
The United States Food and Drug Administration (FDA) Chief, Donald Kessler was recently quoted by *USA Weekend* in regards to drug risks, “...any drug, even the simplest drugs, we take some risks. There is no perfect pharmacological product that just has benefits and doesn’t have risks.” “...don’t for a moment think that the drugs in your medicine cabinet today are without risks.” ▲

■ Adverse Drug Events proliferate

A study to measure the occurrence and preventability of Adverse Drug Events (ADEs) in the July 5, 1995 issue of the *Journal of the American Medical Association* found that slightly more than 6% of adults admitted to the study hospitals surgical units suffered from an ADE of some kind.

Reported incidents were classified by two independent reviewers as ADEs or potential ADEs as well as for severity and preventability

Over a six month period, the study found that out of 4,031 patients admitted, 247 of them experienced ADEs and 194 of the cases were identified as potential ADEs..

1% of the cases were fatal (none preventable), 12% were life-threatening (42% preventable), 30% were serious (also 42% preventable) and 57% were significant. (28% preventable).

Mistakes that resulted in ADEs happened most often when ordering the drug, 56% and giving the drug, 34%. Transcription and dispensing errors made up the remaining 10%.

Reviewing statistics for 1995 reveals ADEs cause:

- \$76.6 billion in medical bills.
- 106,000 – 199,000 deaths.
- 8.8 million hospitalizations.

Statistical data reveals:

- Fatalities due to adverse reactions are greater than those of high-risk sexual behavior, firearms, and motor vehicle injuries – combined.
- Medication errors are the second most frequent and second most expensive malpractice claim.
- Most complications are dose-dependent. Therefore, 70-80 percent of these complications are predictable and preventable. ▲

■ FDA drug oversight lacking

The May 20, 1998 issue of the *Journal of the American Medical Association* contains a very well-referenced commentary that points out some startling statistics on the oversight of drugs and adverse drug reactions in the United States.

According to the commentary, discovering new dangers of drugs after they have been approved for the market is a common occurrence. **"Overall, 51% of approved drugs have serious adverse effects not detected prior to approval."** The authors point out that simply knowing about these adverse effects is not enough protection. **1.5 million people every year are injured by prescription drugs to the point of requiring hospitalization and 100,000 of those die.** What is needed they say is a "more active and effective safety program for marketed drugs [in order] to protect the public health."

The problem with oversight is numbers. The Food and Drug Administration (FDA) currently has about 1400 employees on staff to approve new drugs. A full-time staff of only **52 people** in the Division of Pharmacovigilance and Epidemiology (DPE) are responsible for monitoring the safety of **more than 5000** brand name, generic and over-the-counter drugs already on the market. **Only 9 of the 52 staff members have related, professional degrees.**

The FDA's MedWatch Office is responsible for getting doctors to report adverse drug reactions and product defects to the FDA. They are responsible not only for prescription and over-the-counter drugs but medical devices, biological products and special nutritional products. The MedWatch Office only has **4 employees.** As a result, the FDA estimates that **"only about 1% of adverse drug reactions are ever reported."**

The FDA plans to reorganize the unit in 1998; new computers and software, the staff **may** increase to 65 people and the DPE will be given a new name. How effective it will be remains to be seen. ▲



FDA to increase monitoring of new drugs

The *United States Food and Drug Administration* (FDA) announced that they will be taking steps to reduce the number of deaths caused by approved drugs and medical devices.

One of the steps is to increase surveillance of new drugs and devices after they are introduced and to better analyze the information the FDA collects about adverse reactions. Most drugs are tested on fairly small groups of people and a lot of the problems do not appear until they have been tried out on larger groups after they are put on the market.

Consumer groups have charged that the FDA has approved new drugs too quickly and without proper long-term testing. Studies have reported that about 100,000 people die every year from adverse drug reactions to properly prescribed medications.

FDA Commissioner Jane Henney stressed that no drugs are completely safe saying that adverse reactions can occur from known or unknown side effects, medication errors or defective products. ▲



FDA: Dangerous diabetes drug stays on market

Over the past few months we have been reporting on the attempts to remove the diabetes drug Rezulin from the market. Despite the fact that Rezulin appears to have caused severe liver disease in at least 40 patients, the FDA has decided that the drug can stay on the market.

At least 28 cases of complete liver failure resulting in death have occurred among patients taking Rezulin. Authorities in Britain have banned the drug as a result.

David Graham of the FDA's post-marketing drug risk assessment program estimated the risk of liver injury for patients taking Rezulin for six months was about 1 in 1800. "The longer you stay on Rezulin," Graham says, "the higher the risk you accumulate." ▲



FDA: Popular heartburn drug causes heart problems

On January 24, 2000, the United States Food and Drug Administration (FDA) issued a warning that the popular heartburn drug Propulsid should only be used as a last resort—and then only after the patient has had an EKG to rule out heart problems.

