Is FDA Too Quick To Clear Drugs?

Growing Recalls, Side Effect Risks Raise Questions

By JOHN SCHWARTZ
Washington Post Staff Writer

When Jo Ann Ottmers began taking her new diabetes medicine, the drug suddenly made it much easier for the 59-year-old diabetic to keep her blood sugar levels from rising dangerously high. But soon the Kansas City, Mo., woman began feeling nauseated and weak.

Ottmers finally stopped taking the drug after discovering on the Internet that the medicine could cause rare but life-threatening liver damage. But her health continued to decline, and 16 months after she began taking the drug she was forced to undergo a liver transplant. She has since sued Warner-Lambert, the company that makes the drug, Rezulin.

Warner-Lambert insists that Rezulin is safe if patients are monitored closely. Nevertheless, because of dozens of cases like Ottmers's—28 deaths and seven liver transplants linked to the drug—the FDA this week will consider whether regulation of its use should be tightened.

The questions about Rezulin, however, illustrate a larger debate that is raging over the safety of the medicines that millions of Americans take every day. Pressured by Congress, AIDS activists and drug companies in recent years, the historically sluggish FDA had to remake itself. Today, the agency is approving more drugs every year than ever before, taking half the time to do it.

Consumer advocates, and even some of the agency's own drug reviewers, argue that the agency has become too cozy with the pharmaceutical industry and too lax, putting lives at risk. Five drugs have been pulled off the market over the last two years—a record for such a short time—after dozens of deaths were linked to their use.

The FDA insists that its vetting processes are still the world's gold standard for safety. "I do not believe the standards have been lowered," said Murray Lumpkin, who heads the agency's drug safety programs. "There is no way that we will completely eliminate the risk from the process—if we have drugs with no risks, we will have no drugs."

The record number of drugs pulled off the market is, in fact, in line with the historic 2 percent to 3 percent withdrawal rate for new drugs, said Kenneth I. Kaitin, director of the Tufts University Center for the Study of Drug Development. With so many new medicines being approved, Kaitin said, the number of withdrawals is bound to climb as well. "We're still not any different and not any greater than we have been in the past," he said.

But even if the rate of problem drugs has not increased, drug safety experts say the increased pace of drug approvals means that more problems are bound to make it onto the market. To guard against that, drug safety experts argue that more should be done to conduct follow-up studies on the safety of these drugs after they arrive on pharmacy shelves to catch problems early.

"My concern isn't these disasters—my concern is the disasters that are underway that we don't know about," said Brian Strom, a professor of medicine at the University of Pennsylvania. "No one's minding the store."

Critics point out that the FDA's lead reviewer of Rezulin, John Gueriguian, opposed its approval and was removed from considering the application. Gueriguian said he found the company's safety testing inadequate and its claims of efficacy unconvincing. Even more, he said, his review of animal studies and clinical trials that revealed rare signs of jaundice signaled that the drug had hidden dangers. Nevertheless, the FDA approved the drug in March 1997 with exceptional speed because it offered a new way to control diabetes.

The FDA said it does not remove reviewers because of their positions on drugs but would not elaborate on why Gueriguian was removed. Warner-Lambert officials say Gueriguian used inappropriate language in criticizing the company and its application during meetings in September 1996. An affidavit by a Warner-Lambert official supplied to The Washington Post by the company referred to a Sept. 25, 1996, meeting in which "Dr. Gueriguian removed a bottle of what appeared to be cologne from his desk and said that he had to pour it over the [application] because it smelled 'like garbage' " and excrement. "Later during the meeting, he said that it had been about a half-hour and that 'the [application] was starting to smell again' and pretended to pour the cologne over the boxes containing the [application].' "

As large numbers of patients began taking Rezulin, the liver damage reports started to come into the agency's system for monitoring drug side effects. As evidence mounted that some patients could be harmed or even killed by the drug, the agency changed the labeling on the drug—not once but three times—to require more extensive testing of patient liver function. Since that time, confirmed reports of damage linked to Rezulin have dropped, but unconfirmed reports of liver damage continue to come into the agency. A Washington-based consumer advocacy organization, Public Citizen's Health Research Group, has filed a petition demanding that the agency remove Rezulin from the market.

Patients who believe they have benefited from Rezulin say they would hate to see the drug pulled. "I would half-kill to stay on it," said Laura Wilson-Perry of Memphis. "But if something came along that would regulate my blood sugar in the same way, I'd jump to it in a second because I don't want to risk liver problems."

Drug safety experts say the tests designed to ferret out problems ahead of time can only detect so much. The tests required for new drugs typically involve from 1,500 to 6,000 patients—too few to catch a drug reaction that might be experienced by less than 1 in 10,000 patients. The trials also are too brief to catch reactions that might emerge over years of use. That means the current system of testing drugs is fated to miss uncommon reactions until it reaches a broader market, making the drug-taking public guinea pigs in an ongoing experiment.

Americans could demand that more patients be tested before a drug can be approved—say, 100,000 patients to find reactions that might affect 1 in 20,000, Lumpkin said. And regulators could demand to see the effects of a drug taken over years. Obviously, however, "there is a cost to that—a cost not only in dollars but a cost in time" during which patients cannot take medicines that might help them.

The fact that problems might

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in Kosovo, meanwhile, reported increased harassment by Serbs throughout the province. Many people with U.S. passports have been threatened with personal attack if NATO attacks Yugoslavia, and several humanitarian aid workers reported that food convoys were blocked and at least one driver was beaten.

"The odds are against" gaining Milosevic's acceptance of the peace deal, a senior U.S. official said on condition he not be named. But he cautioned against ruling out an agreement, noting that the current threat of airstrikes is more serious than any Milosevic has confronted so far in the year-long Kosovo crisis.

Under terms of the Western-drafted agreement, which was signed last week by leaders of Kosovo's ethnic Albanian majority, the province would gain substantial political autonomy within Serbia. But Milosevic has objected to a provision requiring that up to 28,000 NATO-led troops be deployed in Kosovo to enforce the agreement.

NATO officials said Holbrooke would demand that Milosevic agree to an immediate cease-fire and halt the current offensive. In addition, the Yugoslav leader will have to sign or initial the peace accord, and he will have to accept in principle that the peacekeeping force can enter Kosovo to supervise terms of the agreement.

"This is the last effort to bring peace to Kosovo without the need to use military force," NATO Secretary General Javier Solana said. "We think that this is the moment of truth. NATO is ready to act if this last effort is a failure."

Holbrooke said there was no question of his getting dragged into prolonged negotiations with Milosevic while Yugoslav and Serbian forces continue to attack ethnic Albanian villages.

NATO military sources said that since Friday, government security forces may have overrun as many as three of seven key strongholds of the rebel's main force, the Kosovo Liberation Army. They said Milosevic clearly was hoping to deliver a knock-out blow to the guerrillas within the week before considering calling off the offensive hopes of averting airstrikes.

But NATO commanders said they are now prepared to accelerate and enlarge the scope of their bombing campaign. "If required, we will strike in a swift and severe fashion," Clark said.

Gen. Klaus Naumann, the German general who is chief of NATO's military committee, said Milosevic is "seriously mistaken" if he believes the alliance will engage simply in pinprick strikes and then sit back awaiting a more conciliatory response. "The bombing will go on as long as Milosevic wants us to continue; he has to blink, and he has to give in and accept the interim settlement," Naumann said. "We have a very substantial and detailed plan for such an air campaign, which can be rather long and protracted."

When NATO members gave Solana power to authorize airstrikes on Jan. 30, the intention was to launch limited raids that would last 48 hours, followed by a pause to allow Milosevic to reconsider. The plan now is to wage an intensive bombing campaign that would include a wider range of targets and last much longer to inflict serious harm to Yugoslavia's military infrastructure.

Correspondent William Drozdiak in Brussels and staff writers Dana Priest, Charles Babington, Thomas W. Lippman and Helen Dewar in Washington contributed to this report.

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not be detected on the front end of drug approval means the agency must do everything it can to catch side effects after approval, safety advocates say. But while the agency is working to upgrade what it calls "postmarket surveillance," it still depends largely on a system of reporting by doctors and companies that probably only catches about 1 percent of such adverse events, according to Raymond Woosley of Georgetown University Medical School. Agency officials point out that this is still enough to send up a red flag for many safety problems, although it does not allow a precise accounting.

The FDA is buried under the 150,000 reports that flow in each year, agency insiders say. And 1992 legislation that brought in industry funds to speed up review times prohibits the use of that money for postmarket surveillance—a fight the agency lost against the industry, said former FDA commissioner David A. Kessler. "That's where we fell down," Kessler said. "We didn't go to the wall."

In a recent article in the Journal of the American Medical Association, Timothy Brewer of Harvard University called for the FDA to go beyond its current reporting system, which relies on doctors and companies to report suspected problems. Brewer advocates more extensive use of data collected by medical researchers and others to sift for drug reactions.

