

FDA Consumer

The Magazine of the U.S. Food and Drug Administration

September–October 2000 • Vol. 34 No. 5



MAY NOT REFILL
DISCARD AFTER

Make No Mistake!

ONE TABLET EVERY 4 HOURS

SOME MAY AFFECT THE ACTION OF THIS MEDICINE

MAY CAUSE DROWSINESS. ALCOHOL MAY INTENSIFY THE EFFECT. USE CARE WHEN OPERATING A CAR OR DANGEROUS MACHINERY.

Medical Errors Can

Be Deadly Serious

BEFORE USING ANY MEDICATION, READ THE PRESCRIPTION. SOME MAY

CAUSE DROWSINESS. ALCOHOL MAY INTENSIFY THE EFFECT. USE CARE WHEN



Donna E. Shalala, Ph.D.

Secretary of Health and Human Services

Jane E. Henney, M.D.

Commissioner of Food and Drugs

Lawrence Bachorik, Ph.D.

Associate Commissioner for Public Affairs

Larry Thompson / Editor

Patricia N. Edwards / Art Director

Michael L. Herndon / Production Manager

Jan Elicker / Copy Editor

Linda Bren, Carol Lewis, Tamar Nordenberg /

Staff Writers

Cover Design: Jack Lefkowitz

FDA on the Internet: www.fda.gov

FDA Consumer (ISSN 00362-1332) is published bimonthly by the Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857, U.S. Public Health Service, Department of Health and Human Services.

Editorial Matters

Address for editorial matters is *FDA Consumer*, Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857. Articles in *FDA Consumer* may be republished without permission. Credit to *FDA Consumer* as the source is appreciated. *FDA Consumer* is indexed in the *Reader's Guide to Periodical Literature*. The current *FDA Consumer Index* is available on FDA's Website at www.fda.gov/fdac/index/conindex.htm.

Subscriptions

Send inquiries concerning subscription problems or address changes to Superintendent of Documents, Government Printing Office, Washington, DC 20402. Include mailing label from the back cover for address changes.

To keep subscription prices down, the Government Printing Office mails each subscriber only one renewal notice. To determine when you will get your renewal notice, check the number that follows ISSDUE on the top line of your mailing label. When the label reads ISSDUE003, a renewal notice will be sent. When the label reads ISSDUE000, you have received your last issue unless you renew.

To continue to receive *FDA Consumer* without interruption, please return your renewal notice promptly. If your subscription has expired, send your mailing label with \$12 (\$15 foreign), using the form on the back cover, to Superintendent of Documents, Government Printing Office, Washington, DC 20402, and your service will be reinstated. Periodicals postage paid at Rockville, MD, and additional mailing offices. POSTMASTER: Send address changes to *FDA Consumer*, 5600 Fishers Lane, Room 15A-19, Rockville, MD 20857.

◀ **Inside Front Cover Photo:**

FDA Consumer

The Magazine of the U.S. Food and Drug Administration

September–October 2000 • Vol. 34 No.5

Cover Story

13 **Make No Mistake: Medical Errors Can Be Deadly Serious**

Thousands of patients die each year from preventable medical errors. FDA and the health-care community are searching for solutions.

8 **Reusing Medical Devices: Ensuring Safety the Second Time Around**

If you think your kid's braces are brand-new, think again. Safety concerns and new guidance regarding recycling single-use medical devices are examined.

10 **New Dietary Guidelines Give Practical Advice for Healthier Living**

Eat more of this food—eat less of that one. Dietary advice can be confusing, but the new dietary guidelines spell it out for consumers in an easy-to-understand booklet.

11 **Precision in Public Health Protection: A Woman's Life's Work in Radiation**

Technician Elizabeth Rodgers plays a key role in making sure x-rays are safe.

19 **Human Gene Therapy: Harsh Lessons, High Hopes**

September marks the 10-year anniversary of the first human gene therapy experiment—and the one-year anniversary of the first death caused by this promising treatment.

25 **User Fees for Faster Drug Reviews**

Resources provided by user fees helped FDA revive its drug and biologic new product review programs. But eliminating delays has not eliminated criticism of the program.

30 **Advisory Committees: FDA's Primary Stakeholders Have a Say**

Think the government doesn't listen to you? Consumers and patient advocates *do* make a difference and bring an important perspective to agency decision-making.