The warning comes after 70 deaths and 200 reports of irregular heartbeat and other heart disturbances since Propulsid was introduced in 1993.

The FDA warning says that patients should not be given Propulsid if they have: heart disease, valve disease, any history of an irregular heartbeat, abnormal EKG, kidney disease, lung disease, low blood levels of potassium, calcium or magnesium, eating disorders, dehydration or prolonged vomiting.

Propulsid should not be taken with antibiotics, antifungals, drugs for irregular heartbeat, protease inhibitors (taken for AIDS), antidepressants, antipsychotics or grapefruit juice.

■ FDA says flu drug dangerous, tells maker to strengthen warnings

Reuters News Service reports that the United States Food and Drug Administration (FDA) has told the maker of the flu drug Relenza to strengthen warning labels on the drug after receiving reports of patient hospitalization and possibly deaths that could be linked to it.

Last year, the British government ruled that Relenza should not be reimbursed on the state-run national health service because there are doubts about its benefits and high costs.

As a result of the FDA's findings, Glaxo, the manufacturer of Relenza, has written to doctors warning them that the drug may have contributed to breathing problems in patients with respiratory problems as well as to a decline in respiratory function in patients without a history of airway disease.

Glaxo hopes to offer new information to show that Relenza is valuable to "older" flu sufferers.

We hope that would not be those older patients who suffer from a decline in respiratory function without a history of airway disease.



FDA drug advisers and conflict of interest

According to a report in the September 25, 2000 *USA Today*, more than half of the experts hired by the U.S. Food and Drug Administration (FDA) to advise the agency on which medicines should be approved had direct financial interests in the drug they were asked to evaluate.

54% of the experts consulted had financial conflicts of interest in the drugs they were evaluating, a violation of federal law. However, since 1998, the FDA had waived the restrictions more than 800 times.

The conflicts involved included being employed by a drug company working on the development of a drug and then serving on an FDA committee to evaluate it, holding stock in the company involved, or receiving consulting fees or research grants from companies involved.

While the FDA does reveal when a conflict of interest exists, it keeps the details of the disclosure secret. As a result there is no way to determine which drug company is involved or the financial interest at stake.

With few exceptions, the FDA follows the advice of the committees that review drugs for approval.

By way of commentary, this article points out one of the reasons that taking drugs has become so dangerous. Patient safety concerns come into question when the people responsible for saying the drug is safe are the same ones who stand to gain financially from its approval.

As previously reported in this publication, studies report that serious adverse drug reactions result in approximately 106,000 deaths every year. This figure accounted for nearly 5% of all causes of recorded death in 1994 making adverse drug reactions the fourth leading cause of death in the United States. These conflicts of interest are intolerable at best and deadly at worst.

■ FDA fees to speed new drug approval tied to drug recalls

On September 24, 2002, *Reuters* news service reported on a government study which found that a law requiring drug companies to pay fees to the U.S. Food and Drug Administration (FDA) to reduce new drug approval times may be linked to a higher rate of drug safety recalls.

According to the Government Accounting Office (GAO), the FDA, in essence, has to match any fees that drug companies pay in order to keep the program fully operational. Various consumer groups say this funneling of money to new drug review programs diverts money from safety monitoring after the drugs are on the market.

The report states that “Our analysis of FDA data found that a higher percentage of drugs has been withdrawn from the market for safety-related reasons since” the enactment of the Prescription Drug User Fee Act (PDUFA).

While the FDA agrees that the law has stretched their resources, they don’t seem to feel it’s a problem.

The facts in the GAO report would seem to disagree. In the early years of the new law, from 1993 to 1996, 1.56 percent of new drugs were withdrawn from the U.S. market for safety reasons. In the years 1997 through 2000, 5.3 percent were withdrawn, a more than 300% increase.

FDA Deputy Drug Unit Director Steve Galson says the numbers are too small to be able to make any conclusions. “They overinterpret tiny, tiny changes in the numbers,” he said.

Commentary: We disagree with Mr. Galson’s opinion which seems to minimize the importance of drug safety monitoring. In this case, “tiny, tiny changes in the numbers” may lead to disability or death for thousands of people from dangerous drug reactions. Easy approval of drugs at the expense of safety monitoring should not be tolerated on any level by anyone.

■ Drug Companies Spend More On Ads Than Research

A July 12, 2001 report issued by *Families USA*, a Washington, DC-based healthcare consumers' group says that leading pharmaceutical companies spend more than twice as much on advertising and marketing as they do on research.

Consumer group's arguments to curtail skyrocketing drug costs often come up against arguments from the drug industry that any effort to curtail these profits will cause fewer dollars to be available for research.

