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THE FDA FIASCO OF *FAUX PAS*, FAILURES AND FRAUD

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"Money, Money, Money Makes The World Go Round" according to a popular song in the musical *Cabaret*. That certainly seems true for the world of contemporary medicine. Over the past few decades, medicine has progressively become more of a trade than a profession. Physicians are now referred to as providers; lumped in not only with all other health care professionals, but also medical equipment and pharmaceutical companies and the people who sell their products.

Managed care companies are making more and more medical decisions, including which patients can be seen, where, when, and how long they can be hospitalized, what procedures can be ordered and which medications can be prescribed. Physicians who fail to comply with regulations are penalized. Patients also must pay additional sums for any deviation.

ALSO INCLUDED IN THIS ISSUE

Quality of care has caved in to cost containment. Commercialism has also compromised the quality of medical information. Recent Newsletters have illustrated how powerful pharmaceutical interests can control or influence the editorial policies and content of medical journals and information fed to the public and physicians by the media. Drug advertisements are an important source of revenue and physicians who conduct clinical trials of drugs are handsomely reimbursed directly or indirectly by their manufacturers.

A book review in one recent Newsletter exposed the power of the cholesterol cartel in perpetuating misinformation to protect their turf. Another showed how medical information is distorted to serve the financial interests of other drug companies. It is interesting but not surprising that both books were authored by distinguished Scandinavian physicians. For U.S. critics who have contrary views or question the accuracy of claims, retaliation can be swift and severe. A case in point is Kilmer McCulley, who was dismissed from Harvard and could not find other employment or renew his NIH grant after proposing that the culprit in heart attacks and strokes was not cholesterol, but homocysteine.

In addition to academia, the power of drug companies also extends to the FDA, other regulatory governmental agencies and Congress.

Are FDA Safety Standards Slipping?

Seven drugs the FDA certified as being safe since 1993 have been banned because they are deadly. What is particularly disturbing is that most of these were approved over the objections of their own reviewers who analyzed foreign and other studies not included in the application that clearly showed their dangers. Equally frightening is evidence that even after receiving reports of significant harm to numerous patients, authorities dragged their feet on withdrawing the drugs.

The FDA's performance was tracked through an examination of thousands of pages of government documents, data obtained under the Freedom of Information Act and interviews with over 60 present and former agency officials. According to FDA records obtained by *Los Angeles Times* investigative reporters, the seven drugs were incriminated in over 1000 deaths. The total number of fatalities is probably much higher since such deaths are reported on a voluntary basis. Doctors and hospitals are not likely to list a medication as contributing to a death if it could trigger a costly lawsuit. In many other instances the relationship may not be recognized. The FDA was formerly viewed as the world's leading protection agency. What happened?

For most of its existence, the FDA approved new drugs at what seemed to be a snail's pace, because of its emphasis on the Hippocratic doctrine *Primum non nocere* (First, do no harm). In the early nineties, because of the demand for new AIDS medications, Congress applied pressure to speed up the approval process. President Clinton urged treating drug companies as "partners, not adversaries", and despite its reputation for being bogged down with bureaucratic bungling, the agency responded with amazing alacrity.

In 1988, only 4 percent of new drugs introduced into the world market were initially approved by the FDA. Within ten years, their first-in-the-world approvals spiked to 66 percent. More than four out of five applications for new drugs were being approved at the end of the nineties compared to less than two of three at the beginning of the decade.

Americans paid a heavy price. Unlike AIDS drugs that precipitated this avalanche of approvals, the seven drugs that were withdrawn, only a few years after being certified as safe, could hardly be described as life saving.