Departments

2 **Observations**

2 **Updates**

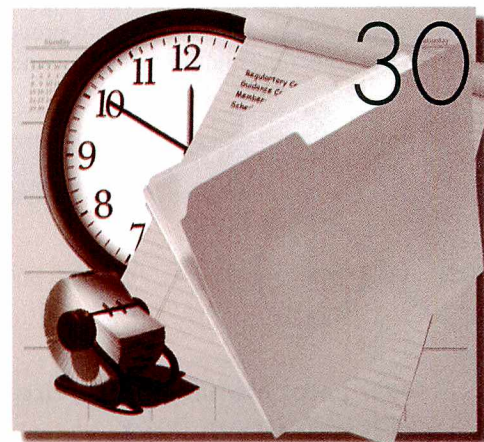
3 **Letters to the Editor**

35 **fda.gov**

36 **Summaries of Court Actions**

39 **Investigators' Reports**

40 **The Last Word**



On Sept. 14, 1990, researchers at the National Institutes of Health injected genetically altered white blood cells into the first patient to receive gene therapy, launching a new field of clinical research. Story on page 19.

OBSERVATIONS

There is an old saying in the newspaper business that doctors bury their mistakes while reporters put them on the front page. These days, doctors' mistakes are too often finding their way onto the front page. Medical errors—from giving the wrong patient the wrong dose of the wrong drug at the wrong time to bypassing the wrong coronary artery—have become too common.

The more sophisticated and complicated medical technology becomes, the more likely it is that something unexpected will go wrong. Patients need to be protected from that something going wrong. That's where the Food and Drug Administration fits in. As a governmental agency, FDA is all about managing risks. When evaluating the risks and the benefits of marketed products—from a new drug or biologic to a medical device, from the safety of foods to the hazards of cosmetics—the agency works to minimize the dangers to the consumer. And once a product goes into widespread use, FDA continues to watch for trouble, putting out warnings when problems arise and even removing products when the risks exceed the benefits.

But it's not a perfect world and FDA will never be able to eliminate all the risks—especially working alone. In its May 1999 report, the FDA Task Force on Risk Management concluded that “FDA plays only a part in the complex system of risk management. Numerous other groups [including doctors, nurses, pharmacists and other care-givers, patients, and medical product manufacturers] participate in decision-making related to the use of medical products.”

Too often, according to a recent report by the Institute of Medicine, there is little that the individual patient can do to avoid mistakes. Both IOM and FDA recommend a systems approach to solving the overarching problem of medical errors. In this issue's cover story, staff writer Tamar Nordenberg explores the IOM report, the challenges raised by medical errors, and the actions taken by FDA to prevent them.

But sometimes nothing can be done to stop a mistake. An



Larry Thompson, Editor

error by scientists conducting clinical research burst onto the nation's front pages last year when the hot field of human gene therapy suffered its first casualty, the death of an Arizona teenager named Jesse Gelsinger. The death came only months before gene therapy researchers appear to have achieved their first concrete victories over illnesses and the field itself is celebrating its 10th anniversary. Gelsinger's death has prompted considerable introspection and the ratcheting up of federal oversight.

But government regulators can never be everywhere; the research community, too, must respond to the Gelsinger case, according to this issue's Last Word commentator, Savio Woo, M.D. He describes the concrete steps taken by the American Society for Gene Therapy to shore up the clinical research apparatus and restore patient confidence that the system will protect them from unnecessary risks.

All this is not to say that consumers have no control or voice in this process of developing and marketing medical products. Staff writer Carol Lewis details the essential role that patient and consumer representatives play in FDA's advisory committee system. Their points of view remind the medical community that real people reap the benefits—and bear the risks—of their decision-making.

All these institutional responses to medical errors are essential, but consumers need to remember that the body in question belongs to them, and they need to be their own advocates. On a trip out West recently, an acquaintance in a leg brace told me the story of how he twisted his knee on the job. At the medical center, a health professional put him on a treadmill and turned up the speed to see what he could do. The resounding pop and shooting pain of a separating medial collateral ligament showed he couldn't do much. Surgery was pending negotiations with the managed care organization.

My acquaintance isn't stupid; he was trusting. He's the kind of guy who figured they know more than he does and did whatever they said. Most of the time, health professionals do know a great deal and use their knowledge to help; no one intentionally does harm. But if someone is proposing something you don't understand, ask questions until you do. If it sounds stupid, don't agree until you know it isn't. And if your knee hurts, stop off the treadmill.

UPDATES



New Fetal Monitoring Device Keeps Better Watch on Baby

A new type of fetal monitoring device that measures the level of oxygen in the baby's blood during labor and delivery will give more information about the fetus's condition than is possible with currently used electronic fetal monitors.

Conventional monitors measure the fetal heart rate and uterine contractions. Health professionals interpret these measure-

ments, along with other factors, to decide if labor can continue, or if a Cesarean delivery is indicated. It's anticipated that being able to monitor the fetal blood oxygen level will give health professionals a more complete picture of how the baby is responding to labor.

