June 9, 1998

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CITIZENS’ PETITION TO IMMEDIATELY STOP THE DISTRIBUTION OF DANGEROUSLY MISLEADING PRESCRIPTION DRUG INFORMATION TO THE PUBLIC

Dear Dr. Friedman:

There is no question that a substantial proportion of the estimated 100,000 Americans who die each year because of adverse drug reactions and the serious injuries to 2.2 million others could be prevented. One of the most important ways of preventing such tragedies is to ensure that patients are adequately informed about the risks and proper use of prescription drugs. As long ago as 1979, FDA stated that: “. . . oral communication of information about prescription drug products by health professionals cannot be relied upon to provide patients with the information they need to use prescription drug products properly.” More recently, the Agency said: “Inadequate access to appropriate patient information is a major cause of inappropriate use of prescription medications, resulting in serious personal injury and related costs to the health care system.”

Public Citizen, a nationwide organization representing 120,000 consumers, and Patricia and Ben Christen, whose only son Cory died as a result of unregulated, misleading, commercially produced written patient drug information, hereby petition the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act, to immediately recall, or seize if necessary, unregulated information that is being distributed with prescription drugs that is not consistent with or derived from a drug’s FDA approved, regulated professional product labeling, commonly known as the package insert. A large proportion of the patient information leaflets (PILs) produced by commercial information vendors and distributed by pharmacists to millions of consumers when prescriptions are dispensed may contribute to thousands of drug
injuries and deaths by giving the public a dangerously false sense of security about the safety of prescription drugs by failing to warn about adverse reactions or proper use including dangerous dosages. FDA’s first priority should be to take action by recalling those PILs whose inaccurate information is most likely to cause substantial harm if not corrected.

Seven-year-old Cory Christen’s death, from a drug-induced cardiac arrhythmia, was needless and preventable and is directly attributable to his parents being deprived of vital dosing and adverse reaction information, information that was omitted from a PIL produced by an unregulated commercial information vendor, Medi-Span, Inc. of Indianapolis, for the antidepressant drug imipramine (Tofranil). In addition to this tragic example, the FDA is in possession of other evidence demonstrating that dangerous informational deficiencies exist in the PILs for other drugs.

Forty-one thousand patients are hospitalized and an estimated 3,300 die each year from gastrointestinal bleeding caused by nonsteroidal anti-inflammatory drugs (NSAIDs), used for treating arthritis or pain. Studies have shown that if patients are not adequately informed to stop the use of such drugs if they develop abdominal pain and therefore do not identify the pain as an adverse reaction to the NSAID, they are much more likely to have serious bleeding sufficient to require hospitalization. Given that many physicians do not routinely provide this kind of information to their patients, the routine use of accurate and complete PILs would save hundreds of lives lost to NSAID-induced gastrointestinal bleeding and thousands of hospitalizations. As discussed below, FDA’s own study has shown serious deficiencies in PILs and a recent Public Citizen’s Health Research Group survey of PILs for 15 NSAIDs found that only a small fraction warned patients to stop using the drug if they developed abdominal pain.

This petition is based on the following which will be discussed in greater detail:

- The FDA has the clear legal authority to regulate all information distributed with a prescription drug, including commercially produced PILs.
- The needless death of Cory Christen could have been prevented if critical safety information had not been omitted from an unregulated PIL for the drug imipramine (Tofranil and generics).
- An FDA survey of PILs has found substantial differences between commercial information vendors in the quality of information provided including the omission of warnings which could be life-saving.
- Two studies conducted by Public Citizen’s Health Research Group have shown that PILs distributed by pharmacists are incomplete with regard to safety information.
Patients who are informed of the risks of a prescription drug and are told what steps to take should an adverse drug reaction occur reduce their likelihood of suffering the most serious consequences of an adverse drug reaction.

THE FDA HAS JURISDICTION OVER DRUG INFORMATION INTENDED FOR USE BY THE PUBLIC WHICH ACCOMPANIES THE DISPENSING OF PRESCRIPTION DRUGS

Patient Information Leaflets (PILs) meet the legal definition of drug labeling

Section 201(m) of the Food Drug and Cosmetic Act defines "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Patient information leaflets fall under part (2) of this definition, and thus constitute "labeling" under the Act.

Drugs are considered misbranded if they are accompanied by PILs which are misleading (fail to reveal important facts, including adverse reactions) or fail to include adequate directions for use, including warnings against unsafe dosages.

Because patient information leaflets are "labeling," the FDA has jurisdiction to regulate their content pursuant to two separate provisions of the Act:

1. Under section 502(a) of the Act, a drug is misbranded if its labeling is "false or misleading in any particular." In determining whether labeling is "misleading," section 201(n) instructs the Agency to take into account, both representations made or suggested and "the extent to which the labeling . . . fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use prescribed in the labeling . . . or under such conditions as are customary or usual."

2. Under section 502(f), a drug is misbranded if its labeling does not include adequate directions for use and "adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users..."

FDA can regulate PILs in order to enforce the labeling provisions of the law

Section 701(a) of the Act authorizes the Agency to promulgate regulations for the efficient enforcement of the Act. The above two misbranding provisions, in combination with section 701(a), empower the Agency to issue and enforce regulations to ensure that patient information leaflets are accurate and not misleading both in terms of what information is included and in terms of what information is omitted. Although
there are currently no regulations on PIL content, the PILs with the most flagrant violations, which are more likely to result in harm to patients, could be recalled or, if necessary, seized because they clearly violate the above-cited sections of the Food, Drug and Cosmetic Act.