Woosley goes further. He proposes creating a drug safety agency independent of the FDA so the regulators who approve drugs are not responsible for figuring out what they did wrong when disaster strikes. "When a plane crashes, you don't ask the FAA if their standards are wrong," Woosley said.

Another problem, however, is that the FDA cannot control how doctors prescribe the medications it regulates. Today's health care system gives doctors and patients less time to discuss medication and its risks, and patients increasingly demand medicines that they have heard about through drug company advertising. So even though the agency had explicitly warned doctors not to prescribe Duract for more than 10 days at a time, physicians prescribed it for longer periods; four patients died and eight required liver transplants before the drug was withdrawn. Similarly, the FDA warned doctors that Posicor could kill patients if taken with some 25 other drugs, yet hundreds of patients had life-threatening reactions.

"If we're getting to a point where we're getting a standard of drug approval that says we can only approve drugs after we have second-guessed how they will be misused and how to keep the misuse from happening, that's going to be a very difficult standard," said the FDA's Lumpkin.

Drug safety advocates urge the creation of new programs to better educate doctors on the one hand and more systematically look for side effects on the other. "We still need to get drugs approved more quickly," Woosley said. "It's not a problem with the drugs, it's a problem with the way they're used and a safety system that doesn't catch problems quickly enough."

Even Gueriguian, who has retired from the FDA and now works as a consultant to drug companies, believes the agency is merely adjusting to a new system of approvals and has not gone seriously astray. "If anyone says the whole system has gone to pot, they are are vastly exaggerating," he said.

Charles Flexner of the Johns Hopkins University Medical School said the FDA was right to speed up its processes, but "we are making a societal trade-off here." More people will be injured from unanticipated side effects, Flexner said, but at the same time far more people can benefit from the presence of new drugs on the market. "This is a very tough line that the FDA has to walk," he said.

For doctors and patients, the wisest course might be to let others take the early risk. Gail Povar, a primary care internist in Silver Spring, said she rarely prescribes a new drug in its first year on the market.

When patients demand a new drug, she makes sure they understand that they are taking part in "an experiment. . . . I have never felt that it was appropriate to jump on a bandwagon, whole hog, when a new drug comes out," she said, "unless it's a syndrome for which there are no other options. You simply don't know what the rare lethal or sublethal clinical side effect is going to be."

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In Pristina, Calamity of War Closes In

As Refugees and Gunfire Arrive, Foreboding Chokes Kosovo Capital

By Peter Finn
Washington Post Foreign Service

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PRISTINA, Yugoslavia, March 22—For most of the last year, this gray valley city with smokestack-fouled air and the cluttered character of a bazaar has largely escaped the violence that has scarred the Serbian province of Kosovo.

But on the eve of possible NATO airstrikes, a grim foreboding is strangling Pristina. The provincial capital of 200,000—seen by ethnic Albanian separatists as a future seat of government and by the Yugoslav government as a nest of sedition—was ringed tonight by heavy police checkpoints manned by hostile Interior Ministry troops. Gunfire rang out in residential neighborhoods. Shelling thundered in the distance.

Late in the day, a bomb hurled through the doorway exploded in a cafe popular among ethnic Albanians, injuring two people. Another restaurant was reportedly sprayed with gunfire. As most other bars and restaurants closed, residents began stockpiling food and water, anticipating shortages they are sure will accompany an attack by NATO.

A withering offensive since the weekend by the Yugoslav army against villages identified with the separatist Kosovo Liberation Army has spread to the city in other ways. About 10,000 refugees have arrived in the capital since last week, adding to the 29,000 already here, according to humanitarian organizations.

Many new arrivals are finding a setting only marginally less violent than the burned-out villages they are fleeing. Yugoslav Army and Interior Ministry troops patrol the capital in armored vehicles, a rare sight just weeks ago. On Sunday night, four Serbian policemen were gunned down in an ambush, the deadliest attack yet on Serb forces in the

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city.

With the offices of international peace monitors boarded up here since their departure from Kosovo on Saturday—and many foreign aid workers and journalists leaving the province—Serbian officials are moving against other voices of opposition. Today, the publisher of the major Albanian-language newspaper in Kosovo, Koha Ditore, said that he expected the paper to be closed within 24 hours after a Pristina court ordered it to pay a fine for allegedly inciting ethnic hatred.

For many refugees, Pristina has become the destination of a tortured odyssey. Last week, Sevdie Krasniqi, 35, left her village of Zhilovda 15 miles north of here when it came under heavy shelling from Yugoslav government forces clearing a large area in the foothills of the Cicovac Mountains. For two days, Krasniqi found shelter for herself, her husband, and their eight children in a mosque in nearby Resnik, but then that village came under heavy shelling. She said she crossed the mountains on an open trailer pulled by a tractor and reached her mother-in-law's house in the village of Shtutica in the Drenica area west of Pristina.

But that village, too, came under fire and she fled again, this time with her mother-in-law, her sister-in-law and her three children. Her husband, fearing he would be arrested, fled to the snow-covered mountains with other local men. Two days ago, the women and children made it to Glogovac, a small town on the edge of the fighting where 20,000 refugees have fled in recent days.

And from there the family took a bus to Pristina. All 14 of them live in two cramped rooms in the city, where they dare not peek out the window because they don't have a permit to live in the city.

"I'm still afraid," said Krasniqi. "I'm terrified."

The Serb offensive in the countryside also continued today, although it appeared to have lost some intensity as government forces have few populated villages left to target. The village of Gornja Klina, five miles north of the deserted city of Srbica in the Drenica region west of Pristina, was burning today. The fighting has paralyzed some refugees who were surrounded by Yugoslav government forces and didn't know where to go, witnesses said.

On Sunday in Srbica, a city of 20,000 that has been cleared of most of its population, a woman with her daughter and grandchild huddled behind a kiosk on an empty street in the city. When reporters approached them they began to cry and shudder-terrorized by any strange faces. "Please, we don't know anything," said the younger woman, anxiously looking around in case she was seen talking to journalists.

Srbica has become a moonscape of desolation and despair. Today Serbian authorities said that seven armed guerrillas were killed in a firefight in the city Saturday morning, disputing the allegations of local witnesses that unarmed male civilians had been summarily executed after being marched into a wooded area.

North of Pristina, along the main road to the Yugoslav capital, Belgrade, government forces continued to target strongholds of the Kosovo Liberation Army, which has fought a year-long guerrilla insurgency seeking independence from Serbia, the dominant republic of Yugoslavia. The population of Kosovo is 90 percent ethnic Albanian.

The KLA has been hammered in the last week by the military action inits former heartland west of this city. Weeks ago, the KLA acted as the authority in the countryside, manning roadblocks, deploying military police to settle local disputes, and checking the identities of reporters seeking to enter areas they controlled.

But on Sunday, on the road from Klina to Srbica, they clustered in forlorn looking groups, although they still struck defiant notes. They could hear the shelling and they knew that the strongholds where they once flew their flag—a black eagle against a blood-red background—were being reduced to smoldering ruins.

The Washington Post
Tuesday, March 23, 1999

ASSOCIATE COMMISSIONER FOR STRATEGIC MANAGEMENT
OFFICE OF MANAGEMENT AND SYSTEMS
OFFICE OF THE COMMISSIONER
U. S. FOOD AND DRUG ADMINISTRATION

5600 Fishers Lane
Rockville, Maryland 20857

TO:

Davora W
Chris Jennings Fax

FROM:

Linda Suydam

Facsimile Phone Number: (202) 456-5557

COMMENTS:

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number of pages
(not including cover sheet)

FAX NUMBER - (301) 443-3100
Voice Confirmation - (301) 827-3330

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REPORT TO THE FDA COMMISSIONER

MANAGING THE RISKS FROM MEDICAL PRODUCT USE

AN ASSESSMENT OF FDA'S APPROACH AND A LOOK TO THE 21ST CENTURY

Task Force on Risk Management

Final Draft

March 1999
U.S. Department of Health and Human Services
FOOD AND DRUG ADMINISTRATION

EXECUTIVE SUMMARY

At one time or another, we all use medical products (human drugs, biological products, and devices) to prevent illness, relieve symptoms, restore health, slow disease progression, and prolong life. Today's medical products provide great public benefit, but their use sometimes leads to injury or death. No medical product is risk-free. The Food and Drug Administration (FDA) has the role of protecting the public from unsafe products or false claims while promoting public health by ensuring that beneficial medical products are available and labeled with adequate information on their risks and benefits.