The new monitor, the OxiFirst Fetal Oxygen Saturation Monitoring System, was approved by the Food and Drug Administration on May 12, and represents the first major technological development in fetal monitoring since electronic monitoring was introduced in the 1960s and 1970s. The system measures the level of oxygen in the fetus's blood using pulse oximetry, a technology first developed in the 1970s that detects the amount of red and infrared light reflected by

The Value of Breast Implants

As a breast cancer survivor, I was saddened to read the article on saline breast implants which appeared in the July-August 2000 issue of *FDA Consumer*. The title itself casts a shadow on the issue even before the reader can continue to evaluate the information contained in the article, "Saline Breast Implants—Stay on the Market as Experts Warn About Risks." The title alone does a disservice to the issue and to the unfortunate one out of eight women who will be diagnosed with breast cancer.

Most women are terrified when diagnosed with breast cancer. The additional threat of the risks of implants only adds to the devastating blow of losing a breast. Breast reconstruction holds out hope for mastectomy patients—the hope of one day looking normal.

The author does state that "... after breast cancer surgery, (women with breast implants) reported that they had experienced significant improvement in the quality of their lives." Could the author have said a little more about the positive psychological impact of knowing you will live your life after breast cancer surgery with more than just scars?

I have always been grateful to have had the hope from the day of diagnosis that I would someday look "normal." I ask that you please consider your audience before you quote the "experts."

Eileen Rhoads
Silver Spring, Md.

Editor's note: Ms. Rhoads is an FDA employee expressing her personal view.

Counting Juvenile Diabetes

In the July-August 2000 issue of *FDA Consumer*, the article "Overcoming Juvenile Diabetes With a Little Planning and High-Tech Tools" claimed that "More than 400,000 new cases (of Type 1 diabetes) are reported ... in the United States each year. And more than 1 million Americans currently live with the condition."

If these figures were correct, people with Type 1 diabetes would have an exceedingly short life expectancy after diagnosis. In fact, the numbers reported in the article are not accurate. According to the Juvenile Diabetes Association (JDF), the number of new cases reported each year is about 30,000. And according to the American Diabetes Association (ADA), the number of Americans living with Type 1 diabetes is estimated to be between 500,000 and 1 million.

Using the figures of the JDF and the ADA, one arrives at a slightly more hopeful life expectancy, but still one that reflects the seriousness of managing a chronic disease that affects a significant portion of the American population.

Except for the arithmetic, the article was commendable. Our compliments to the author for an otherwise accurate and well-reported article.

James Hazlett
Editor

Diabetes Self-Management magazine

FDA Consumer accepts letters to the editor. Letters can be e-mailed to FDAC-letters@oc.fda.gov, or mailed to *FDA Consumer*, Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857. Letters should be 300 words or less, signed, and include a telephone number for verification. The editor reserves the right to edit letters for space and appropriateness.

oxygen-carrying red blood cells. The device uses a sensor that is inserted into the mother's uterus and placed against the fetus's temple or cheek. It is only to be used along with conventional electronic fetal monitoring when the fetal heart rate is "non-reassuring," meaning that the baby may not be responding normally to the stress of labor. It is intended for use only with single, not multiple, fetuses of at least 36 weeks gestation, where the mother's water has broken and the baby is in the head-down position for delivery.

Studies done before approval assessed whether use of the new monitor would reduce the number of Cesareans done due to a non-reassuring heart rate. These studies showed that the Cesarean rate for non-reassuring heart rate did decline when the OxiFirst monitor was used. But the overall Cesarean rate stayed about the same, because more women

using the new monitor had Cesarean deliveries due to difficult or prolonged labor. Analysis of the study data showed that the increase was not related to the device itself. The manufacturer will conduct a large study as the device is used in general medical practice to further understand how its use will impact the Cesarean rate in this country. Currently, about one-fifth of the 3.9 million births in the United States each year are Cesarean deliveries.

The rate of adverse events in pre-approval studies was comparable between births using the OxiFirst monitor and those managed with conventional monitoring, showing that the monitor is safe for both mother and baby.

The OxiFirst Fetal Oxygen Saturation Monitoring System is manufactured by Mallinckrodt/Nellcor Perinatal Business, Pleasanton, Calif.

New Treatment Approved for Severe Premenstrual Symptoms

The popular antidepressant Prozac now has another use and another name. FDA approved fluoxetine (Sarafem) in July for the treatment of Premenstrual Dysphoric Disorder (PMDD). Fluoxetine was approved in 1987 under the name of Prozac for treating depression, and has also been approved for treating obsessive-compulsive disorder and bulimia. The manufacturer, Eli Lilly, of Indianapolis, Ind., renamed the drug Sarafem for its new use to treat PMDD.