COMMERCIAL INFORMATION VENDORS, PHARMACISTS, AND DRUG COMPANIES ARE ALL RESPONSIBLE FOR THE INFORMATION CONTAINED IN PILs

The Responsibility of Companies Producing PILs

First, section 301(k) of the Act prohibits doing any act with respect to a drug, while the product is held for sale after shipment in interstate commerce, that results in the drug being misbranded. A company that makes and distributes a misleading patient information leaflet causes a product to be misbranded, and thus commits a prohibited act. (Although the company's act may in some cases precede the shipment of the specific item purchased by the consumer, the act comes after the drug in general has entered interstate commerce.)

The Responsibility of Pharmacists

Second, a pharmacist could be held accountable under this same theory. That is, that the pharmacist has rendered the product misbranded by giving the consumer a misleading patient information leaflet at the time of sale.

The Responsibility of Drug Companies

Third, if a drug manufacturer knows that a patient information leaflet concerning its product is misleading, the Agency should hold the manufacturer responsible for the consequent misbranding, even if a manufacturer is not involved in producing or distributing the leaflet. (It is highly unlikely that drug manufacturers are unaware of the content of the PILs which are being dispensed with their drugs.) The Agency's "intended use" regulation provides precedent for holding drug manufacturers accountable for what a third party says about or does with the manufacturer's product. See 21 C.F.R. § 201.128 ("if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.")

THE NEEDLESS DEATH OF CORY CHRISTEN RESULTED FROM CRITICAL SAFETY INFORMATION BEING OMITTED FROM AN UNREGULATED PIL FOR THE DRUG IMIPRAMINE (TOFRANIL AND GENERICS)
Cory was diagnosed with Attention Deficient Hyperactivity Disorder (ADHD) on December 8, 1995 and referred to a psychiatrist on May 10, 1996 who prescribed three drugs for Cory: (1.) imipramine (Tofranil), a tricyclic antidepressant, a drug that is not approved by the FDA for the treatment of ADHD\textsuperscript{10}; (2.) divalproex (Depakote), a drug approved for mania and epilepsy, not for ADHD\textsuperscript{11}; and (3.) pemoline (Cylert), a drug that is approved by the FDA for Attention Deficit Disorder\textsuperscript{12}.

Cory’s parents did not know that imipramine could cause serious potentially fatal heart rhythm disturbances (see Appendix I). This information was omitted from the Medi-Span PILs given to Cory’s parents by the pharmacist. If this information had been made available to his parents, Cory would not have been given the drug.

Cory was started on a dose of imipramine of 2.2 milligrams per kilogram (a total of 50 milligrams per day) on May 21, 1996. By the time he died on September 19, 1996 his doctor had increased his dose to 8.8 milligrams per kilogram (a total of 200 milligrams per day). The package insert for imipramine clearly states that a dose of 2.5 milligrams per kilogram per day should not be exceeded in childhood (see Appendix I). Cory was receiving 3.5 times the recommended dose of imipramine when he died. As seen in Appendix I, this information about maximum childhood dose is in the package insert but was not in the PIL which Cory’s parents were given with the prescription.

During the four months that Cory was taking imipramine his parents had reported to his doctor on three separate occasions that he had experienced hallucinations (6/10/96), headache and “seeing an eye” (6/27/96), and a fine tremor in his hands and he was staring off into space (8/29/96). Again, the package insert lists hallucinations and tremors as adverse reactions for imipramine (see Appendix I). But, Cory’s parents did not know these were adverse reactions to imipramine, this vital information was not contained in the Medi-Span PIL (see Appendix I).

On the morning of September 19, 1996 Cory went to school. At 8:15 AM he complained to his teacher that he had a headache. After lunch, Cory was on his way to his physical education class when he stopped at a water fountain where he collapsed. His teacher administered cardiopulmonary resuscitation (CPR) within minutes. Cory was transported to the local emergency and pronounced dead at 1:41 PM.

**The Medical Examiner’s Report concluded:**

Based on the anatomic findings at autopsy, and investigation information available at this time, it is my conclusion that CORY CHRISTEN, a 7 year-old white male died as a result of toxic effects of imipramine overdose, causing cardiac arrhythmia (heart rhythm disturbance).\textsuperscript{13}

The Medi-Span PIL given to Cory’s parents omitted the most important information, the potentially serious and deadly adverse effects of this drug. Instead, Medi-Span only warned of the minor, nuisance effects of imipramine which are
expected to go away with the use of the drug. Cory’s parents were deprived of information they had a right to know in order to make an informed decision about their child’s medical care. The effect was to give Cory’s parents a false sense of security about the safety of imipramine and this led directly to Cory’s death.

If Cory’s parents had been given an imipramine PIL that was consistent with or derived from the drug’s approved product labeling they would have known four critical pieces of information, any one of which might have saved the life of their son:

1. That imipramine can cause heart rhythm disturbances that are potentially fatal.

2. That the imipramine prescribed for their son was for an “off-label” use, a use that was not approved by the FDA. Imipramine is approved only for depression and pediatric enuresis (bed wetting), not ADHD.

3. That Cory had been prescribed a dose of imipramine that was 3.5 times greater than the maximum dose recommended for children in the imipramine approved product labeling.