- Lotronex, a drug for treating irritable bowel syndrome was linked to five deaths, the removal of a patient's colon and other bowel surgeries.
- Redux, a diet pill approved despite an Advisory Committee's vote against it in April 1996, was banned after seventeen months because it caused heart-valve damage. The FDA later received reports identifying Redux as being responsible for 123 deaths.
- Raxar, an antibiotic, was approved in November 1997 despite evidence that it might have caused several fatal deaths due to disturbances in heart rhythm. FDA officials decided not to mention this on the drug's label. It was withdrawn in October 1999 after it was associated with the death of at least 13 patients.
- Posicor was approved for hypertension in June 1997 over the objection of FDA specialists who warned it could cause fatal heart rhythm disturbances. It was yanked 12 months later after at least 100 deaths.
- Rezulin was approved for diabetics in January 1997 over a medical officer's warning that it caused severe liver damage. Internal memos show that his boss assured the company the officer would be "eased out". He was removed from the case in 1996 and his damaging report was never shown to the Advisory Committee. Rezulin was withdrawn in 1999 after being linked to 391 deaths and dozens of cases of liver failure, but the company had already taken in $2.1 billion.
- Duract was approved in July 1997 as a painkiller despite the repeated warnings of FDA physicians of its liver toxicity. Senior officials sided with the manufacturer in softening the label's

warning of liver damage. It was withdrawn in 11 months after voluntary reports cited it as a suspect in 68 deaths, including 17 due to liver failure.

- Propulsid was approved in 1993 for reflux esophagitis despite evidence that it caused serious heart rhythm disturbances. Review officials never consulted their own cardiac specialists. Pediatricians were not warned to never give the medication to children, although eight youngsters died during clinical trials, and routinely prescribed it for gastric reflux, a common problem in infants. **In August 1996, the FDA found Propulsid "not approvable" for children but never informed doctors or parents.** One father whose 3 month-old son died suddenly 14 months after this was revealed complained "We never knew that. To me, that means they took my kid as a guinea pig to see if it would work." **Propulsid was not recalled until last July after it was found to be responsible for over 300 fatalities, including two dozen sudden deaths in children under the age of 6.** By then, the drug had already generated U.S. sales of $2.5 billion for Johnson & Johnson.

Other recently approved products like the flu drug Relenza may also have to be banned. Although the FDA advisory committee concluded that Relenza had not been proved safe and effective, it was approved in February 1999. Eleven months later, the agency issued a "public health advisory" to doctors warning that seven patients had died after taking Relenza.

Never before have so many medications been withdrawn in such a short period of time. These were not low-profile drugs. They were taken by more than 22 million Americans or about 10 percent of the population, and pharmaceutical companies raked in over $5 billion before their products were recalled. Drugs that were approved before 1993 have also recently been banned. Seldane was approved in 1985 and quickly became the leading antihistamine. Although evidence of fatalities due to interaction with other drugs was clear in 1992, it was not withdrawn until 1998, after its patent expired. Phenylpropanolamine, a common ingredient in over the counter cold remedies and diet pills for over fifty years was just banned because it can cause strokes.

What does the FDA have to say about all of this? Dr. Janet Woodcock, director of the FDA drug review center's response was that the withdrawn medications were "very valuable, even if not lifesaving, and their removal from the market represents a loss, even if a necessary one." She said that once a drug is approved, the FDA depends on doctors "to take into account the risks, to read the label. We have to rely on the practitioner community to be the learned intermediary. That's why drugs are prescription drugs." Nevertheless, in an interview after the last few drug withdrawals, she admitted that the FDA can't simply rely on labeling precautions to insure safety." As medical practice has changed, it's just much more difficult for doctors to manage "the expanded drug supply. They rely upon us much more to make sure the drugs are safe."

In a May 12, 1999 article published in the *Journal of the American Medical Association*, Woodcock wrote "The FDA and the community are willing to take greater safety risks due to the serious nature of the illnesses being treated. Compared to the volume of new drugs approved, the number of recent withdrawals is particularly reassuring." Not everyone agrees with this. Woodcock and her staff control both the approval of drugs and the decision to ban them. When a product is withdrawn, it repudiates their original approval, especially when this happens within two or three years.