The report says that this argument doesn't hold water since the drug companies are not spending current profits on research, choosing instead to spend more than twice the amount on expensive direct-to-consumer advertising than they do on research.

The report, based on information from the drug companies own financial disclosures to the Securities and Exchange Commission (SEC), also says that the largest drug companies continue to pay their top executives tens of millions per year. They also typically sell the same products in other countries for much less than they do in the U.S.

Last year for example, Pfizer, Inc. reported \$30 billion in revenues. 39% of that was spent on advertising, marketing and administration. Only 15% of revenue went to research and 13% went to profits. Chairman William C. Steere was paid more than \$40 million in salary and bonuses in 2000.

"The industry is hiding behind research and development as a way of increasing prices and therefore increasing profits," said Ron Pollack, executive director of Families USA. "The research and development mantra they use is clearly extremely misleading."

■ Magazine Drug Ads Too Vague

The October 6, 2001 issue of the British journal *The Lancet* finds that direct-to-consumer (DTC) magazine ads for prescription drugs may rely more on emotional appeal rather than supplying any substantive evidence that the drugs actually work.

The researchers, led by Dr. Steven Woloshin of Dartmouth Medical School in Hanover, New Hampshire, studied ads in 70 issues of 10 leading US consumer magazines. They found that 87% of the ads chose "vague, qualitative terms" such as "proven relief" to describe the drug's benefits instead of research evidence.

"This strategy," Woloshin says, "probably leaves many readers with the perception that the drug's benefit is large and that everyone who uses the drug will enjoy the benefit."

The authors go on to say that there is also a danger that the ads "medicalize" minor, run-of-the-mill problems. "A runny nose all of a sudden becomes allergic rhinitis."

The Pharmaceutical Research and Manufacturers of America, a drug industry trade group, says that DTC ads help educate the public about diseases and treatments they might otherwise be unaware of.

Woloshin disagrees, especially since his team found few hard facts in the ads they studied. Indeed, bold print lines like "Is it just forgetfulness...or Alzheimer's disease?" are more likely to increase reader's anxiety rather than their awareness.

While the FDA does require drug manufacturers to list drug's side effects in their advertisements, Woloshin suggests that the FDA also require them to list research data on benefits and side effects in easy-to-read information boxes similar to nutrition labels on food.

In 1999, drug companies spent \$1.8 Billion dollars on direct-to-consumer ads for prescription drugs.

■ 20 Deaths Not Enough For Recall Of ADD/ADHD Drug

On February 10, 2005, the U.S. Food and Drug Administration (FDA) said that U.S. drug safety reports of 20 deaths linked to the attention deficit drug Adderall XR are not enough to remove the drug from the market.

Health Canada banned sales of the drug the previous day. Their decision was based on a review of adverse event reports released by the producer of the drug, Shire Pharmaceuticals Group of Basingstoke, England.

Robert Temple, director of medical policy for the FDA said “the cases are not convincing evidence the drug is clearly responsible for these deaths.” He went on to say that while the FDA is deciding whether to conduct its own study of Adderall XR, the drug will continue to be available in the U.S., its biggest market.

U.S. House and Senate committees have been studying drug safety since the painkiller Vioxx was removed from the market after it was tied to heart risks and antidepressants were linked to an increased risk of suicide in children.

In a letter to FDA chairman Lester Crawford, Iowa Senator Charles Grassley contends that the FDA may be slow to act on Adderall “because there was concern that FDA could not handle another ‘drug safety crisis.’” Calls to the FDA for comment were not immediately returned.

Adderall already carries a “black box warning”, the strongest the FDA requires. It warns that amphetamines “have a high potential for abuse” and they “should be prescribed or dispensed sparingly.”

Michigan Representative Bart Stupak questioned the FDA’s ability to inform people about drug dangers. “If you’re going to keep this thing on the market,” he said, “have a signed informed-consent for the patient, and make it mandatory.”

■ Drug Complaints Reach Record High

USA Today reports on March 13, 2005 that the number of adverse drug events (ADEs) reported to the U.S. Food and Drug Administration (FDA) reached an all-time high in 2004.

There were approximately 422,500 ADE reports received by the FDA from pharmaceutical companies, health professionals and patients. This is a 14% increase over the 370,887 reports in 2003.

While the FDA requires the manufacturer to file ADE reports, doctor's and nurse's reports are voluntary, leading government officials to believe that the reported events represent only a portion of the actual number.

Paul Seligman, director of the FDA's Office of Pharmacoepidemiology and Statistical Sciences blames the increase in ADEs on the fact that there are more drugs on the market and use has increased. "Clearly," he said, "when you have more products on the market, you're likely to have more side effects."

Prescription sales cost Americans more than \$235 billion in 2004, a record that beat the 1995 volume by more than 300%.