4. That the hallucinations and tremors experienced by Cory were actually adverse drug reactions.

AN FDA SURVEY OF PILs HAS FOUND SUBSTANTIAL DIFFERENCES BETWEEN COMMERCIAL INFORMATION VENDORS IN THE QUALITY OF INFORMATION PROVIDED, INCLUDING THE OMISSION OF WARNINGS WHICH COULD BE LIFE-SAVING.

The FDA has compared the PILs produced by eight commercial information vendors for three commonly prescribed prescription drugs for consistency with the drugs’ approved product labeling. The PILs were produced by the American Society of Health-Systems Pharmacists, Clinical Reference Systems, Ltd., Facts and Comparisons, First Data Bank, Medi-Span, Inc., Medi CHEX, Inc., Pharmex, and the United States Pharmacopeia. The specificity of the information communicated was judged on the basis of whether the directions for use were clear and whether the risk information conveyed the significance of the risk, how to recognize negative consequences, and the proper response to take should they occur.14

The FDA found substantial differences between the commercial vendors and the quality of information provided. For example, none of the eight vendors mentioned the contraindications for the use of the high blood pressure lowering drug enalapril (Vasotec), i.e., allergic reactions or swelling (angioedema) on previous treatment with other drugs in the same family. Two vendors failed to warn the patient about the
symptoms of angioedema, a potentially deadly allergic reaction. Of the six vendors including such symptoms (i.e., swelling of the face, extremities, eyes, lips, tongue or difficulty in swallowing or breathing), only one advised the patient experiencing such symptoms to take no more drug and to seek medical attention immediately.

PILS CONTAIN INCOMPLETE SAFETY INFORMATION

Public Citizen’s Health Research Group has conducted two studies of the information content of PILs being distributed by pharmacists to the public. In the first, we examined the PILs for 15 nonsteroidal anti-inflammatory drugs (NSAIDs) for sufficient information for patients to reduce their likelihood of severe NSAID-associated gastrointestinal (GI) toxicity should it occur. PILs were assessed for the following information: (1) GI toxicity is identified as a potentially serious adverse effect; (2) GI toxicity is identified as potentially life-threatening; (3) the symptoms of NSAID associated GI toxicity are listed; and (4) instruction is given to stop the NSAID and contact the prescriber should symptoms of GI toxicity appear. None of these PILs produced by commercial information vendors met all four criteria and only 15 out of 59 (25.4%) warned about stopping the drug if symptoms of GI toxicity such as abdominal pain occur.15

In the second study, the content of four categories of information in PILs for five fluoroquinolone antibiotics (drugs such as ciprofloxacin (Cipro) and ofloxacin (Floxin)) were compared to the information given in the approved product labeling for these drugs (package insert). The information content of the fluoroquinolone PILs contained less than one-half of the information listed in the approved product labeling for these drugs.16

INFORMED PATIENTS CAN AVOID SERIOUS DRUG INDUCED INJURY

GI bleeding and perforation are common and serious adverse effects of the nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin), nabumetone (Relafen), and oxaprozin (Daypro).

Wynne and Long17 studied 50 consecutive patients with arthritis admitted to the hospital with acute GI bleeding who had taken any of four commonly used (NSAIDs) in the preceding three day and 100 control patients matched for age, gender, NSAID, and dosage who had not experienced GI bleeding. All patients were visited in their homes by a nurse to assess their knowledge of their arthritis treatment. The nurse asked whether the patients had received any information about the possible adverse effects of NSAIDs, if so from where, and what they been told to do if an adverse effect occurred. The nurse asked the patients who had bled, “Did you have any stomach problems, such as indigestion or pain before your stomach bleed?” And the patients who had not bled, “Have you had any stomach problems, such as indigestion or pain?” The nurse
also asked the patients to estimate how much of the prescribed dose they actually took and, if it was less than prescribed, why.

The patients whose use of these drugs had led to bleeding knew less about the adverse effects of their NSAIDs or what to do when they occurred than did the patients who had not bled. The patients who bled were also more compliant with their prescribed dosage of drug. Fewer patients who bled (16%) than patients who had not bled (41%) remembered having been told of the possible adverse effects of their drug or about what to do if they developed an adverse reaction (4% vs. 21%). In addition, 18 (36%) of the patients who bled experienced stomach pain before bleeding and all but two had continued to take their drug, whereas only 15 (15%) of the patients who did not bleed had stomach upset, of whom 10 had reduced their dosage of drug.

One of the world’s most respected drug safety experts, Dr. Andrew Herxheimer, commented on this study: “... it looks as if ignorance about side effects led to failure to recognize warning symptoms and to inappropriate compliance [by NSAID users].”

VOLUNTARY REGULATION OF PILS CANNOT WORK

Voluntary self-regulation by the warnings companies such as Medi-Span, Inc. has proven to be unsuccessful. Companies selling these warnings are willing to omit information about deadly adverse effects resulting in inadequately-educated patients who are therefore less reluctant to use or question their prescribed medications. Medi-Span, Inc. has testified through its vice-president of operations, that it allowed the marketplace to help determine the content of its warnings. Several documents attributable to Medi-Span, Inc. indicate that the Medi-Span, Inc. monographs (PILs) are intended to “stand alone” in the absence of counseling, and are considered a safety net in terms of risk management. The dangerously deficient sheets demonstrate the dangers of not requiring scientifically-based regulation: In claiming that “no consistently inferior product would survive in the marketplace”, a company abdicates even its voluntarily-assumed responsibility to “insure accuracy”. The marketplace should not judge the quality of these items; scientists should.