The FDA - An Agency Under Stress

A 1998 FDA progress report describing the work of agency chemists, said that "too many reviews are coming 'down to the wire' against the goal date**. This suggests a system in stress**." According to a former aide to Commissioner Kessler, "The clock is always running, whereas before the clock was never running. And that changes people's behavior." Dozens of other interviewed officials made similar comments.

The director of the FDA's metabolic and endocrine drugs division throughout the 1990's told one interviewer "The pressure to meet deadlines is enormous ... and **the pressure is not merely to complete the reviews. The basic message is to approve**."

The present problems seem to have started in 1992 when new regulations were adopted giving the FDA discretion to "accelerate approval of certain new drugs for serious or life-threatening conditions." While this was meant to speed up approval of new drugs for AIDS, the pharmaceutical companies quickly jumped on the word "serious". They argued that most conditions were "serious" for patients suffering from them and successfully lobbied Congress and the FDA to open the door to a wide range of diseases that would normally not qualify for such special treatment.

That same year, a Democrat-controlled Congress approved and President Bush signed the Prescription Drug User Fee Act. It established goals that called for the FDA to review drugs within six months or a year instead of the average two-year wait. To obtain funding for the extra personnel that would have to be hired to achieve this, it also mandated that pharmaceutical companies pay a user fee to the FDA for filing any new drug application. This was to be adjusted periodically and is currently around $310,000 per application.

The new Clinton administration quickly climbed aboard with its new "Reinventing Government" program. Headed by Vice President Al Gore, the project mandated that by January 2000, the FDA would reduce by an average of twelve months "the time required to bring important new drugs to the American public", without defining "important".

Easier said than done since all drugs are "important". Every review involves agency physicians, pharmacologists, chemists and biostatisticians. **A new application comes with medical information that could fill 1,000 or more Manhattan yellow page phone books.** Reviewers must scrutinize all data to evaluate efficacy and safety claims and coordinate conclusions with those of colleagues. They often have to do this for several drugs simultaneously, in addition to juggling other assignments such as post approval surveillance.

Some have quit not only because of the unreasonable workload, but the realization that even when their findings are not favorable, superiors are still likely to approve the drug. A biostatistician with excellent credentials assigned to review the Relenza flu drug recommended rejection in 1999 because "The drug has no proven efficacy for the treatment of influenza in the U.S. population, no proven impact on preventing influenza and many patients would be exposed to risks while deriving no benefit". After the Advisory board voted 13 to 4 against Relenza, he was rebuked by senior FDA officials who removed him from reviewing another flu drug and told him he could no longer make presentations to any advisory committee. These officials also approved Relenza as being a safe and effective drug. As noted, seven people died within a year and it is still being prescribed.

One 19-year FDA medical officer, who opposed the approval of Rezulin, the ill-fated diabetes drug, said "The people in charge don't say, 'Should we approve this drug?' They say, 'Hey, how can we get this drug approved?'" Another who retired in 1997 after 11 years told interviewers "If you raise concern about a drug, it triggers a whole internal process that is difficult and painful. You have to defend why you are holding up the drug to your bosses. You cannot imagine how much pressure is put on the reviewers." This was echoed by still another medical officer, who in 1998 formed a union chapter to represent the reviewers, explaining that "People feel swamped. People are pressured to go along with what the agency wants." Talk about job stress!

Do Fiscal Forces Influence The FDA?

In a March 1997 article in *the Food and Drug Law Journal*, FDA Commissioner Woodcock wrote "Consumer protection advocates want to have drugs worked up well and thoroughly evaluated for safety and efficacy before getting on the market. On the other hand, **there are economic pressures to get drugs on the market as soon as possible, and these are highly valid**." This statement was very

carefully worded, but just exactly what does it mean? When asked about this in a recent interview, she acknowledged the difficulty her department has had in rejecting a drug that might have taken a company several years to develop at a cost of $150 million or much more.

Few doubt the $100-billion pharmaceutical industry's clout. Over the last decade, drug companies have disclosed contributing over $44 million to political parties, candidates for both houses of Congress and the White House. Millions have undoubtedly also been steered to elected officials and influential individuals by lobbyists and others that are difficult to trace. The FDA reviewers said that they and their bosses fear that if drug applications are not approved, companies will complain and Congress will retaliate by refusing to renew the user fees. This would cripple FDA operations and jeopardize jobs.