Recently questions have been raised about how well the Agency is performing its role. During the last several years, five drugs were withdrawn from the market for safety reasons. In addition, in April 1998, the *Journal of the American Medical Association (JAMA)* published a meta-analysis estimating that more than 100,000 people die each year from the side effects of medical products. These heightened concerns about adverse effects have arisen at a time when Agency programs under the Prescription Drug User Fee Act (PDUFA), and other legislative and managerial initiatives, are resulting in faster FDA reviews for new drugs and biologics. PDUFA was passed in 1992 to provide FDA with additional funds from user fees to hire more staff, and it has helped the Agency reduce the average review time from 30 to 12 months, thus making drugs and biologics available to the public sooner. Although not covered by PDUFA, the review time for device premarket applications also has decreased, from 27 months in 1994 to 12 months in 1998. Yet some critics have claimed that PDUFA has

increased pressures on the Agency to approve medical products, and that it may have lowered the quality of FDA's analyses and decisions and lowered the standards for marketing approval.

This report is the result of a Task Force review prompted by FDA Commissioner Dr. Jane Henney, who established a Task Force to look into public concerns about the safety of medical products. The report examines the current medical product risk management system and evaluates FDA's role in that system. The Task Force evaluation and report concentrate on safety because most public concerns have focused on injuries from medical product use. The Task Force looked at how FDA fulfills its responsibilities as well as the results of its work. We also analyzed ways the Agency could restructure its activities to more effectively meet its objectives. In this report, we discuss recommendations and options that we hope will be used as the basis for a dialog among all of the players in the risk management system, with the goal of improving the model for risk management for the 21st Century.

FDA'S ROLE IN MANAGING MEDICAL PRODUCT RISK

FDA's current role in evaluating medical product safety involves two key elements: (1) its premarketing review process and (2) its postmarketing surveillance and risk assessment programs. During premarketing review, the Agency assesses the evidence demonstrating the benefits and describing the risks of medical products. The Agency approves a product when FDA judges that the benefits of using a product outweigh the risks for the intended population and use. (Figure 1).

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A major part of the premarketing review is to ensure that products are truthfully and adequately labeled for use. Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk to the healthcare community and patients. However, once medical products are on the market, ensuring safety is principally the responsibility of healthcare providers and

patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information to select and use products wisely, thereby minimizing adverse events.

To assist with postmarketing risk management, the Agency maintains a complex surveillance and risk assessment program to identify adverse events that are not identified during drug development and premarketing review. FDA monitors adverse events associated with the use of approved medical products and uses this information to make labeling changes and, when necessary, to reevaluate the marketing decision.

QUALITY OF FDA'S PREMARKETING REVIEWS REMAINS HIGH

As discussed in detail in Part 2 of this report, the Task Force evaluated whether the heightened sense of time pressure on review teams has reduced the quality of FDA review or caused poor decision making. We studied how often previously unrecognized serious adverse events were identified after approval in drugs reviewed since the implementation of PDUFA. We then compared the numbers to those collected by a 1990 General Accounting Office report on serious adverse events for drugs reviewed prior to PDUFA. We also examined FDA's quality assurance systems for premarketing review and marketing decisions to see if they are functioning well enough. Finally, we identified factors inherent in the drug development process that could be limiting the Agency's ability to identify some risks during drug development and premarketing review.

Rate of withdrawals remains low

The Task Force found that, despite shortened FDA review time, evidence suggests that previously unidentified serious adverse events are occurring less frequently, or at least no more frequently, than in the past. Of the five drugs withdrawn for safety reasons after PDUFA, two were approved before PDUFA was

implemented.[1] Comparisons of drugs reviewed and approved under the PDUFA program to those approved previously shows that the rate of market withdrawals for safety reasons is as low or lower for drugs reviewed and approved after PDUFA as it was before PDUFA.[2] The 1990 GAO report found that previously unrecognized serious adverse events occurred after marketing in 51.5 percent of drugs. Among drugs reviewed ***after*** PDUFA, we found a 30.3-percent rate of such events. Over time, this rate could go up, but it is unlikely to exceed 51.5 percent.

QA/QC system is working

Auditing FDA's current quality assurance (QA) and quality control (QC) activities led us to conclude that the key elements of an International Standards Organization (ISO)-modeled QA/QC program for premarketing review are in place. FDA has consistently used supervisory re-review, conducted by subject matter experts, for 100 percent of the marketing decisions as the cornerstone of its QC function. These QC reviews are conducted on at least one supervisory level, and regularly at three levels, before a final approval decision is made. However, some QA/QC areas are still under development and these should be targeted for continued focus.

Finally, our analysis of premarketing product development identified several aspects of the development process that limit our ability to observe adverse events before marketing. Factors with the potential for change include the relatively small size and short duration of clinical trials and the representativeness of the patients studied. For example, as discussed in Part 2, rare side effects are often not observed before marketing because of the number of patients exposed to a drug before approval. And, most trials do not

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[1] Redux, Pondimin, Seldane, Duract, and Posicor were withdrawn from the market in 1997 and 1998; Seldane and Pondimin were approved prior to PDUFA.

[2] Friedmanm, M.A., J. Woodcock, M. Lumpkin, J. Shuren, et al., "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is a Problem?" in press.

last long enough to enable identification of potential long-term side effects. In addition, patients in clinical trials are often not representative of all the types of people who will be exposed after marketing. Changing these aspects of drug development could increase our ability to identify risks before the marketing phase — of course some of these changes could increase development costs and delay product availability.

In addition, consideration should be given to how rapidly some drugs are rolled out for widespread use. Slowing down a rapid rollout could limit the impact of some unexpected serious adverse events. Modified rollout strategies could change the economics of drug development in ways that are difficult to predict.

No achievable premarketing dataset can make up for inherent limitations in the drug development process. There will always be limits on what can be learned about a drug before it goes on the market. For this reason, postmarketing risk assessment activities are extremely important.

POSTMARKETING SURVEILLANCE AND RISK ASSESSMENT IS PERFORMING AS DESIGNED

In Part 3 of this report, we discuss whether the Agency's surveillance systems are adequate to address the emerging changes in today's healthcare environment. We found that the postmarketing surveillance and risk assessment programs are performing well for the purposes they were designed to achieve, but an increasingly complex healthcare system and the emerging global marketplace present some challenges that should be addressed.

Today, the Agency relies principally on a ***passive*** adverse event reporting system, relying to a great extent on voluntary reporting by the healthcare community It rapidly alerts the Agency to the occurrence of rare, serious adverse events not previously identified and provides an increased understanding of the range of severity in known product-associated adverse side effects. However, the

system provides little useful information, for example, on the ***rate***, of adverse events. The Agency is able to make limited use of other sources of postmarketing safety data, including large healthcare databases, epidemiological studies, and prospective cohort data collection studies, to obtain more complete information on adverse events. The Agency is neither funded to access such systems to any great extent, nor authorized to require manufacturers to collect such data for pharmaceutical products.

The Task Force has presented some options for expanding the use of automated systems for reporting, monitoring, and evaluating adverse events and product defects. Implementing these changes would require additional funding. We also have concluded that FDA's ability to assess postmarketing product safety could be strengthened through increased access to data sources that would supplement and extend its passive reporting systems. Examples of such sources include broad-based health information databases and data from sentinel user facilities where staff are trained to rapidly recognize and accurately report adverse events. In addition, FDA's efforts to identify and understand product-related injuries could be enhanced through additional support of research into how to design state-of -the-art surveillance systems and analyze surveillance data. Increased knowledge in these area could contribute substantially to the Agency's ability to reduce the effects of adverse events.

MANAGING THE RISKS FROM MEDICAL PRODUCT USE

Part 4 of this report examines other Agency efforts to help manage the risks associated with using medical products. Of particular interest is FDA's role as a government agency in the overall system of risk management. During our analysis, we used a risk management model that has been developed for other health and safety sectors[3] (see Figure 2). When applied to medical products, we found that what started as individualized care by one

[3] Presidential/Congressional Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Management —Final Report Volume 1*, 1997.

practitioner has evolved into a complex system of risk management that involves manufacturers, the FDA, practitioners, many other elements of the healthcare delivery system, and patients. In some cases, roles are clearly defined. For example, most FDA efforts are devoted to pre- and postmarketing risk assessment (Figure 3), and the FDA approval/nonapproval decision is the Agency's central risk management action. Once a product is approved, the key risk manager is the prescriber, who is responsible for maximizing benefit and minimizing risk to the individual patient. However, in today's healthcare environment, the roles of all of the players in the overall system for reducing and managing risk are not as clearly defined as they could be.

Put Figure 2 and Figure 3 here.

The source of risks is important when assessing risk management

To evaluate the current system, the Task Force considered what is known about the sources of risk from medical products. Most injuries and deaths result from their known side effects (Figure 4). Some side effects are unavoidable, but others can be prevented or minimized by careful product choice and use. It is estimated that more than half the side effects of pharmaceuticals are avoidable. Other sources of preventable adverse events are medication or device errors. Injury from product defects is unusual in the United States because of the great attention paid to product quality control and quality assurance in manufacturing. A final category of potential risk involves the remaining uncertainties about a product As pointed out earlier, knowledge about a product is necessarily limited at the time of approval. For example, rare side effects and long-term outcomes (both positive and negative) may not be known when a product is approved. In addition, effects on populations not studied in the clinical trials (e.g. pregnant patients, children, people with other diseases) may be discovered if these groups are treated after marketing.