CONCLUSION

The majority of PILs now being distributed contain incomplete safety information. Incomplete, inaccurate or out-of-date safety information misrepresents the risks of prescription drugs and thus presents a hazard to the public’s health that is leading to needless drug induced deaths and injury and, in the case of Cory Christen, the tragic, preventable death of a seven-year-old child.

The FDA has attempted since 1979 to require the distribution of objective prescription drug information written for consumers in non-technical language, but their
efforts have been consistently thwarted by the drug industry and professional trade associations, such as the American Medical Association (A.M.A.) and the American Pharmaceutical Association (A.Ph.A). These groups have effectively prevented the Agency from requiring the distribution of vital, potentially life-saving, information to prescription drug consumers.

After Congress killed the FDA's 1995 effort to ensure the public had useful written drug information, a legislatively mandated voluntary process produced guidelines for the information content of PILs that were agreed to by representatives of the drug industry, medicine, pharmacy, and consumers in 1996 and these guidelines were accepted by the Secretary of the Department of Health and Human Services in early 1997. Central to these guidelines is useful written information for consumers which for the purposes of the guidelines was defined, in part, as being scientifically accurate or "information consistent with or derived from FDA approved labeling . . . ."

The drug industry and the professional trade associations maintain a patently disingenuous stance by saying on the one hand they support the distribution of high quality, objective drug information to the public, while on the other they will only support the voluntary implementation of the agreed upon guidelines. These groups know full well that the Congressionally mandated plan that created the voluntary guidelines is unenforceable. This means no useful drug information in the hands of the public for the foreseeable future.

Distinguishable from the issue of the current inability of the FDA to require PILs to be dispensed with prescriptions is the issue raised in this petition: If PILs are going to be voluntarily provided with a prescription, as they currently are for the majority of prescriptions being dispensed, the FDA has the legal authority, indeed is required by law, to ensure that the content of the PILs is not dangerously incomplete and misleading as in the cases found by FDA's own study, in the studies done by Public Citizen's Health Research Group and in the case of Cory Christen.

The safety of any prescription drug to the individual consumer cannot be separated from the quality of information that accompanies the drug. By being incomplete, unregulated PILs increase the risks of adverse drug reactions by misleading consumers about the safety of their drugs.

The FDA clearly stated in 1995 that it believes that: "Inadequate access to appropriate patient information is a major cause of inappropriate use of prescription drugs resulting in serious personal injury and related costs to the health care system." Cory Christen's death was a needless and tragic example of the effect of inappropriate patient information in the form of unregulated PILs distributed by a pharmacist. Had Cory's parents received a PIL that was consistent with or derived from imipramine's approved product labeling Cory's parents would have made the decision not to administer the drug and Cory would be alive today. There will continue to be more Corys until the public is guaranteed access to objective information, written in non-

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technical language, that places the risks of prescription drugs in a context that is useful to the general public.

The Agency has the clear legal authority and mandate to ensure that when the public receives PILs, the information is written in non-technical language that is consistent with or derived from a drug's approved product labeling and must do so now.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Larry D. Sasich, Pharm.D., M.P.H., FASHP
Public Citizen’s Health Research Group

Sidney M. Wolfe, M.D.
Director,
Public Citizen’s Health Research Group

Allison Zieve
Attorney,
Public Citizen Litigation Group

Patricia Christen

Ben Christen
APPENDIX I

The bolding in the imipramine professional product labeling was added for emphasis. It is present in the FDA-approved labeling but was missing in the Medi-Span PIL.

<table>
<thead>
<tr>
<th>Selected Sections of the Impramine Professional Product Labeling 1996</th>
<th>Medi-Span PIL for Imipramine Given to Cory Christen’s Parent’s in 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDICATIONS AND USAGE</strong></td>
<td>COMMON USES: This medicine is used to treat depression. It may also be used to treat other conditions as determined by your doctor.</td>
</tr>
<tr>
<td>Depression</td>
<td>CAUTIONS: DO NOT STOP TAKING THIS MEDICINE without checking with your doctor. BEFORE YOU BEGIN TAKING ANY NEW MEDICINE, either prescription or over-the-counter, check with you doctor or pharmacist. DO NOT DRINK ALCOHOL while you are taking this medicine. THIS MEDICINE MAY CAUSE drowsiness, dizziness, or lightheadedness. Do not drive, operate machinery, or do anything else that could be dangerous until you know how you react to this medicine. TO PREVENT OR REDUCE DIZZINESS OR LIGHTHEADEDNESS, get up slowly from a lying or sitting position. TELL YOUR DOCTOR OR DENTIST that you are taking this medicine before you have surgery or emergency care.</td>
</tr>
<tr>
<td>Childhood Enuresis (bed wetting)</td>
<td>POSSIBLE SIDE EFFECTS: SIDE EFFECTS, that may go away during treatment, include dry mouth, constipation, blurred vision, drowsiness, dizziness, headache, nausea, unpleasant taste, or an increased appetite especially for sweets. If they continue or are bothersome, check with your doctor. If you notice other effects not listed above, contact your doctor, nurse, or pharmacist.</td>
</tr>
<tr>
<td><strong>WARNINGS</strong></td>
<td></td>
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<tr>
<td>Children: A dose of 2.5 mg/kg/day of Tofranil should not be exceeded in childhood. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.</td>
<td></td>
</tr>
<tr>
<td><strong>ADVERSE REACTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular: Orthostatic hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, ECG changes, precipitation of congestive heart failure, stroke.</td>
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<tr>
<td>Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.</td>
<td></td>
</tr>
<tr>
<td>Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.</td>
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</tr>
<tr>
<td><strong>OVERDOSAGE</strong></td>
<td></td>
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<tr>
<td>Children have been reported to be more sensitive than adults to an acute overdosage of imipramine hydrochloride. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.</td>
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</tr>
<tr>
<td>Signs and Symptoms: These may vary in severity depending upon factors such as the amount of the drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment.</td>
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<tr>
<td>CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions.</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