Drug company funding currently covers about 50% of the costs for reviewing new drugs; persuading Congress to renew user fees into 2007 has become a top priority. The user fees have enabled the FDA to hire the additional medical and other personnel necessary to increase the number of reviews per year and to speed up the process as mandated. In 1999, 240 medical officers examined new drug applications compared with only 162 in 1992, the year before the user fees took effect. In 1994, the FDA said its "goal" would be to finish 55 percent of new drug reviews on time. It was 95 percent successful and the goal was progressively raised each year after that. In both 1997 and 1998, the goal was 90 percent and the agency reviewed 100 percent. From 1993 to 1999, it approved 232 drugs compared with 163 during the previous seven years.

Within the FDA, these arbitrary "goals" were treated as regulations, or at least deadlines that had to be complied with. You could meet the goal by deciding to either approve or disapprove a drug, but it seemed clear that it was not a decision, but approval, that was required. Reviewers as well as their immediate superiors were under relentless and constant pressure to quickly conclude their deliberations and approve drugs.

Indeed, the FDA drug center's 1999 annual report actually referred to the review goals as "the laws deadlines." When questioned about this, Dr. Woodcock, the director explained "In exchange for the user fees, FDA makes a commitment to meet certain goals for review times. The agency has exceeded almost all of the goals, and it expects to continue to exceed them. Basically, the number of new approved drugs has doubled, and the review times have been cut in half." But at what price for its personnel and the public? Even Woodcock acknowledged in a FDA publication last fall that the increased workloads and tight performance goals "create a sweatshop environment that's causing high staffing turnover."

The perception of FDA coziness with drug makers is perpetuated by potential conflicts of interest within its 18 Advisory Committees. These are the influential panels that recommend which drugs deserve approval, and equally important, whether they should be allowed to remain on the market if subsequent reports suggest safety hazards. **The FDA allows some appointees to work as consultants or researchers for the same companies whose products they are presumably evaluating on the public's behalf.** This occurred for committee appraisals of several recently withdrawn drugs, including Lotronex and Posicor. Reporters found that in a majority of meetings, half or more of the panel members had financial conflicts of interest. In some cases they had participated in developing a competing compound. In others, they consulted for a drug company or owned stock in it. However, it is important to remember that their decision is not binding. The commissioner and her staff have the final decision and can pick and choose.

More FDA Financial Finagling?

The FDA is also responsible for making absolutely certain that all prescription as well as non-prescription drugs available to the public continue to be safe. But they really don't have the resources to do this since all their medical officers are preoccupied with reviewing new

drugs. They are also under fire for lapses in meat and fish inspection and other food safety issues; hiring additional qualified inspectors has a much higher priority for allocations from Congress. Although the budget for drug approval reviews has soared, there has been no increased funding to evaluate safety after they are being prescribed. Even if user fees are continued or increased, the FDA is prohibited from spending this revenue for anything other than new drug applications.

As one epidemiologist who has studied the problem protested, "It's shocking. **How can you say, 'Release drugs to the market sooner,' and not know if they're killing people**?" Although the FDA receives over 250,000 reports annually of injuries and deaths due to drugs, he believes **the number of such "adverse drug events" is probably closer to 2.5 million**. Reports are voluntary and there is no incentive for doctors to submit them. The cause of death might be listed as "heart failure" without any mention of drug involvement. Even when a drug is included as a contributor, companies consistently dispute that their product is the cause by pointing to other factors such as a preexisting disease or the concomitant use of some other medication.

Once the FDA approves a drug, the manufacturer promotes it aggressively with carefully crafted claims that fall within the guidelines but can still be deceptive and misleading. When problems do occur, it can take months or years before the FDA receives enough reports of disturbing side effects or dangers for it to consider taking action. Even when they do, it is usually to suggest changing the package labeling to, in their words, "manage" risks. However, it is not known if the tiny print and lengthy labeling precautions are ever read or obeyed by doctors and patients, especially when changes are made.