A woman is diagnosed with PMDD when she experiences at least five of eleven symptoms regularly between ovulation and menstruation (about one to two weeks before her period). One of the five symptoms must be: markedly depressed mood, noticeable anxiety or tension, sudden sadness or tearfulness, or persistent anger or irritability. The other symptoms may include: decreased interest in activities, difficulty concentrating, lack of energy, change in appetite, sleeping too much or too little, a sense of being overwhelmed, or physical symptoms (headache, joint and muscle pain, weight gain, bloating, or breast tenderness).

"Women who have PMDD are likely to miss work or school, and have increased interpersonal and domestic problems," says Thomas Laughren, M.D., a medical officer in FDA's Center for Drug Evaluation and Research. The symptoms of PMDD are more severe than those of premenstrual syndrome (PMS), according to Laughren. About 3 to 5 percent of women of child-bearing age are estimated to have the condition.

Available by prescription only, Sarafem comes in packages of 28 pills and is priced the same as Prozac, according to the manufacturer. The drug is to be taken daily—not just on the days the patient isn't feeling well.

In studies, Sarafem was found to be significantly more effective than a placebo. Its effectiveness in women taking birth control pills is not yet known, since this group was excluded from the studies. Side effects of the drug include nausea, tiredness, nervousness, dizziness, and difficulty concentrating.

New Cancer Drug Approved for Some Leukemia Patients

A new cancer drug may extend the lives of some leukemia patients who are poor candidates for more traditional chemotherapy. The Food and Drug Administration approved Mylotarg for older patients with CD33 positive acute myeloid leukemia whose cancer has returned after chemotherapy treatment. Patients with this type of leukemia quickly accumulate abnormal white blood cells in the blood and bone marrow, causing severe anemia, infection, and hemorrhage during the course of the disease. Acute myeloid leukemia is more commonly found in older adults, and requires aggressive, immediate treatment.

The standard treatment for leukemia, chemotherapy, is given in the hospital for seven days and requires the patient to remain in the hospital for an extended period of time following treatment. The new Mylotarg treatment, which is given in place of chemotherapy, is a two-hour intravenous infusion delivered in two doses, 14 days apart. Although it does not always require a hospital stay, the majority of patients are hospitalized over the course of treatment.

Mylotarg works by attaching itself to an antigen found on the surface of the tumor cells. Antigens are proteins that the body's immune system recognizes as foreign and destroys. The leukemia cells then die after absorbing the drug's toxic chemical. The major side effects of Mylotarg include prolonged myelosuppression (inhibited bone marrow activity causing decreased production of blood cells and platelets) and liver toxicity. Rare allergic reactions have also been reported.

The drug is approved only for patients 60 years and older, since the prognosis in younger patients may be better with conventional treatments.

Mylotarg (gemtuzumab ozogomicin for injection) is manufactured by Wyeth-Ayerst of Philadelphia, Penn.

Overweight? Not My Kid!

Most parents of overweight children do not consider them to be overweight, say researchers from the Bassett Healthcare Research Institute in Cooperstown, N.Y., and Columbia University. This conclusion was drawn from a survey of over 1,400 parents or guardians of children aged 1 to 5 who were participants in the Supplemental Nutrition Program for Women, Infants, and Children (WIC) in New York state. Study results were reported at the Pediatric Academic Societies 2000 meeting in Boston.

The researchers found, for example, that 68 percent of parents of children with a Body Mass Index above the 95th percentile, which is considered to be obese, reported that their child's weight was "OK, just right" and 8 percent even reported their child was "underweight." Body Mass Index, or BMI, is a measurement of overweight and obesity that is calculated using height and weight.

In other results of the study, the researchers found that the prevalence of childhood obesity was more than twice as high as the national rate in the 1970s. Lead researcher Barbara A. Dennison, M.D., observed that, where one would expect about 15 percent of all children to be overweight, instead more than 35 percent of the children in the study were overweight. "Increasing rates of child obesity have been noted before, but these rates are even higher than previously reported," Dennison noted.

The study also suggested that parents of obese children who believe their child is overweight more often limit how much food their child eats and they report more frequently using dessert as a reward for finishing dinner. Researchers found, in addition, that overweight children watched significantly more television than non-overweight children, and that the risk of being overweight was directly related to the number of hours of television per week that the children watched. (*Pediatric Academic Societies*, May 14, 2000)

Some Weight-Loss Ads Are Enough to Make You Sick: Group Urges Responsible Marketing

"Ad Nauseam," a campaign launched in May by the Partnership for Healthy Weight Management, focuses attention on dubious weight-loss claims and the media that carry advertisements touting the claims. The Partnership is a coalition of scientific, academic, health-care, government, commercial, and public interest representatives that promotes the responsible marketing of weight-loss products and programs. Its other goals include encouraging more effective screening of ads for weight loss products and services, and increasing public awareness of the obesity epidemic in the United States.