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Known side effects cause the majority of serious adverse events and death

Of all these risks, known side effects cause the vast majority of injuries and deaths. However, not enough is known about the causes, incidences, and relative contribution of the various sources of risks, or about which ones are avoidable. Better information is needed if these risks are to be managed optimally. FDA's postmarketing surveillance programs were not designed to capture these kinds of data. As the risk management model shows (Figure 5) many players, including the FDA, have a role in minimizing the risks from using marketed drugs. The Task Force believes that these stakeholders need to collaborate to determine how better data on risks can be collected so that efforts and interventions can be targeted to the most serious problems, and the effects of interventions can be evaluated.

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Part 4 of the report also examines FDA's activities in risk confrontation, risk intervention, and risk communication (Figure 6). Although the Agency participates in many such activities, they have had lower priority than the Agency's pre- and postmarketing scientific risk assessment responsibilities.

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FDA should engage stakeholders to examine the current risk management system

We recommend that FDA take the opportunity to engage all stakeholders to reexamine the current system for managing the risks associated with the use of medical products. The adequacy of the current system for collecting information on injuries and deaths should be evaluated. We encourage a public policy discussion that focuses on defining more clearly the roles and responsibilities of all components of the risk management system — FDA, industry, healthcare provider organizations, healthcare practitioners, patients, and the public. Only by examining the roles of these various groups can gaps and misallocation of efforts be identified

and improvements made. The Agency also should expand and formalize its efforts in confronting risks and engaging stakeholders when deciding which risks are acceptable to those who will suffer their consequences.

RECOMMENDATIONS AND OPTIONS

The Task Force is making a number of recommendations as a result of its review. Recommendations center around ways that FDA, within the confines of the current system, could further improve its risk management activities. Many of these improvements already are underway. In addition, we present a series of options for consideration that could help expand FDA's efforts in communicating risk information to the healthcare community and the public. Some options, if implemented, could make it possible for the FDA to learn more, more quickly, about serious adverse events, allowing the Agency to intervene sooner to minimize their effects.

These options also could serve as the start of a dialog among the stakeholders in the healthcare community on ways to improve the current system for managing the risks associated with using medical products. The new system could be based on the model we propose in this report, which is in use in other health and safety sectors.

Recommendations — premarketing QA/QC

To improve FDA's premarketing QA/QC, we recommend the Agency take the following actions:

- Initiate steps to have each center establish separate QA/QC units to support QA/QC as a normal part of all activities including the following:

  - Peer review a sample of product approval review

administrative records for quality of the analysis and completeness of the documentation.

- Establish procedures for continuation of review when there has been an administrative disruption of the process.

- Prospectively track scientific disputes among reviewers and evaluate whether the disputed issue is predictive of problems after marketing.

- Ensure and document ongoing professional education and current core competency training for all reviewers.

- Complete the Good Review Practice (GRP) documents and keep them current.

- Systematically analyze significant postmarketing events, incorporating them into GRPs as lessons learned.

Recommendations — postmarketing surveillance

For spontaneous reporting we recommend the Agency take the following actions:

- Rapidly complete the pharmaceutical products Adverse Event Reporting System (AERS), and correspondingly enhance the medical device Manufacturers and User Device Experience (MAUDE) system.

- Integrate existing postmarketing information systems so analytic tools, data entry, and editing can be uniformly applied, and all information is readily available to every reviewer.

- Develop new methodological tools for inference from available datasets.

Recommendations — risk management

For overall risk management activities we recommend the Agency take the following actions:

- Join in, or convene, public forums with other agencies and groups involved in healthcare to examine the current system of managing the risks of medical products. These forums might focus on the costs and value of better data on the incidence and causes of injuries from medical products and the roles of all stakeholders in risk management.

- Increase stakeholder engagement in FDA risk management activities — both in product decision making and in indication-specific or class-specific guidance.

Additional options

We have identified a number of additional options for consideration, which, if adopted, might contribute to improved risk management. These ideas need full public policy analysis and review to understand their potential value, costs, and acceptability to the various stakeholders in medical product risk management. Some of the options would require significant new resources and legislative changes. For these reasons, we suggest that these options be evaluated in the context of the stakeholder risk confrontation activities recommended above. Only by working with all other participants in the overall risk management system for medical products can the Agency arrive at the most effective approach for managing those risks.

Additional options — premarketing QA/QC

Additional premarketing options that could, in part, address the inherent limits of premarketing development include the following:

- Evaluate the practicality and value of wider use of large, community-based simple trials designed to identify serious adverse events in a larger and more representative patient population prior to approving the product for widespread use.

- Develop tools to concentrate early postapproval use in populations for whom an advantage of the new product over alternative products has been demonstrated.

- Evaluate the practicality and value of limiting exposure in the early postmarketing period by restrictions on market rollout for particular drugs.

Additional options — postmarketing surveillance

For spontaneous reporting —

- Coordinate premarketing and postmarketing information to ensure full consideration of all available safety data at each stage of review.

For active and other postmarketing surveillance options —

- Supplement existing reporting channels by establishing and supporting institutions to serve as sentinel sites for adverse event reporting. Such sites would produce a higher rate of event reports and more completely analyze each event, further enhancing the value of their reports.

- Provide cross-agency access to external healthcare databases. This would allow the Agency to more quickly investigate signals generated by spontaneous reports and would be particularly valuable in determining the rate of adverse events.

- Design, implement, and maintain prospective product use registries (the bulk of support should come from manufacturers).

- Enhance clinical and laboratory studies to develop new methods to improve product safety.

- Increase resources to conduct focused epidemiological

studies when support of these studies by manufacturers is not feasible.

For research —

- Support staff to conduct methodological research on the costs and value of various approaches to understanding adverse events among marketed products.

Additional options — risk management

Additional risk management options include:

- Develop and implement risk communication strategies that more effectively target information to risk managers (i.e., prescribers and patients).
- Increase postmarketing risk intervention, such as restricting distribution of products or requiring mandatory educational programs.
- Establish an independent advisory body to evaluate the effectiveness of risk management in the healthcare system.
- Seek legislative changes for other types of risk intervention, such as suspension authority for drugs.
- Develop programs to systematically evaluate the effectiveness of FDA's risk management activities.

CONCLUSIONS

In summary, we evaluated the FDA's current risk management activities for medical products. We found that the premarketing review processes for these products are detecting serious risks at least as well as in previous decades. But, premarketing development and review is limited in scope because of factors inherent in the drug development process. As a result, rare, late

appearing, and novel types of adverse events may only be discovered during routine on-the-market use.

We then evaluated FDA's postmarketing surveillance and risk assessment systems for these products. The systems in place are good at rapidly detecting most unexpected serious adverse events that occur during the postmarketing period. However, the Agency's passive surveillance systems were not designed to capture all of the types of data that are needed to gain a thorough understanding of medical product risks. The Agency's postmarketing surveillance programs could benefit greatly from acquiring access to additional data sources. Finally, we analyzed the current system of risk management for medical products in the United States and concluded that more extensive discussions with a wide range of stakeholders should be undertaken to better confront and manage medical product risks in the 21st Century.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the General Counsel

Office of the Chief Counsel
Food and Drug Administration
5600 Fishers Lane, GCF-1
Rockville, MD 20857

November 3, 1998

MEMORANDUM

To: Harriet S. Rabb
General Counsel

From: Margaret Jane Porter
Chief Counsel
Food and Drug Administration

Subject: Legal Authority to Issue Medication Guide Final Rule for Selected Prescription Drug Products

Issue

This memorandum discusses the legal authority of the Secretary of Health and Human Services (HHS) and the Acting Commissioner of the Food and Drug Administration (FDA) to issue a final rule requiring distribution of approved patient labeling ("Medication Guides") for selected prescription drug products. The specific issue is whether section 601 of the 1997 FDA Appropriations Act, Pub. L. 104-180, bars not only issuance of a final rule providing for a comprehensive program of Medication Guides, but also a final rule requiring Medication Guides for selected prescription drug products. Our legal conclusion is that the Appropriations Act bars only a final rule establishing a comprehensive program.

Background

In August 1995, the Secretary and Commissioner published a proposed rule on Medication Guides with two main elements: (1) a comprehensive program to ensure that patients receive accurate, thorough, and understandable information about most prescription drug products by the year 2006 and (2) a limited program that would require distribution of FDA-approved patient labeling only for certain products that pose a "serious and significant public health concern" (60 FR 44182-44252; August 24, 1995).