The agency may also try to resolve safety questions by asking companies to conduct appropriate surveillance studies after the product is approved. Based on official records and interviews, the FDA apparently rarely follows up or enforces such requests although it has the power to punish any company that does not comply. The Inspector General of the Department of Health and Human Services ruled in 1996 that "The FDA can move to withdraw drugs from the market if the post-marketing studies are not completed with due diligence." Since then, **the FDA has not withdrawn any drug due to a company's failure to complete a post-approval safety study and officials recently admitted they still do not know how often such studies are performed.**

Even if a company complied, their results would be reviewed by the same Advisory Board that originally approved the drug. It is doubtful that these referees would be eager to admit they made a mistake or had not been sufficiently thorough. Federal employees cannot own stock in or accept gifts, money, vacations or any other inducements from the industry they regulate. If they did, they could be fired and perhaps even prosecuted. But the FDA frequently calls on outside physicians with clear conflicts of interest. These are often the same doctors that did the original research on the drug in question and later promoted it. They have been generously reimbursed for each patient entered in a clinical trial, speaking at conferences and serving as consultants. Many also receive stock options as an added inducement, since these skyrocket in value if the drug is approved and continues to be sold.

Yet, these are the very experts who are frequently hired to serve on Advisory Boards that decide if a drug should be approved as well as subsequently banned. If a sporting event umpire made a decision that allowed a team to win and it was found that the official had received any form of reimbursement from that team, it would be a major scandal that would lead to dismissal. In the pharmaceutical world, the FDA is the final umpire. Many feel that FDA "referees" should be held to the same standards as their sport counterparts.

Monitoring Mishaps And Deadly Drugs

Many safety problems do not surface until years after a medication has been in wide use and there are reports of unsuspected serious complications, as was

the case with Redux only a year or two after it had been approved for weight loss over objections warning of this. Phenylpropanolamine (PPA) has been available without a prescription for over fifty years! It is a common ingredient in cold and weight loss products, including Contac, Dimetapp, Comtrex, Coricidin, Tavist-D, Triaminic, Robitussin, Dexatrim, Accutrim, as well as Alka-Seltzer Plus. **Americans bought 6 billion doses last year, many of which were for children and infants.**

It was banned only a few months ago following a five year study by Yale researchers showing that the likelihood of hemorrhagic stroke was up to fifteen times higher in people who took the drug within the previous 72 hours. Eighteen to forty-nine year-old women and first time users had the highest risk rates. Consuming caffeine can also greatly increase risk. Originally scheduled for publication in the December 21 issue of the *New England Journal of Medicine*, the results were so startling that they were released seven weeks earlier. The FDA said that pulling PPA products from the market could prevent between 200 and 500 disabling and fatal strokes a year.

Congress ruled way back in 1962 that the FDA require manufacturers of non-prescription drugs to prove their effectiveness or discontinue their use, and there is not a shred of evidence to support the efficacy of PPA. Indeed, it had long been known that it could cause elevations in blood pressure and a 1981 article in the *Journal of the American Medical Association* warned against its use. Yet, it was not until 1991 that the FDA said it would study the problem. It did nothing. Ironically, the five year Yale study, which started in 1995, was funded by the Consumer Healthcare Products Association, a trade group that represents makers of over-the-counter drugs. They immediately and vigorously attacked the findings on grounds that the number of patients in the study taking PPA-containing products was too small and that many had other stroke risk factors, such as being a smoker. However, the results were incontrovertible.

Rezulin, which was approved for diabetes despite strong protests, was allowed to be sold in the U.S. for two years after it had been banned in Britain because it caused liver failure. The FDA simply suggested "frequent laboratory testing" for patients taking the drug, without any scientific assurance that such tests would be of any benefit. A former FDA advisory committee member told interviewers "They just kept increasing the number of liver-function tests patients should have," and that this "**was clearly designed to protect the FDA, to protect the manufacturer, and to dump the responsibility on the patient and the physician. If the patient developed liver disease and didn't have the tests done, somebody was to blame and it wasn't the manufacturer and it wasn't the FDA**."