To launch the Ad Nauseam campaign, the Partnership contacted nine major media sources that carried 12 dubious

weight-loss claims, asked the publications to explain their ad screening policies, and urged them to adopt policies that require proof of extravagant claims. The Partnership contacted the magazines *Cosmopolitan*, *Esquire*, *McCall's*, *Redbook*, and *Woman's Day*, *The Atlanta Journal-Constitution*, *The [Denver] Rocky Mountain News*, *USA Today*, and *Smart Source*. Only one publication, *USA Today*, responded to this inquiry, and no publishers provided information showing an effective ad screening policy. The Partnership will follow up by encouraging all mainstream media to demand proof before accepting advertising copy that contains extravagant promises of weight-loss success.

The public is invited to assist by collecting examples of dubious ads and sending them to the Partnership for Healthy Weight Management, Federal Trade Commission, S-4302, 601 Pennsylvania Ave., N.W., Washington, DC, 20580. Or call FTC's toll-free helpline at 1-877-FTC-HELP (1-877-382-4357), or e-mail the information using FTC's online complaint form at <https://www.ftc.gov/ftc/complaint.htm>.

Consumers can get the Partnership's brochure, "Finding a Weight Loss Program that Works for You," from the Partnership's Website at www.consumer.gov/weightloss/. Copies can also be requested by writing to the FTC mailing address above.

Coffee and Cola—The Good News and the Bad News

Caffeine May Protect Against Parkinson's Disease

Caffeine drinks such as cola, coffee and tea may lower the risk of developing Parkinson's disease (PD). Researchers at the Veterans Administration Medical Center in Honolulu can't explain how beverages that make people jittery can help prevent a disease that results in tremors. Nevertheless, they found that men who drank coffee were less likely to get PD. And the more coffee they drank, the better. Non-coffee-drinking men were two to three times more likely to get PD than those who drank from 4 ounces to 28 ounces a day. But they were five times more likely to develop PD than those who drank 28 ounces or more a day, or about 4-1/2 6-ounce cups.

Caffeine was identified as the protective ingredient in coffee after niacin and eight other nutrients were determined to be unrelated to PD. The addition of milk or sugar to coffee did not make any difference in the findings.

Lead researcher G. Webster Ross, M.D., suggests several theories to explain the findings. Men who have a propensity to develop PD may have an intolerance to caffeine. Another possibility is that caffeine may protect against the nerve cell destruction that causes PD.

The findings were based on data from the Honolulu Heart Program, an ongoing study of 8,004 Japanese-Americans, which began in 1965. As the study considered only men with this ethnic background, the researchers said it is unclear whether the same results would be found in women and other ethnic groups. "It is too early to recommend coffee drinking to prevent Parkinson's disease," says Ross. (*Journal of the American Medical Association*, May 24/31, 2000)

Sodas May Boost Bone Breakage

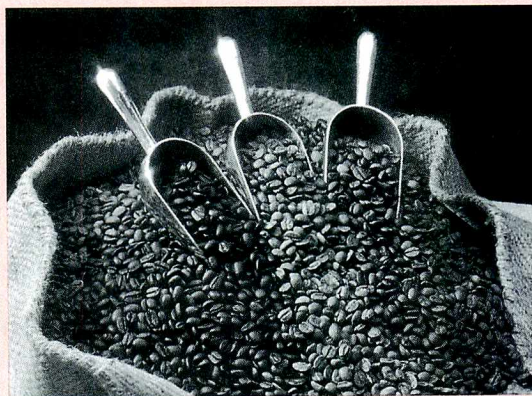
Carbonated beverages and physical activity may not mix, according to a study by the Harvard School of Public Health and Harvard Medical School. The study concluded that active girls who drink carbonated beverages, especially cola, are five

times more likely to have bone fractures than those who don't drink these beverages. The study was done on 460 ninth- and tenth-grade girls who reported their activity levels, carbonated beverage

drinking habits, and history of bone fractures. The greatest increases in likelihood of bone fractures were for those who drank carbonated beverages and engaged in high-level or vigorous physical activity. In previous studies, the researchers also found a similarly strong relationship between

carbonated beverage consumption and bone fractures in active postmenopausal women and teenagers.

The researchers don't know why this occurs, but allow for the possibility that cola and other carbonated drinks contain phosphoric acid, which affects calcium metabolism and bone mass. Another theory is that more young people replace milk in their diets with soda, giving bodies less calcium with which to build strong bones. (*Archives of Pediatric and Adolescent Medicine*, June 2000)



Sealant Makes Lungs Air-tight

A surgical “glue” recently approved by FDA offers a new option for patching air leaks that commonly occur in patients’ lungs after the removal of cancerous tumors.