FDA proposed two alternative approaches to how the agency could defer implementation of the comprehensive Medication Guide program under part 1 of the proposal, both of which alternatives provided an opportunity for industry voluntarily to meet

performance standards for distribution of patient information for most prescription drugs. Regardless of the alternative chosen for the comprehensive program, FDA also proposed that the limited mandatory program, requiring distribution of FDA approved Medication Guides for products posing a serious and significant public health concern, would be implemented within 30 days of publication of a final rule.

Prior to the 1995 proposal, FDA had on occasion required patient labeling describing risks and benefits for specific categories of prescription drug products such as estrogens (21 C.F.R. 310.515; 55 FR 18723, May 4, 1990) and progestational drug products (21 C.F.R. 310.516; 43 FR 47181, October 13, 1978, as amended at 46 FR 53657, October 30, 1981; 54 FR 1163, Jan. 12, 1989). The 1995 proposal and the limited draft final rule on Medication Guides built on this established precedent. However, instead of using the past approach of promulgating a separate regulation for each class of drug products, the draft final rule specifies format and content criteria for patient labeling for any human prescription drug product that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information.

As the agency was reviewing comments submitted on all of the proposed Medication Guide regulations, Congress enacted appropriations legislation that included a provision on prescription drug patient labeling limiting the agency's authority to implement the proposal (section 601 of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, for the fiscal year ending September 30, 1997, Pub. L. 104-180, 110 Stat. 1509, 1593) (the Appropriations Act). This legislation established a voluntary private-sector process under which national organizations representing health care providers, consumers, pharmaceutical companies, and other interested parties were to collaborate in the development of a long-range plan to achieve the goals of FDA's proposed rule concerning comprehensive patient labeling. The law required that the plan developed by these organizations be submitted to the Secretary for acceptance, rejection, or modification before implementation. The collaborative process established by this legislation has been completed and the long-range private-sector plan has been accepted by the Secretary.

Construing the Appropriations Act not to affect the proposed rule requiring distribution of Medication Guides for products posing a serious and significant public health concern, the Secretary and Acting Commissioner forwarded to the Office of Management and Budget (OMB) for review a final rule that would establish this requirement for the small number of products meeting the narrow criteria. Since this final rule has been pending at OMB, individuals representing affected industry groups have argued that the Appropriations Act also bars even this

limited final rule. Some industry representatives apparently believe that an October 11, 1996, memorandum prepared by an attorney in the American Law Division of the Congressional Research Service (CRS memorandum) supports the argument against the agency's authority. The Secretary has also recently received the attached September 17, 1998, letter from the Chair of the Subcommittee on Agriculture and Related Agencies Appropriations and others that take this position as well.

We have been asked to set forth in more detail than was contained in the preamble to the final rule pending at OMB the legal argument that the agency has the legal authority, given the Appropriations Act, to issue this limited Medication Guide regulation.

Analysis

Subsection 601(a) of the Appropriations Act required the Secretary to request certain organizations to "collaborate to develop a long-range comprehensive action plan to achieve goals consistent with the goals of the proposed rule of the Food and Drug Administration on 'Prescription Drug Product Labeling: Medication Guide Requirements' (60 Fed. Reg. 44182; relating to the provision of oral and written prescription information to consumers)." Subsection 601(b) identified these goals as "the distribution of useful written information to 75 percent of individuals receiving new prescriptions by the year 2000 and to 95 percent by the year 2006"--the goals of the agency's proposed comprehensive program. Subsection 601(c) described the plan to be developed, including a mechanism for assessing the quality of the information and the frequency with which the information is provided to consumers.

Under subsection 601(d) of the Appropriations Act, the Secretary "shall have no authority to implement the proposed rule described in subsection (a), or to develop any similar regulation, policy statement, or other guideline specifying a uniform content or format for written information voluntarily provided to consumers about prescription drugs" if the national organizations develop the comprehensive plan, the Secretary accepts the plan, and implementation begins within specified timeframes. Subsection 601(e) provides that by January 1, 2001, the Secretary is to review the status of the private-sector initiatives to achieve the goals of the plan. If the goals have not been achieved, then "the limitation in subsection (d) shall not apply."

The Appropriations Act restriction on the Secretary's authority to implement regulations, therefore, explicitly applies only to the "proposed rule described in subsection (a)" or a "similar regulation ... for written information voluntarily

provided to consumers about prescription drugs" (emphasis added). The described proposed rule refers only to the comprehensive plan (and the opportunity for industry to voluntarily meet performance standards) and its goals. There is no mention of the limited mandatory program to require Medication Guides for products that pose a "serious and significant public health concern." Consequently, under the plain language of the law, the prohibition in subsection 601(d) does not apply to the limited final rule pending at OMB.

Even if the language of section 601 were to be considered ambiguous (perhaps because of the reference in subsection 601(a) to the general title of the entire Medication Guide proposal or to the first page of the entire Federal Register notice), the agency would still have authority to issue the limited final rule. The agency's interpretation of section 601 is a permissible construction that is consistent with the legislative history and is, under the Chevron doctrine, to be given deference. See Chevron, Inc. v. National Resources Defense Council, Inc., 467 U.S. 837 (1984).

The legislative history of section 601 states clearly that this section

> [i]s not to be construed as prohibiting the FDA from using its existing authority or regulatory authority to require as part of the manufacturers' approved product labeling the dispensing of written information inserts to consumers on a case-by-case basis with select prescription drugs to meet certain patient safety requirements.

Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Bill, 1997, S. Rep. No. 104-317, 104th Cong., 2d sess., p. 132, July 11, 1996.

The floor debate in the Senate provides the following elaboration on this point:

> MR. COCHRAN. This conference report retains the language, as adopted by the Senate, that prevents further finalization or implementation of the medguide regulation.
>
> MR. COATS. At this point, I would like to make sure I understand that this provision does not preclude the FDA from using its existing authority to require, on a drug-by-drug basis, the provision of written information prepared by the manufacturer to consumers about prescription drugs that pose a serious risk.
>
> We have been informed by the FDA that it will only be required to use its existing authority to require patient

information for a very limited number of products.

MR. COCHRAN. That is the committee's understanding, as well. The committee believes that the FDA's current authority to require written patient information is essential for certain prescription drugs, on a drug-by-drug basis, in cases where they pose a serious risk to the patient if used inappropriately.

MR. COATS. I thank the Chairman for clarifying this and appreciate his leadership and assistance in helping us craft a compromise that is acceptable to the committee and to the FDA.

Mr. KENNEDY. The provision we are enacting on medication guides places certain limitations on the FDA regarding its pending medication guide regulation as it pertains to voluntary information provided by pharmacists. However, as you know, there was another part of the pending FDA regulation that was not intended to be affected by this provision. That was the FDA's intention to require FDA-approved patient leaflets for drugs that pose a serious and significant public health risk. . . .

Mr. BUMPERS. Your understanding is correct. . . .

142 Cong. Rec. S9337 (daily ed. Aug. 1, 1996).

While Senator Cochran's and Coats' statements are ambiguous and could be read to refer either to the approach used by FDA prior to the 1995 Medication Guide proposal or to the limited part of the proposal, Senator Kennedy's and Senator Bumper's statements clearly indicate that their understanding was that the limited proposal would not be barred. Therefore, taking all this legislative history together, the agency's interpretation is reasonable and should be upheld. Whether this legislative history is considered at step one or step two of the Chevron analysis, the statute should be read as permitting issuance of the final regulation. The agency's action in going forward with the limited final rule requiring dispensing of Medication Guides on a case-by-case basis when the drug poses a serious and significant public health concern is consistent with both the language of section 601 and the legislative history.

Without discussing either the exact language of section 601 or any of its legislative history, the CRS memorandum concludes that the appropriations provision "appears" to prohibit the Secretary from implementing any part of the regulations proposed on August 24, 1995 (CRS memorandum at p. 8). However, the CRS memorandum also states that "it appears that the agency could continue to exercise its statutory and regulatory authority to

develop and implement rules mandating [patient package inserts] for certain prescription drugs. . . . Thus, it could be argued that the agency could continue to require patient labeling information for drugs which pose serious and significant risks (or benefits) in order to better assure safety and effectiveness" (CRS memorandum at p. 9).

The underlying statutory authority for the agency to require Medication Guides is described in detail in the preamble to the regulations proposed in 1995 (60 FR 42210; August 24, 1995). This interpretation of the agency's authority to require patient labeling for prescription drug products has been upheld in federal court. See Pharmaceutical Manufacturers Ass'n v. FDA, 484 F. Supp. 1179 (D. Del. 1980), aff'd per curiam, 634 F.2d 106 (3d Cir. 1980). In the absence of federal law prohibiting FDA from exercising this statutory authority, the agency is authorized to require distribution of approved Medication Guides as set forth in the final rule now pending at OMB. As set forth above, the agency may legally issue the final rule now pending at OMB.