4. 21 U.S.C. § 321(m)

5. 21 U.S.C. § 352 (a)

6. 21 U.S.C. § 321(n)

7. 21 U.S.C. § 352(f)

8. 21 U.S.C. § 371(a)

9. 21 U.S.C. § 331(k)


13. Medical Examiner's Report for Cory Christen, Colorado County, Texas signed by Elizabeth Peacock, MD, Deputy Medical Examiner, dated October 29, 1996.


Patient Information Leaflets Offer False Information on Prescription Drugs

Many Leaflets Contain Incomplete Safety Information

WASHINGTON, D.C. -- Inaccurate, completely unregulated, commercially produced drug information leaflets, distributed by pharmacists with prescription drugs, cause many deaths and serious injuries every year, said consumer group Public Citizen and others in a petition filed with the Food and Drug Administration (FDA) today.

"A large proportion of the patient information leaflets (PILs) produced by commercial information vendors and distributed by pharmacists to hundreds of millions of consumers when prescriptions are dispensed may contribute to thousands of drug injuries and deaths by giving the public a dangerously false sense of security about the safety of prescription drugs," said the petition, which was co-signed by Public Citizen's Health Research Group and Patricia and Ben Christen of Houston, Texas, whose 7-year-old son Cory died as a result of misleading patient drug information leaflets.

Cory Christen died in September 1996 from an adverse reaction to imipramine, which had been prescribed to treat his Attention Deficiency Hyperactivity Disorder. The commercially produced patient information leaflet given to Cory's parents failed to provide information about drug-induced hallucinations and tremors, which Cory experienced, and about the potentially deadly adverse effects of the drug, such as cardiac arrhythmias, from which he died. Instead, it warned only of minor, nuisance reactions caused by imipramine, giving the Christens a false sense of security about the safety of the drug.

"If the leaflet had told us about the seriousness of the potentially harmful affects of imipramine, we would never had given it to Cory, and he would be alive today," Patricia Christen said.

Studies conducted by Public Citizen's Health Research Group show that a large
June 9, 1998
Statement by Sidney M. Wolfe, M.D.
Director, Public Citizen's Health Research Group
Concerning Petition to Require FDA to Start Regulating the
Content of Patient Information Leaflets for Prescription Drugs
June 9, 1998

A substantial proportion of the estimated 100,000 Americans who die each year
because of adverse drug reactions and the serious injuries to 2.2 million others which
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preventing such tragedies is to ensure that patients are adequately informed about the
risks and proper use of prescription drugs. As long ago as 1979, FDA stated that: "...oral
communication of information about prescription drug products by health
professionals cannot be relied upon to provide patients with the information they need
to use prescription drug products properly." More recently, the Agency said:
"Inadequate access to appropriate patient information is a major cause of inappropriate
use of prescription medications, resulting in serious personal injury and related costs to
the health care system."³

The most recent survey by FDA, published last year, found that only a minority of
the 1000 people interviewed by researchers reported that their physicians told them
about the precautions or adverse effects of the drugs they were prescribing for them.
Concerning precautions about the drugs, only 35% were informed by their physicians
and only 33% were told about adverse effects. Although some patients also reported
that they received counseling about their prescription drugs from their pharmacists—and
many of these probably also had received information from their doctors—it is clear from
this important study that a large proportion of patients do not receive any oral
information about precautions (at least 40%) or adverse effects (at least 48%) from
either their physician or pharmacist. ⁴

Public Citizen, a nationwide organization representing 120,000 consumers, and
Patricia and Ben Christen, whose only son Cory died as a result of unregulated,
misleading, commercially produced written patient drug information, hereby petition the
Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and
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Seven-year-old Cory Christen's death, from a drug-induced cardiac arrhythmia, was needless and preventable and is directly attributable to his parents being deprived of vital dosing and adverse reaction information, information that was omitted from a PIL produced by an unregulated commercial information vendor, Medi-Span, Inc. of Indianapolis, for the antidepressant drug imipramine (Tofranil). In addition to this tragic example, the FDA is in possession of other evidence demonstrating that dangerous informational deficiencies exist in the PILs for other drugs.