Approved in May after an expedited review of safety and effectiveness studies, the FocalSeal-L Surgical Sealant can complement standard tools for closing air leaks, such as stitches and staples. The product is painted on the lung and forms a seal after light activates a chemical process called polymerization.

The main clinical study of FocalSeal involved 180 patients being treated at four U.S. medical centers. Of the 125 patients treated with FocalSeal plus standard sealing techniques, 39 percent remained free of air leaks through their discharge from the hospital, compared to 11 percent of the 55 patients who received only standard treatments.

Side effects were similar in the two groups, but infections were more frequent in FocalSeal patients.

FocalSeal is made by Focal Inc., Lexington, Mass. As a condition of approval, the company will conduct five years of follow-up studies to see whether the product affects the rate of cancer recurrence.

Living Skin Substitute Can Heal Diabetic Foot Ulcer Wounds

A manufactured skin made from living human cells is now available to help heal open wounds in the feet of individuals with diabetes. Previously approved in 1998 to treat leg ulcers caused by circulatory problems, Apligraf was approved by the Food and Drug Administration in June to treat hard-to-heal diabetic foot ulcers.

Apligraf is a wound dressing that contains human skin cells combined with collagen from cattle to simulate human skin. This skin substitute is bi-layered; that is, it has both an upper epidermal and a lower dermal layer. Its unique composition is purported to protect the wound while promoting the growth of new, healthy skin.

Apligraf is to be used along with standard procedures for treating diabetic foot ulcers, which include cleansing the wound, treating infection, and keeping weight off the affected foot.

In clinical studies of 208 patients, 112 were treated with Apligraf and standard care and 96 were treated with standard care alone. After three months, 56 percent of the patients in the Apligraf group had complete wound closure compared to 39 percent of the patients who received the standard care alone. More than 80 percent of the ulcers remained closed after four weeks for both groups.

Apligraf is manufactured by Organogenesis Inc. of Canton, Mass.

Non-Invasive Test May Detect Heart Disease

Magnetic resonance imaging (MRI) can accurately detect re-narrowed heart arteries in patients who have had balloon angioplasty or other artery-clearing procedures, according to researchers at Wake Forest University Baptist Medical Center and the University of Texas Southwestern Medical Center. The researchers tested 17 patients with chest pain at least three months after balloon angioplasty. Testing was done with both non-invasive MRI and invasive heart catheterization. Catheterization, which is the current standard test to evaluate artery blockage, involves passing a tube through the blood vessels into the heart, releasing dye into the vessels, and taking x-rays to view any narrowing. The two tests were found to be equally accurate at detecting blockages.

One-third of the people who undergo balloon angioplasty will develop re-narrowed arteries within six months, according to the American Heart Association.

Although this study applies MRI technology to patients with re-narrowed arteries, researchers predict it can also be used in seemingly healthy people to detect heart disease in time to prevent heart attacks or angina. (*Circulation*, May 23, 2000)

Mosquitoes Zoom In on Pregnant Women

Mosquitoes seem to be attracted to pregnant women, according to scientists at the University of Durham, England, and the Medical Research Council, Gambia, who found that pregnant women are bitten by mosquitoes twice as often as non-pregnant women. The particular mosquito studied was the African malaria-carrying mosquito. The researchers suggest that the physiological changes that take place during pregnancy could cause the increased mosquito-biting. For example, women in later stages of pregnancy exhale greater volumes of air than non-pregnant women, and the several hundred components in exhaled human breath may help mosquitoes track their targets. In addition, mosquitoes can zoom in on the bacteria that form on the warm skin of pregnant women, who have a slightly higher body temperature and sweat more easily.

The researchers hope these findings will lead to the development of more effective repellents that block the mosquito-attracting odors. The study, which took place in rural Gambia, shows that pregnant women in this part of the world are at increased risk for malaria, a disease that kills over 1 million people each year. (*The Lancet*, June 3, 2000)

Serious Product Problem? Report It

Health professionals can report serious adverse reactions or other product problems to FDA’s MedWatch program by:

- Mail: Use the postage-paid MedWatch form
- Phone: 1-800-FDA-1088 (1-800-332-1088)
- Fax: 1-800-FDA-0178 (1-800-332-0178)
- Internet: www.fda.gov/medwatch/

Call the 800 number or visit the Website for forms or for further assistance.

FDA encourages consumers to report through their doctors, but if they prefer, they may submit the MedWatch form themselves.