Conclusion

The Secretary and the Acting Commissioner have the legal authority to issue a final rule requiring distribution of FDA-approved Medication Guides for prescription drugs that pose serious and significant public health concerns.

Attachment

1001 Pennsylvania Ave, N.W.
Suite 760 North
Washington, D.C. 20004
202-661-7070 – direct line
202-661-7060 – firm line
202-661-7066 (FAX)

Legislative Strategies Group, LLC

Fax

To: Chris Jennings
EOB

From: John M. Coster, Ph.D., R.Ph.

Fax: 456-5557

Pages: Multiple

Phone:

Date: 11/10/98

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- Comments: MedGuide letters as requested.

NACDS
Ronald L. Ziegler
President and Chief Executive Officer

COMMUNITY RETAIL PHARMACY COALITION

NCPA
Calvin J. Anthony, R.D.
Executive Vice President

August 25, 1998

Chris Jennings
Assistant to the President for Health
The White House
Old Executive Office Building, Room 216
Washington, D.C.

Dear Chris:

On behalf of the Community Retail Pharmacy Coalition, we are writing to express our serious concerns with FDA's stated intent to finalize part of the original MedGuide regulation. The agency indicated that it was moving forward with this action as part of its recent "unified agenda", which was published in the Federal Register.

We strongly believe that consumers should be provided with useful information - both written and oral - about their prescriptions. However, we are surprised that the agency is moving forward with this action. We believe that the language included in the FY 97 Agriculture Appropriations bill regarding MedGuide specifically prohibits the Secretary of HHS from finalizing any part of the proposed rule, not just the voluntary part, as the agency states. This prohibition is lifted in 2001 if certain specific statutory goals are not achieved.

We believe that this comprehensive prohibition was written to prevent this very action by the agency. Congress was concerned then, as we are now, that finalizing even part of the rule would result in a uniform, government-mandated format for all written prescription information. We do not believe that patients are served by such an outcome. Moreover, we believe that the agency can continue to mandate under its existing authority that written information be distributed with certain prescription medications. This new regulation, however, would give it much broader authority, which we believe is contrary to Congressional intent.

Should the regulation be finalized it would, in our opinion, represent a breach of the understanding that community retail pharmacy entered into with the Congress and the Secretary regarding this issue. Pharmacy committed to a voluntary process to increase the quality and quantity of written prescription information being provided to consumers. We

National Association of Chain Drug Stores
413 N. Lee Street, Alexandria, Virginia 22314
Tel: (703) 549-3001, Fax: (703) 836-4869

National Community Pharmacists Association
(formerly NARD)
205 Daingerfield Road, Alexandria, Virginia 22314
Tel: (703) 683-8200, Fax: (703) 683-3619

believe that we are well on our way to achieving these goals for all prescription drugs, not just those that could result in serious and significant side effects.

We ask that the Secretary respect the intent of the law and the spirit of the agreement which pharmacy and many other affected parties entered into regarding the provision of written information to consumers. Thank you for your interest and concern with this matter.

Sincerely,

Calvin J. Anthony
Executive Vice President
NCPA
National Community Pharmacists Association

Ronald L. Ziegler
President and CEO
NACDS
National Association of Chain Drug Stores

DAN COATS
INDIANA

404 RUSSELL SENATE OFFICE BUILDING
(202) 224-5623

INDIANAPOLIS OFFICE:
1180 MARKET TOWER, 10 WEST MARKET STREET
INDIANAPOLIS, INDIANA 46204
(317) 226-5555

United States Senate

WASHINGTON, DC 20510

COMMITTEES:
ARMED SERVICES
LABOR AND HUMAN RESOURCES
SELECT COMMITTEE ON INTELLIGENCE

September 17, 1998

The Honorable Donna Shalala, Ph.D., Secretary
U.S. Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Ave, S.W.
Washington D.C. 20201

Dear Madame Secretary:

We are concerned with the Food and Drug Administration's (FDA) intention to finalize part of the proposed "MedGuide" regulation, which was prohibited under a provision enacted as part of the FY 97 Agriculture Appropriations Bill. This regulation, which was proposed by the FDA in August 1995, would set government-mandated standards for the quality and quantity of information distributed to consumers with their prescription medications.

We strongly support the distribution of quality, useful written and oral information to consumers with their prescription medications. However, we believe that the Secretary is prohibited by statute from implementing any part of this proposed regulation at least until the year 2001. This action was taken to give the private sector an opportunity to develop its own action plan to meet the goals of the original proposed regulation. A private sector action plan was developed through a collaborative process, and was accepted by you in January 1997. The private sector is now engaged in various activities to meet these goals, which is consistent with the spirit and intent of the law as enacted.

The agency's intent to finalize part of the proposed rule was published as part of the FDA's "Unified Agenda" in a recent Federal Register. Finalizing this part of the regulation would, according to the original proposed rule, give the FDA authority to require standardized, written information leaflets with certain drugs or drug classes. The proposed rule refers to these drugs as those with "serious and significant" side effects. The agency indicates in this agenda that the 1996 legislation enacted "places the proposed rule as it relates to the voluntary program in abeyance - and did not address the provisions that would have required mandatory medication guides in relatively rare instances."

We disagree with this assessment made by the agency regarding the legislative intent of this language. Finalizing part of the proposed MedGuide regulation would violate the intent and spirit of the legislation enacted in 1996. Congress intended that the entire rule, not just the voluntary part, be held in abeyance. In fact, the attached analysis done by the Congressional Research Service in October 1996, confirms that the "statutory provision prohibits the Secretary from implementing the entire proposed rule and all components thereof (or a similar MedGuide program) as published in the Federal Register on August 24, 1995."

Finalizing this part of the proposed rule would ostensibly achieve the outcome sought by the FDA in the original proposed rule. For both legal and practical reasons, an FDA requirement to provide written information in a standardized, government-mandated format for an ever-increasing number of drugs will likely result in adoption of this format for all drug information producers and practitioners in the private sector. This is the outcome that Congress sought to prohibit in 1996, and the reason why it was the intent of Congress that no part of the original MedGuide rule be finalized.

Moreover, Congress did recognize the need for the agency to retain its existing regulatory authority to require, on a drug-by-drug basis, the dispensing of written information with drugs that could result in "serious and significant" side effects. This intent was reflected through a colloquy we placed in the record which indicates that the language being adopted did not "preclude the FDA from using its existing authority to require, on a drug by drug basis, the provision of written information prepared by the manufacturer to consumers about prescription drugs that pose a serious health risk." It was clear that the legislative intent was for the agency to continue to require such written information on a limited basis using existing authority, but did not provide for the agency to seek or obtain the additional broader regulatory authority which the agency now seeks.

On another issue, we have several questions about a survey that the FDA intends to fund in order to assess the quality of the written information currently being distributed to consumers with their prescription medications. As we understand, the intent of this survey is to provide an interim report to the private sector regarding progress made toward meeting the "quality" goals specified by the private-sector action plan. Could you please provide answers to the attached questions about this survey in as expeditious manner as possible.

We urge the agency to suspend implementation of part of the proposed MedGuide regulation, an action which we believe is contrary to law and ignores Congressional intent. Thank you for your prompt attention to these issues. We look forward to your response.

Sincerely,

Thad Cochran
Chairman, Subcommittee on Agriculture and Related Agencies Appropriations
Committee on Appropriations

Dan Coats
Committee on Labor and Human Resources

Mitch McConnell
Committee on Labor and Human Resources
Subcommittee on Agriculture and Related Agencies Appropriations
Committee on Appropriations

QUESTIONS TO FDA REGARDING INTERIM SURVEY OF QUALITY OF WRITTEN PRESCRIPTION INFORMATION

We understand that the agency is in the process of developing a survey of the quality of written information being provided to consumers with their prescription medications. What are the objectives of the survey?

The MedGuide language requirement in the FY 97 Agriculture Appropriations bill requires that the Secretary review the status of private sector initiatives designed to achieve the goals of the private sector action plan before January 1, 2001. Is this survey being done for that purpose? What are the agency's plans in terms of assessing the quality and quantity of written information being provided as the January 1, 2001 date more closely approaches?

How was the survey designed and developed? What input was obtained from members of the working group that developed the original collaborative action plan about the survey methods? What are the criteria that are being used to assess the quality of the written information, and who will do this assessment? Have these criteria been tested, and are they considered to be an accurate representation of the information that consumers would, in fact, find useful to help them take their prescription medications? Are other private-sector entities testing such criteria at this time? What process is being used to collect this written information? What are the types of written information that the survey would examine? Would it be limited to pharmacies only, or all available written information that could be used by consumers? Would all pharmacies at which consumers obtained prescriptions be surveyed? Has this survey process been designed and validated by an objective third party?