Forty-one thousand patients are hospitalized and an estimated 3,300 die each year from gastrointestinal bleeding caused by nonsteroidal anti-inflammatory drugs (NSAIDs), used for treating arthritis or pain. Studies have shown that if patients are not adequately informed to stop the use of such drugs if they develop abdominal pain and therefore do not identify the pain as an adverse reaction to the NSAID, they are much more likely to have serious bleeding sufficient to require hospitalization. Given that many physicians do not routinely provide this kind of information to their patients, the routine use of accurate and complete PILs would save hundreds of lives lost to NSAID-induced gastrointestinal bleeding and thousands of hospitalizations. As discussed below, FDA's own study has shown serious deficiencies in PILs and a recent Public Citizen's Health Research Group survey of PILs for 15 NSAIDs found that only a small fraction warned patients to stop using the drug if they developed abdominal pain.

This petition is based on the following which will be discussed in greater detail:

- The FDA has the clear legal authority to regulate all information distributed with a prescription drug, including commercially produced PILs.

- The needless death of Cory Christen could have been prevented if critical safety information had not been omitted from an unregulated PIL for the drug imipramine (Tofranil and generics). If Cory's parents had been given an imipramine PIL that was consistent with or derived from the drug's approved product labeling they would have known four critical pieces of information, any one of which might have saved the life of their son:

  That imipramine can cause heart rhythm disturbances that are potentially fatal.

  That the imipramine prescribed for their son was for an "off-label" use, a use that was not approved by the FDA. Imipramine is approved only for depression and pediatric enuresis (bed wetting), not ADHD.

  That Cory had been prescribed a dose of imipramine that was 3.5 times greater than the maximum dose recommended for children in the
imipramine approved product labeling.

That the hallucinations and tremors experienced by Cory were actually adverse drug reactions.

- An FDA survey of PILs has found substantial differences between commercial information vendors in the quality of information provided including the omission of warnings which could be life-saving. Drugs involved included the tranquilizer alprazolam (Xanax), antibiotic amoxicillin and high blood pressure/heart failure drug enalapril (Vasotec).

- Two studies conducted by Public Citizen’s Health Research Group have shown that PILs distributed by pharmacists are incomplete with regard to safety information. An important, possibly life-saving instruction in the FDA-approved labeling was to tell patients to stop the NSAID and contact the prescriber should symptoms of GI toxicity (such as abdominal pain) appear. Only 15 out of 59 (25.4%) patient information leaflets (involving 18 different NSAIDs) warned about stopping the drug if symptoms of GI toxicity such as abdominal pain occur. Other drugs with dangerously incomplete or misleading PILs which we have obtained include bromocriptine (Parlodol), short-acting nifedipine (Adalat, Procardia), the pain-killer tramadol (Ultram) and the antibiotic ciprofloxacin (Cipro).

- Patients who are informed of the risks of a prescription drug and are told what steps to take should an adverse drug reaction occur reduce their likelihood of suffering the most serious consequences of an adverse drug reaction.

In summary, voluntary self-regulation by the warnings companies such as Medi-Span, Inc. has proven to be unsuccessful. Companies selling these warnings are willing to omit information about deadly adverse effects resulting in inadequately-educated patients who are therefore less reluctant to use or question their prescribed medications. Medi-Span, Inc. has testified through its vice-president of operations, that it allowed the marketplace to help determine the content of its warnings. Several documents attributable to Medi-Span, Inc. indicate that the Medi-Span, Inc. monographs (PILs) are intended to “stand alone” in the absence of counseling, and are considered a safety net in terms of risk management. The dangerously deficient sheets demonstrate the dangers of not requiring scientifically-based regulation: In claiming that “no consistently inferior product would survive in the marketplace”, a company abdicates even its voluntarily-assumed responsibility to “insure accuracy”. The
marketplace should not judge the quality of these items; scientists should. It is time for FDA to exercise its legal authority and start regulation of the content of patient information leaflets used by hundreds of millions of people like the Christens. There is little questions that the lives of thousands or more people like their son Cory could be spared if patients were aware of information neither their doctors nor pharmacists are regularly informing them of.


PHARMACISTS CONTINUE TO DISTRIBUTE DANGEROUSLY OUT-OF-DATE PILS FOR THE PAIN DRUG TRAMADOL (ULTRAM)

June 9, 1998 - Tramadol (Ultram) is an old German drug that was first marketed in 1977 and subsequently approved in this country in 1995 for the treatment of moderate to moderately severe pain. Almost 10 million prescriptions were issued for this drug by community pharmacists ranking tramadol as the 36th most frequently dispensed drug in the U.S. in 1997.¹

By the time tramadol had been on the market for one year, the FDA had received 115 spontaneous reports of adverse events described as drug abuse, dependence, withdrawal, or intentional overdose. There had been 83 reports of adverse events described as seizures or convulsions. Seizures had been reported after the first dose, and at the recommended dosage range. Only one year after this drug was approved the professional product labeling (package insert) was revised to reflect the drug’s potential to cause seizures, anaphylactoid reactions, and addiction.²

In addition, from March 1995 when tramadol was first approved through July 31, 1996, a period of 16 months, the FDA had received 124 unduplicated seizure cases from the U.S. Of those, 121 reports that had descriptions of the types of seizures, 52 (43.0%) were described as generalized tonic-clonic or grand mal seizures, 47 (38.8%) just as “seizure,” and 22 (18.2%) were described as miscellaneous.³

Below is a comparison of the warnings contained in the FDA approved professional product labeling (package insert) for tramadol and the information given in a commercially produced PIL by Medi-Span, Inc. obtained by Public Citizen from a California pharmacist on June 4, 1998. This PIL contains no information about the drug’s seizure risk, or the other drugs which when taken with tramadol that will increase


²Dear Health Care Professional Letter from Thomas Gibson, M.D., Executive Director, Medical Affairs, Ortho-McNeil Pharmaceutical date March 20, 1996.

the risk of seizure, its risk of severe allergic reactions (anaphylactoid reactions), or the drug's potential to cause addiction.