Warning to Parents: *E. coli* and Antibiotics Don't Mix

If your child could be infected with *E. coli* bacteria (found, for example, in raw or undercooked hamburger), get expert medical advice before giving antibiotics, say researchers at the University of Washington School of Medicine. A study found that children with gastrointestinal infections from the *E. coli* O157:H7 strain of bacteria are seven times more likely to develop a potentially fatal kidney disease, hemolytic uremic syndrome (HUS), when given antibiotics. HUS developed in five of the nine children in the study infected with O157:H7 and given antibiotics (56 percent) as compared with five of the 62 children who were infected and not given antibiotics (8 percent). The researchers suspect that antibiotics cause the toxic bacteria to be released from the intestine, making the toxin more available for absorption by the body. Antibiotics should not be given, they add, until a stool culture rules out *E. coli* infection.

FDA reports that up to 15 percent of all people who get hemorrhagic colitis, the acute disease caused by O157:H7, develop HUS, which can lead to permanent kidney failure and death.

Symptoms of *E. coli* O157:H7 bacterial infection include bloody diarrhea, severe abdominal cramps, and dehydration. It can occur a few days after eating bad meat, raw milk, contaminated water, unpasteurized ciders and juices, or tainted produce. (*New England Journal of Medicine*, June 29, 2000)

Pig Ears, Cow Hooves, Other Dried Pet Treats Can Make You Ill

Dogs love them. They're blissfully chewy and delightfully smelly to your pet—but treats made from the leftover parts of food-producing animals can make you and your family very sick.

Pet treats made from the dried ears, hooves, lungs, and bones of pigs and cows have been implicated in *Salmonella* poisoning in humans. In late 1999, Canadian health officials alerted the Food and Drug Administration to more than 35 human cases of *Salmonella* poisoning that occurred in Canada over the past year and were linked to contact with pig ears produced in that country. Some of these illnesses required children to be hospitalized.

"It's alarming to find that number of serious illnesses," says Gloria Dunnavan, the director of the Division of Compliance in FDA's Center for Veterinary Medicine. "We want to make sure there is no *Salmonella* in dried animal parts being sold as pet treats in the United States."

Earlier this year, FDA alerted U.S. distributors of both the suspect Canadian products and U.S.-manufactured dried animal parts. After U.S. retail store Costco tested and found *Salmonella* in samples of Medalist brand pig ears produced in this country, manufacturer Treat Makers L.L.C. recalled the products in May. The recall covers treats sold at Costco stores in 11 states: Washington, Oregon, California, Arizona, New Mexico, Nevada, Utah, Colorado, Idaho, Montana, and Hawaii. The products are packaged in 25-count plastic bags and stamped with lot numbers 07600EXU3 or 08300EX01 on a white sticker on the back of the bag.

In June, another U.S. manufacturer, Products Carousel, Inc., recalled its Pets Carousel 100% Choo-Hooves Pressed Sticks, Item #90010-S because of possible contamination with *Salmonella*. The Pets Carousel products were sold by Petsmart in Ohio and Arizona.

Although no illnesses from these products have been reported in the United States, consumers should handle dried animal parts like they would handle raw meat, according to Dunnavan. In other words, wash your hands with soap and hot water after handling, avoid putting the treats on food contact surfaces (such as kitchen countertops), and don't allow children to touch their mouths after handling until they've washed their hands. Dunnavan also advises consumers not to purchase unpackaged dried treats, which are more likely to be contaminated by *Salmonella*.

While healthy pets rarely become ill from the bacteria, they can become carriers of *Salmonella* and infect humans or other animals. This means that you could become infected if Fido licks your face after chewing a contaminated product.

Salmonella can cause vomiting, diarrhea, fever and stomach cramps in otherwise healthy individuals and can be fatal in young children, the elderly, or people with weakened immune systems.

Consumers may return the recalled Medalist and Pets Carousel products to the store where they purchased them for a full refund. Customers with questions about the recall should call Treat Makers at 1-888-250-7369 or Products Carousel at 1-800-231-3572. FDA continues to work with pet treat manufacturers to investigate the cause of the problem and ways to prevent it in the future.



Reusing Medical Devices

Ensuring Safety The Second Time Around

By Carol Lewis



Orthodontics. Adolescent angst. Two seemingly endless years of contorted expressions that ultimately keep many a teen's mouth clamped shut in a perpetual scowl. Some may regard this behavior as a small price to pay for the rite of passage that braces represent, especially when the impact of the future investment is so dramatic—a set of perfectly straight pearly whites. But for all their misery, let alone their parents' money, at the very least kids deserve a fresh set of braces that haven't been glued onto someone else's teeth first.

It's a thought that would leave a bad taste in anyone's mouth, but under today's economic health-care constraints, and in a disposable society, the medical and dental professions have found that recycling pays.

Until recently, the advent of cheap, modern plastics and the risk of infectious diseases led doctors and dentists to

use a device once and then toss it. It was cheaper, more convenient, and safer. Recycling single-use products became more attractive as devices became more complex, prices went up, and new sterilization methods allowed a wider variety of products to be sterilized. As a result, a new industry sprang up to reprocess medical devices intended for disposal after one use—and with it came some new worries for the Food and Drug Administration. This new industry of third-party reproducers increased FDA's concern for patient safety and raised questions about how to regulate the original manufacturers and reprocessing firms equitably.