In what format and timeframe will feedback obtained under this survey be provided to the developers and providers of written prescription information?

When does the agency expect to start and conclude the survey?

What is the anticipated total cost of this survey?

REPORT TO THE FDA COMMISSIONER

MANAGING THE RISKS FROM MEDICAL PRODUCT USE

AN ASSESSMENT OF FDA'S APPROACH AND A LOOK TO THE 21ST CENTURY

Task Force on Risk Management

Final Draft

March 1999
U.S. Department of Health and Human Services
FOOD AND DRUG ADMINISTRATION

EXECUTIVE SUMMARY

At one time or another, we all use medical products (human drugs, biological products, and devices) to prevent illness, relieve symptoms, restore health, slow disease progression, and prolong life. Today's medical products provide great public benefit, but their use sometimes leads to injury or death. No medical product is risk-free. The Food and Drug Administration (FDA) has the role of protecting the public from unsafe products or false claims while promoting public health by ensuring that beneficial medical products are available and labeled with adequate information on their risks and benefits.

Recently questions have been raised about how well the Agency is performing its role. During the last several years, five drugs were withdrawn from the market for safety reasons. In addition, in April 1998, the *Journal of the American Medical Association (JAMA)* published a meta-analysis estimating that more than 100,000 people die each year from the side effects of medical products. These heightened concerns about adverse effects have arisen at a time when Agency programs under the Prescription Drug User Fee Act (PDUFA), and other legislative and managerial initiatives, are resulting in faster FDA reviews for new drugs and biologics. PDUFA was passed in 1992 to provide FDA with additional funds from user fees to hire more staff, and it has helped the Agency reduce the average review time from 30 to 12 months, thus making drugs and biologics available to the public sooner. Although not covered by PDUFA, the review time for device premarket applications also has decreased, from 27 months in 1994 to 12 months in 1998. Yet some critics have claimed that PDUFA has

increased pressures on the Agency to approve medical products, and that it may have lowered the quality of FDA's analyses and decisions and lowered the standards for marketing approval.

This report is the result of a Task Force review prompted by FDA Commissioner Dr. Jane Henney, who established a Task Force to look into public concerns about the safety of medical products. The report examines the current medical product risk management system and evaluates FDA's role in that system. The Task Force evaluation and report concentrate on safety because most public concerns have focused on injuries from medical product use. The Task Force looked at how FDA fulfills its responsibilities as well as the results of its work. We also analyzed ways the Agency could restructure its activities to more effectively meet its objectives. In this report, we discuss recommendations and options that we hope will be used as the basis for a dialog among all of the players in the risk management system, with the goal of improving the model for risk management for the 21st Century.

FDA'S ROLE IN MANAGING MEDICAL PRODUCT RISK

FDA's current role in evaluating medical product safety involves two key elements: (1) its premarketing review process and (2) its postmarketing surveillance and risk assessment programs. During premarketing review, the Agency assesses the evidence demonstrating the benefits and describing the risks of medical products. The Agency approves a product when FDA judges that the benefits of using a product outweigh the risks for the intended population and use. (Figure 1).

Put Figure 1 here

A major part of the premarketing review is to ensure that products are truthfully and adequately labeled for use. Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk to the healthcare community and patients. However, once medical products are on the market, ensuring safety is principally the responsibility of healthcare providers and

patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information to select and use products wisely, thereby minimizing adverse events.

To assist with postmarketing risk management, the Agency maintains a complex surveillance and risk assessment program to identify adverse events that are not identified during drug development and premarketing review. FDA monitors adverse events associated with the use of approved medical products and uses this information to make labeling changes and, when necessary, to reevaluate the marketing decision.

QUALITY OF FDA'S PREMARKETING REVIEWS REMAINS HIGH

As discussed in detail in Part 2 of this report, the Task Force evaluated whether the heightened sense of time pressure on review teams has reduced the quality of FDA review or caused poor decision making. We studied how often previously unrecognized serious adverse events were identified after approval in drugs reviewed since the implementation of PDUFA. We then compared the numbers to those collected by a 1990 General Accounting Office report on serious adverse events for drugs reviewed prior to PDUFA. We also examined FDA's quality assurance systems for premarketing review and marketing decisions to see if they are functioning well enough. Finally, we identified factors inherent in the drug development process that could be limiting the Agency's ability to identify some risks during drug development and premarketing review.

Rate of withdrawals remains low

The Task Force found that, despite shortened FDA review time, evidence suggests that previously unidentified serious adverse events are occurring less frequently, or at least no more frequently, than in the past. Of the five drugs withdrawn for safety reasons after PDUFA, two were approved before PDUFA was

implemented.[1] Comparisons of drugs reviewed and approved under the PDUFA program to those approved previously shows that the rate of market withdrawals for safety reasons is as low or lower for drugs reviewed and approved after PDUFA as it was before PDUFA.[2] The 1990 GAO report found that previously unrecognized serious adverse events occurred after marketing in 51.5 percent of drugs. Among drugs reviewed ***after*** PDUFA, we found a 30.3-percent rate of such events. Over time, this rate could go up, but it is unlikely to exceed 51.5 percent.

QA/QC system is working

Auditing FDA's current quality assurance (QA) and quality control (QC) activities led us to conclude that the key elements of an International Standards Organization (ISO)-modeled QA/QC program for premarketing review are in place. FDA has consistently used supervisory re-review, conducted by subject matter experts, for 100 percent of the marketing decisions as the cornerstone of its QC function. These QC reviews are conducted on at least one supervisory level, and regularly at three levels, before a final approval decision is made. However, some QA/QC areas are still under development and these should be targeted for continued focus.

Finally, our analysis of premarketing product development identified several aspects of the development process that limit our ability to observe adverse events before marketing. Factors with the potential for change include the relatively small size and short duration of clinical trials and the representativeness of the patients studied. For example, as discussed in Part 2, rare side effects are often not observed before marketing because of the number of patients exposed to a drug before approval. And, most trials do not

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[1] Redux, Pondimin, Seldane, Duract, and Posicor were withdrawn from the market in 1997 and 1998; Seldane and Pondimin were approved prior to PDUFA.

[2] Friedmanm, M.A., J. Woodcock, M. Lumpkin, J. Shuren, et al., "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is a Problem?" in press.

last long enough to enable identification of potential long-term side effects. In addition, patients in clinical trials are often not representative of all the types of people who will be exposed after marketing. Changing these aspects of drug development could increase our ability to identify risks before the marketing phase — of course some of these changes could increase development costs and delay product availability.

In addition, consideration should be given to how rapidly some drugs are rolled out for widespread use. Slowing down a rapid rollout could limit the impact of some unexpected serious adverse events. Modified rollout strategies could change the economics of drug development in ways that are difficult to predict.

No achievable premarketing dataset can make up for inherent limitations in the drug development process. There will always be limits on what can be learned about a drug before it goes on the market. For this reason, postmarketing risk assessment activities are extremely important.

POSTMARKETING SURVEILLANCE AND RISK ASSESSMENT IS PERFORMING AS DESIGNED

In Part 3 of this report, we discuss whether the Agency's surveillance systems are adequate to address the emerging changes in today's healthcare environment. We found that the postmarketing surveillance and risk assessment programs are performing well for the purposes they were designed to achieve, but an increasingly complex healthcare system and the emerging global marketplace present some challenges that should be addressed.

Today, the Agency relies principally on a ***passive*** adverse event reporting system, relying to a great extent on voluntary reporting by the healthcare community It rapidly alerts the Agency to the occurrence of rare, serious adverse events not previously identified and provides an increased understanding of the range of severity in known product-associated adverse side effects. However, the

system provides little useful information, for example, on the ***rates*** of adverse events. The Agency is able to make limited use of other sources of postmarketing safety data, including large healthcare databases, epidemiological studies, and prospective cohort data collection studies, to obtain more complete information on adverse events. The Agency is neither funded to access such systems to any great extent, nor authorized to require manufacturers to collect such data for pharmaceutical products.

The Task Force has presented some options for expanding the use of automated systems for reporting, monitoring, and evaluating adverse events and product defects. Implementing these changes would require additional funding. We also have concluded that FDA's ability to assess postmarketing product safety could be strengthened through increased access to data sources that would supplement and extend its passive reporting systems. Examples of such sources include broad-based health information databases and data from sentinel user facilities where staff are trained to rapidly recognize and accurately report adverse events. In addition, FDA's efforts to identify and understand product-related injuries could be enhanced through additional support of research into how to design state-of-the-art surveillance systems and analyze surveillance data. Increased knowledge in these area could contribute substantially to the Agency's ability to reduce the effects of adverse events.