The adverse effects information in this Medi-Span PIL only warns of nuisance effects that are expected to go away with treatment, rather than warning patients of this drug's known serious risks.

Clearly, the omission of important information gives patients a false sense of security about tramadol's safety making these PILS dangerous when handed to them by America’s most trusted professional, the pharmacist.
| WARNINGS | HOW TO USE THIS MEDICINE: Follow the directions for using this medicine provided by your doctor. **IF YOU MISS A DOSE OF THIS MEDICINE, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. DO NOT TAKE 2 doses at once.** Ask your doctor or pharmacist if you have question about which medicines cause drowsiness. **BEFORE YOU BEGIN TAKING ANY NEW MEDICINE, either prescription or over-the-counter, check with your doctor or pharmacist.** POSSIBLE SIDE EFFECTS: SIDE EFFECTS, that may go away during treatment, include dizziness, nausea, drowsiness, dry mouth, constipation, headache, or sweating. If they continue or are bothersome, check with your doctor. **CHECK WITH YOUR DOCTOR AS SOON AS POSSIBLE** if you experience skin rash or itching. If you notice other effects not listed above, contact your doctor, nurse, or pharmacist. |
| Seizure Risk | | |
| Seizures have been reported in patients receiving ULTRAM within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of ULTRAM above the recommended range. Concomitant use of ULTRAM increases the risk in patients taking: | |
| • Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or Opioids. | |
| Administration of ULTRAM may enhance the seizure risk in patients taking: | |
| • MAO inhibitors Neuroleptics, or other drugs that reduce the seizure threshold. | |
| Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In ULTRAM overdose, naloxone administration may increase the risk of seizures. | |
| Anaphylactoid Reactions | |
| Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with ULTRAM. These reactions often occur following the first dose. Other reported reactions include pruritus, hives, bronchospasm, and angioedema. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRAM. | |
| DRUG ABUSE AND DEPENDENCE | |
| Ultram has a potential to cause psychic and physical dependence of the morphine-type (μ-opioid). The drug has been associated with craving, drug-seeking behavior and tolerance development. Cases of abuse and dependence on ULTRAM have been reported. ULTRAM should not be used in opioid-dependent patients. ULTRAM can reinitiate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence, or are chronically using opioids, treatment with ULTRAM is not recommended. | |
FDA APPROVED PATIENT INFORMATION IS NOT ALWAYS DISTRIBUTED TO THE PUBLIC

June 9, 1998 - Food and Drug Administration (FDA) approved patient information is required by regulation to be given to patients at the time of dispensing for only four drugs. This was done, in part, to warn patients of potential adverse drug reactions, contraindications, or precautions. For a relatively small number of other drugs, well under 1 percent of the number of drugs marketed in the U.S., the FDA has approved written patient information, negotiated by the agency with the drug company, as part of the product's labeling at the time a drug was approved. Sometimes, companies have voluntarily submitted or have agreed to include written patient information in the drug's labeling after the drug was approved for marketing for safety reasons.

The intent of manufacturers must be that this information is read by patients before using their drug, and it is the FDA's expectation that pharmacists are distributing this information at the time a drug is dispensed. Some evidence shows that pharmacists are substituting incomplete or out-of-date patient information leaflets (PILS) produced by commercial information vendors rather than distributing FDA approved written patient information. This has potentially life-threatening consequences with some drugs.

DRUGS REQUIRING PATIENT INFORMATION BY REGULATION

Since 1968, the Food and Drug Administration has required through regulation the distribution of patient information written in nontechnical language at the time the drug was dispensed. The Agency's stated reasons for this regulatory requirement is to . . . “alert patients of adverse reactions associated with the drug product or to provide information about the product's use, contraindications, precautions, and effectiveness.”

A small number of drugs have been required through regulation to be dispensed with written patient information. These include:

• 1968 - The asthma inhalation drug isoproterenol (Isuprel)
• 1970 - Oral contraceptives
• 1977 - Estrogens
• 1978 - Progestins

For these products the manufacturer usually attaches the required information to the drug’s packaging. For example, in the calendar packs used for the oral contraceptives the manufacturer pastes the required patient information inside the lid to ensure that it is distributed to the drug’s user.

DRUGS WITH PATIENT INFORMATION AS A PART OF A DRUG’S LABELING

The FDA has also approved written patient information as part of a drug’s labeling requirements for a small number of individual drugs. A 1995 estimate made by an FDA official places the number of these drugs at 32.2 Some examples are:

• terfenadine (Seldane), an antihistamine withdrawn from the market
• alendronate (Fosamax), a drug for osteoporosis
• triazolam (Halcion), a sleeping pill
• finasteride (Proscar), a drug for enlarged prostate
• isotretinoin (Accutane), an oral medication for acne
• metformin (Glucophage), a drug for diabetes

The patient information for these drugs may be physically attached to the drug’s professional product labeling, or package insert. For the patient to receive the FDA approved patient information the pharmacist would have to do one of two things: (1) give the patient the entire product labeling or package insert that includes the patient information; or (2) separate the patient information from the rest of the package insert and then give it to the patient.