In other instances, safety hazards are not apparent until evidence of adverse interactions with other medications that could never have been anticipated from the original trials. Seldane was approved in 1985 and rapidly became the second leading antihistamine. But by 1992, the FDA had received numerous reports that it could cause fatal heart rhythms in patients taking erythromycin or ketaconazole, widely prescribed antibiotic and antifungal medications. Dangerous reactions with grapefruit juice soon surfaced. As noted in a past Newsletter, **one healthy 29 year-old man died suddenly after taking his regular dose with two glasses of grapefruit juice**. Although action was taken in other countries, Seldane was not removed from the U.S. market until 1998, 12 full months after the FDA announced it would be banned. It was no coincidence that this coincided with the patent expiration and competitors announced they would offer a less costly generic version. Critics also claim that the FDA deliberately dragged its feet until the company's substitute product, Allegra, could replace it, and this was actually mentioned in official memos.

Based on hospital records alone, it is estimated that 196,000 Americans die and 2.2 million are seriously injured every year because of adverse reactions to medications.

There Is Still No Silver Lining On The FDA Cloud And Thunderstorms Are Looming

Numerous problems persist. Despite five warning letters since 1998, Schering Plough has repeatedly failed to meet manufacturing standards in making Claritin, its allergy medication that generated almost $2 billion in sales in 2000 and Proventil, an asthma inhaler. **Schering recalled 60 million Proventil inhalers in March 2000 after finding that many had none of the active ingredient that helps patients breathe, after having recalled 80,000 three months previously for the same reason.** Schering's Nasonex nasal spray was recently reported to stunt growth in children, 10 to 20 per cent of whom suffer from allergic rhinitis. **A Virginia Congressman who introduced legislation designed to help Schering is now being investigated** following evidence that he received a $25,000 "unsecured loan" at a very low interest rate from the company's lobbyist.

Texas and Congress are investigating the marketing of Schering's Rebetron kit for treating hepatitis C that consists of injectable alpha interferon and ribavirin, a pill it exclusively licensed from another company. **Treatment can cost up to $18,000 annually** and Texas agencies that provide pharmaceuticals to prisoners, state employees and Medicaid are complaining. Schering refuses to allow the pill to be given with other less expensive interferon products stating there is no proof that they would work as well, but will not make the pill available for such tests. Nearly 60 percent of Schering's 1999 $719 million in interferon sales was for hepatitis. In a closed door meeting, former Surgeon General Koop told aides to the subcommittee that has jurisdiction over the FDA that Rebetron marketing was "sound." **Schering contributed $1 million to one of Koop's non-profit groups and is also a sponsor of his financially troubled web site.**

Purdue Pharma's **Oxycontin sales hit $1 billion in a little over four years, beating out Viagra**. While designed as an alternative to morphine for severe, chronic pain, salesmen have promoted it to thousands of doctors as safe for treating short term pain, offering them all expense paid 3 day junkets to top resorts to attend a conference dealing with this. The company also recruited doctors and paid them large sums to speak at 7000 "pain management" seminars all over the U.S. **Oxycontin has been responsible for at least 120 deaths.** No other drug has been abused by so many people so soon after its introduction. The FDA admitted it failed to research this potential problem adequately and is taking steps to insure that it will never happen again.

The fatal flu drug Relenza is still sold despite lack of evidence of any efficacy, the Advisory Board's 13-4 vote against it, and a recent report that, despite a tutorial session, more than two out of three senior citizens for whom it was aimed were still unable to operate the delivery system. It gets worse and there are no solutions in sight. A future issue will deal with the mishandling and politics of FDA medical device approvals currently being investigated and other problems. Until then, get rid of those bottles of Tavist-D, Robitussin and Dimetapp lying around - and stay tuned.

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