MANAGING THE RISKS FROM MEDICAL PRODUCT USE

Part 4 of this report examines other Agency efforts to help manage the risks associated with using medical products. Of particular interest is FDA's role as a government agency in the overall system of risk management. During our analysis, we used a risk management model that has been developed for other health and safety sectors[3] (see Figure 2). When applied to medical products, we found that what started as individualized care by one

[3] Presidential/Congressional Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Management —Final Report Volume 1*, 1997.

practitioner has evolved into a complex system of risk management that involves manufacturers, the FDA, practitioners, many other elements of the healthcare delivery system, and patients. In some cases, roles are clearly defined. For example, most FDA efforts are devoted to pre- and postmarketing risk assessment (Figure 3), and the FDA approval/nonapproval decision is the Agency's central risk management action. Once a product is approved, the key risk manager is the prescriber, who is responsible for maximizing benefit and minimizing risk to the individual patient. However, in today's healthcare environment, the roles of all of the players in the overall system for reducing and managing risk are not as clearly defined as they could be.

Put Figure 2 and Figure 3 here.

The source of risks is important when assessing risk management

To evaluate the current system, the Task Force considered what is known about the sources of risk from medical products. Most injuries and deaths result from their known side effects (Figure 4). Some side effects are unavoidable, but others can be prevented or minimized by careful product choice and use. It is estimated that more than half the side effects of pharmaceuticals are avoidable. Other sources of preventable adverse events are medication or device errors. Injury from product defects is unusual in the United States because of the great attention paid to product quality control and quality assurance in manufacturing. A final category of potential risk involves the remaining uncertainties about a product As pointed out earlier, knowledge about a product is necessarily limited at the time of approval. For example, rare side effects and long-term outcomes (both positive and negative) may not be known when a product is approved. In addition, effects on populations not studied in the clinical trials (e.g. pregnant patients, children, people with other diseases) may be discovered if these groups are treated after marketing.

Put Figure 4 here.

Known side effects cause the majority of serious adverse events and death

Of all these risks, known side effects cause the vast majority of injuries and deaths. However, not enough is known about the causes, incidences, and relative contribution of the various sources of risks, or about which ones are avoidable. Better information is needed if these risks are to be managed optimally. FDA's postmarketing surveillance programs were not designed to capture these kinds of data. As the risk management model shows (Figure 5) many players, including the FDA, have a role in minimizing the risks from using marketed drugs. The Task Force believes that these stakeholders need to collaborate to determine how better data on risks can be collected so that efforts and interventions can be targeted to the most serious problems, and the effects of interventions can be evaluated.

Put Figure 5 here.

Part 4 of the report also examines FDA's activities in risk confrontation, risk intervention, and risk communication (Figure 6). Although the Agency participates in many such activities, they have had lower priority than the Agency's pre- and postmarketing scientific risk assessment responsibilities.

Put Figure 6 here.

FDA should engage stakeholders to examine the current risk management system

We recommend that FDA take the opportunity to engage all stakeholders to reexamine the current system for managing the risks associated with the use of medical products. The adequacy of the current system for collecting information on injuries and deaths should be evaluated. We encourage a public policy discussion that focuses on defining more clearly the roles and responsibilities of all components of the risk management system — FDA, industry, healthcare provider organizations, healthcare practitioners, patients, and the public. Only by examining the roles of these various groups can gaps and misallocation of efforts be identified

and improvements made. The Agency also should expand and formalize its efforts in confronting risks and engaging stakeholders when deciding which risks are acceptable to those who will suffer their consequences.

RECOMMENDATIONS AND OPTIONS

The Task Force is making a number of recommendations as a result of its review. Recommendations center around ways that FDA, within the confines of the current system, could further improve its risk management activities. Many of these improvements already are underway. In addition, we present a series of options for consideration that could help expand FDA's efforts in communicating risk information to the healthcare community and the public. Some options, if implemented, could make it possible for the FDA to learn more, more quickly, about serious adverse events, allowing the Agency to intervene sooner to minimize their effects.

These options also could serve as the start of a dialog among the stakeholders in the healthcare community on ways to improve the current system for managing the risks associated with using medical products. The new system could be based on the model we propose in this report, which is in use in other health and safety sectors.

Recommendations — premarketing QA/QC

To improve FDA's premarketing QA/QC, we recommend the Agency take the following actions:

- Initiate steps to have each center establish separate QA/QC units to support QA/QC as a normal part of all activities including the following:

  - Peer review a sample of product approval review

administrative records for quality of the analysis and completeness of the documentation.

- Establish procedures for continuation of review when there has been an administrative disruption of the process.

- Prospectively track scientific disputes among reviewers and evaluate whether the disputed issue is predictive of problems after marketing.

- Ensure and document ongoing professional education and current core competency training for all reviewers.

- Complete the Good Review Practice (GRP) documents and keep them current.

- Systematically analyze significant postmarketing events, incorporating them into GRPs as lessons learned.

Recommendations — postmarketing surveillance

For spontaneous reporting we recommend the Agency take the following actions:

- Rapidly complete the pharmaceutical products Adverse Event Reporting System (AERS), and correspondingly enhance the medical device Manufacturers and User Device Experience (MAUDE) system.

- Integrate existing postmarketing information systems so analytic tools, data entry, and editing can be uniformly applied, and all information is readily available to every reviewer.

- Develop new methodological tools for inference from available datasets.

Recommendations — risk management

For overall risk management activities we recommend the Agency take the following actions:

- Join in, or convene, public forums with other agencies and groups involved in healthcare to examine the current system of managing the risks of medical products. These forums might focus on the costs and value of better data on the incidence and causes of injuries from medical products and the roles of all stakeholders in risk management.

- Increase stakeholder engagement in FDA risk management activities — both in product decision making and in indication-specific or class-specific guidance.

Additional options

We have identified a number of additional options for consideration, which, if adopted, might contribute to improved risk management. These ideas need full public policy analysis and review to understand their potential value, costs, and acceptability to the various stakeholders in medical product risk management. Some of the options would require significant new resources and legislative changes. For these reasons, we suggest that these options be evaluated in the context of the stakeholder risk confrontation activities recommended above. Only by working with all other participants in the overall risk management system for medical products can the Agency arrive at the most effective approach for managing those risks.

Additional options — premarketing QA/QC

Additional premarketing options that could, in part, address the inherent limits of premarketing development include the following:

- Evaluate the practicality and value of wider use of large, community-based simple trials designed to identify serious adverse events in a larger and more representative patient population prior to approving the product for widespread use.

- Develop tools to concentrate early postapproval use in populations for whom an advantage of the new product over alternative products has been demonstrated.

- Evaluate the practicality and value of limiting exposure in the early postmarketing period by restrictions on market rollout for particular drugs.

Additional options — postmarketing surveillance

For spontaneous reporting —

- Coordinate premarketing and postmarketing information to ensure full consideration of all available safety data at each stage of review.

For active and other postmarketing surveillance options —

- Supplement existing reporting channels by establishing and supporting institutions to serve as sentinel sites for adverse event reporting. Such sites would produce a higher rate of event reports and more completely analyze each event, further enhancing the value of their reports.

- Provide cross-agency access to external healthcare databases. This would allow the Agency to more quickly investigate signals generated by spontaneous reports and would be particularly valuable in determining the rate of adverse events.

- Design, implement, and maintain prospective product use registries (the bulk of support should come from manufacturers).

- Enhance clinical and laboratory studies to develop new methods to improve product safety.

- Increase resources to conduct focused epidemiological

studies when support of these studies by manufacturers is not feasible.

For research —

- Support staff to conduct methodological research on the costs and value of various approaches to understanding adverse events among marketed products.

Additional options — risk management

Additional risk management options include:

- Develop and implement risk communication strategies that more effectively target information to risk managers (i.e., prescribers and patients).
- Increase postmarketing risk intervention, such as restricting distribution of products or requiring mandatory educational programs.
- Establish an independent advisory body to evaluate the effectiveness of risk management in the healthcare system.
- Seek legislative changes for other types of risk intervention, such as suspension authority for drugs.
- Develop programs to systematically evaluate the effectiveness of FDA's risk management activities.

CONCLUSIONS

In summary, we evaluated the FDA's current risk management activities for medical products. We found that the premarketing review processes for these products are detecting serious risks at least as well as in previous decades. But, premarketing development and review is limited in scope because of factors inherent in the drug development process. As a result, rare, late

appearing, and novel types of adverse events may only be discovered during routine on-the-market use.

We then evaluated FDA's postmarketing surveillance and risk assessment systems for these products. The systems in place are good at rapidly detecting most unexpected serious adverse events that occur during the postmarketing period. However, the Agency's passive surveillance systems were not designed to capture all of the types of data that are needed to gain a thorough understanding of medical product risks. The Agency's postmarketing surveillance programs could benefit greatly from acquiring access to additional data sources. Finally, we analyzed the current system of risk management for medical products in the United States and concluded that more extensive discussions with a wide range of stakeholders should be undertaken to better confront and manage medical product risks in the 21st Century.