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PHARMACISTS MAY BE SUBSTITUTING DANGEROUSLY MISLEADING PILS FOR FDA APPROVED PATIENT INFORMATION

There is some evidence, at least for one drug, that pharmacists have substituted dangerously misleading commercially produced PILS when FDA approved written patient information was available.

The once popular antihistamine, terfenadine (Seldane), was noted for a number of drug interactions that could lead to potentially life-threatening heart rhythm disturbances. The dangers of this drug prompted the FDA to begin the administrative procedures necessary to have terfenadine removed from the market on January 14, 1997. The marketing and distribution of terfenadine finally stopped in February of 1998.

In 1996, researchers from the Georgetown University Medical Center presented 50 pairs of prescriptions for the potentially life-threatening combination terfenadine and erythromycin to Washington, D.C., pharmacies. Sixteen (32%) of the 50 pharmacies filled the two prescriptions without comment. Of these 16 pharmacies, 14 pharmacists were asked, "Is there any problem with taking these two medications together?" Nine (64%) said that the two could be taken together. Of the 10 pairs of prescriptions filled without comment by chain pharmacies, nine were accompanied by written information. Six of these nine suggested checking with your physician if terfenadine and erythromycin were prescribed together, while three contained the general statement, "Report any other drugs you take or diseases you have."

Terfenadine was one of those drugs that was distributed to pharmacies with FDA approved patient information as part of its product labeling. The following statement from the FDA approved patient information for terfenadine appears in bold upper case letters clearly warning patients not to take terfenadine and erythromycin together:

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What are the Important Warnings About Using SELDAINE?
WARNING: DO NOT USE SELDAINE IF YOU ARE USING KETOCONAZOLE (NIZORAL),
ITRACONAZOLE (SPORANOX), ERYTHROMYCIN, CLARITHROMYCIN (BIAxin), OR
TROLEDANDOMYCIN (TAO). IF YOU HAVE ANY LIVER OR HEART PROBLEMS, TALK
TO YOUR DOCTOR BEFORE YOU USE SELDAINE.

In contrast to the above clear warning about the terfenadine-erythromycin
interaction the drug interaction section of the commercially produced PIL being
distributed on August 22, 1996, by a Washington, D.C., CVS chain pharmacy contained
the following ambiguous statement:

DRUG INTERACTIONS: Tell your doctor what other medications you take, especially if you
are taking erythromycin or drugs related to it (clarithromycin, troleandomycin) or itraconazole,
ketoconazole or cisapride.

It is plain from the Georgetown University Medical Center study results that the
FDA approved patient information was not being distributed when terfenadine was
dispensed. If it had been, the results of this study would have shown that every person
receiving the terfenadine-erythromycin combination was adequately warned not to take
these two drugs together.

When commercially produced PILs containing incomplete information are
distributed by Americas most trusted professional, the pharmacist, the public is
dangerously misled about the safety of prescription drugs.
Ben Christen

We found out the hard way that you cannot rely on your doctor or pharmacist. These take-home sheets were our only hope, we found out, and there was no section on the most severe toxic side effects. We learned after Cory died that the serious toxic effects were well known to doctors and pharmacists and were published in the medical literature, but nobody told us.

We learned that the warnings company had a policy to disclose toxic effects. Nobody enforced the policy. We are here asking the FDA to use its power to regulate these companies who profit by selling these sheets, so that this doesn’t happen to anyone else.

Pat Christen

[Photo] This is our son, Cory. He liked sports. He was very smart and loving. He had ADHD. He would still be here today if we had received the proper warning, instead of the warning sheets that we did get for imipramine.

We kept those sheets, took them home, and referred to them. There was never a warning about the most dangerous toxic effects. The sheets gave us a false sense of security.

(Attached is the Medi-Span patient information sheet for imipramine that the Christens were given)
COMMON USES: This medicine is used to treat depression. It may also be used to treat other conditions as determined by your doctor.

HOW TO USE THIS MEDICINE: Follow the directions for using this medicine provided by your doctor. AFTER YOU START USING THIS MEDICINE, several weeks may pass before you feel the full benefit. IF YOU MISS A DOSE OF THIS MEDICINE, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once. If you take 1 dose daily at bedtime, do not take a missed dose the next morning.

CAUTIONS: DO NOT STOP TAKING THIS MEDICINE without checking with your doctor. BEFORE YOU BEGIN TAKING ANY NEW MEDICINE, either prescription or over-the-counter, check with your doctor or pharmacist. DO NOT DRINK ALCOHOL while you are taking this medicine. THIS MEDICINE MAY CAUSE drowsiness, dizziness, or lightheadedness. Do not drive, operate machinery, or do anything else that could be dangerous until you know how you react to this medicine. TO PREVENT OR REDUCE DIZZINESS OR LIGHTHEADEDNESS, get up slowly from a lying or sitting position. TELL YOUR DOCTOR OR DENTIST that you are taking this medicine before you have surgery or emergency care.

POSSIBLE SIDE EFFECTS: SIDE EFFECTS, that may go away during treatment, include dry mouth, constipation, blurred vision, drowsiness, dizziness, headache, nausea, unpleasant taste, or an increased appetite especially for sweets. If they continue or are bothersome, check with your doctor. If you notice other effects not listed above, contact your doctor, nurse, or pharmacist.