can submit a completed form to MedWatch's fax number at 1-800-332-0178

MEDWATCH**The FDA Safety Information and
Adverse Event Reporting Program**For **VOLUNTARY** reporting of
adverse events and product problems

Page ____ of ____

FDA USE ONLYTriage unit
sequence #**A. PATIENT INFORMATION**

1. Patient Identifier	2. Age at Time of Event: or _____ Date of Birth: _____	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or ____ kgs
-----------------------	--	--	---

In confidence

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)	
2. Outcomes Attributed to Adverse Event (Check all that apply)	<input type="checkbox"/> Disability <input type="checkbox"/> Congenital Anomaly <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage <input type="checkbox"/> Other: _____
<input type="checkbox"/> Death: _____ (mo/day/yr) <input type="checkbox"/> Life-threatening <input type="checkbox"/> Hospitalization - initial or prolonged	
3. Date of Event (mo/day/year)	4. Date of This Report (mo/day/year)
5. Describe Event or Problem	

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)	
#1 _____	
#2 _____	
2. Dose, Frequency & Route Used	3. Therapy Dates (If unknown, give duration from/to (or best estimate))
#1 _____	#1 _____
#2 _____	#2 _____
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#1 _____	#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2 _____	#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot # (if known)	7. Exp. Date (if known)
#1 _____	#1 _____
#2 _____	#2 _____
9. NDC# (For product problems only)	8. Event Reappeared After Reintroduction?
#1 _____	#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2 _____	#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

D. SUSPECT MEDICAL DEVICE

1. Brand Name	
2. Type of Device	
3. Manufacturer Name, City and State	
4. Model #	5. Operator of Device
Catalog #	<input type="checkbox"/> Health Professional
Serial #	<input type="checkbox"/> Lay User/Patient
6. If Implanted, Give Date (mo/day/yr)	<input type="checkbox"/> Other: _____
7. If Explanted, Give Date (mo/day/yr)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor	
10. Device Available for Evaluation? (Do not send to FDA)	
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: _____ (mo/day/yr)	
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

E. REPORTER (See confidentiality section on back)

1. Name and Address	Phone #
2. Health Professional? <input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Occupation	4. Also Reported to:
	<input type="checkbox"/> Manufacturer
	<input type="checkbox"/> User Facility
	<input type="checkbox"/> Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: <input type="checkbox"/>	



Mail to: **MEDWATCH**
5600 Fishers Lane
Rockville, MD 20852-9787

-or- FAX to:
1-800-FDA-0178

DO NOT USE!

Dangerous Antidepressant Nefazodone (SERZONE) Withdrawn From The Market In Canada

Health Research Group Files Amended Petition to Ban Nefazodone in U.S.

Nefazodone (SERZONE), a dangerous antidepressant long linked to liver toxicity and deaths, has been withdrawn from the Canadian market effective November 27, 2003. The drug is produced by Bristol-Myers Squibb in both Canada and the U.S.

In the October 2, 2003 notification of the drug's withdrawal the company stated "...no risk factor to predict patients who will develop irreversible liver failure with nefazodone has been identified," and that "...no clinical strategy, such as

routine liver function tests, could be identified to reduce the risk of liver failure." In other words, there is no way to ensure that this drug can be used safely.

Since its introduction in Canada in 1994, nefazodone has been associated with liver adverse events such as jaundice, hepatitis (inflammation of the liver) and hepatocellular necrosis (liver cell death) in patients receiving the drug. As of December 2002, there were 51 Canadian reports of liver toxicity associated with the use of nefazodone. Two patients required

liver transplantation, one of whom died. In the Canadian reports, liver injury occurred as early as a few weeks after starting the drug or after continuous use for up to three years.

Serzone's U.S. professional product labeling, or package insert, states that "The physician may consider the value of liver function testing." It also adds that, "Periodic serum transaminase [liver function] testing has not been proven to prevent serious injury." As a result, there is no means available to reliably monitor and

continued on page 9

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