The idea of reusing a medical device is not a new one. Decades ago, everything was reused. Medical manufacturers made tools from durable materials like glass, rubber and metal, and early reprocessing of reusable devices, such

as probes and surgical instruments, involved little more than hand wiping, dipping and soaking in a disinfectant, and a trip through the autoclave—a giant pressure cooker that scalded infectious organisms into oblivion. But market demand for disposable equipment and the development of new plastics influenced manufacturers to make and sell single-use devices (SUDs). The practice of reprocessing SUDs expanded when an increasing number of hospitals decided that reuse was a cost-saving measure

and when the amount of medical waste generated by disposable devices became noticeable. If, for example, a cardiac catheter—a tube that snakes its way from the femoral artery in the groin to the coronary arteries of the heart—costs a considerable amount for a single patient, the hospital could cut the cost almost in half by using it on two patients.

Sounds reasonable, but cleaning and sterilizing devices intended for a single use appears to be more difficult than sterilizing old-style devices designed to survive autoclaving. Between August 1996 and December 1999, FDA's Medical Device Reporting (MDR) system documented 245 adverse events associated with the reuse of SUDs, including seven deaths, 72 injuries, 147 malfunctions, and 19 "other" incidents, as reported by manufacturers. The reports listed 70 different types of products, but FDA could not discern a pattern of

failures with reused SUDs that differs from those observed with their initial use.

“When you reuse single-use devices, such as orthodontic products, the risk increases for both infection and product failure,” says Tim Ulatowski, director of FDA’s Division of Dental, Infection Control, and General Hospital Devices. But the MDR reports do not allow an accurate assessment of the failure rates, since device failures in general are underreported. Also, it would be hard to trace infections that may have resulted from improperly reprocessed SUDs back to the reused devices.

“Despite a lack of clear data that suggests that many injuries are occurring due to reprocessing practices,” says David W. Feigal, M.D., director of FDA’s Center for Devices and Radiological Health (CDRH), “FDA has concluded that the practice of reusing single-use devices needs additional attention and regulatory controls.”

In an effort to provide closer oversight of the growing recycling practice, FDA conducted research and developed a new regulatory approach for hospitals and third-party device reprocessors.

First, CDRH implemented a research program to explore the safety and effectiveness of reprocessing SUDs. From that, the center gleaned information on the difficulty of cleaning the devices, the effect of sterilization and resterilization on materials, and changes in device performance. SUDs were examined after one-time use and compared both to devices that had never been used and to those that were reused in simulated laboratory studies. The research turned up several problems, including the loss of elasticity in inflatable balloons, breakdown of products because of repeated use, and loss of original lubricants.

The agency’s current policy requires that a medical device be safe, effective, and manufactured in accordance with a quality control system. If a SUD is prepared for reuse by cleaning, repairing or refurbishing, it is in fact being remanufactured, but until recently SUDs haven’t been subject to the same regula-

tions that original equipment manufacturers are required to follow.

That policy changed in August, when FDA issued a final guidance that requires third-party reprocessors and hospitals to follow the same regulations as those required by original manufacturers. This includes premarket notification and approval requirements, registration and listing of firms, submission of adverse event reports, manufacturing and labeling requirements, tracking of devices, and correcting or removing from the market unsafe medical devices. FDA’s enforcement of the premarket clearance requirements for SUDs will be phased in based on the traditional device

Some Commonly Reprocessed Single-Use Devices

Surgical saw blade

Surgical drill

Surgical stapler

Laparoscopy scissors

Orthodontic (metal) braces

Electrophysiology catheter

Electrosurgical electrodes and pencils

Endotracheal tube

Balloon angioplasty catheter

Biopsy forceps

Umbilical scissors

Gas mask

Ophthalmic knife

Irrigating syringe

Surgical gown

classification scheme (i.e., Class I, II and III, with Class III having the most rigorous premarket requirements). The agency intends to enforce premarket submission requirements within six months for all Class III devices (requiring submission of safety and effectiveness data), within 12 months for all Class II non-exempt devices, and within 18 months for all Class I non-exempt devices. (Manufacturers of Class I and II non-exempt devices need only prove that the device is “substantially equivalent” to one already on the market.) Third-party reprocessors are already subject to enforcement of the other, non-premarket regulatory requirements, and will continue to be under the new guidance. However, FDA intends to phase in enforcement of these non-premarket requirements for hospital reprocessors within the next year, and will use this time to educate hospitals about the requirements.

FDA believes that such a phased-in approach for enforcement of regulatory requirements for third-party and hospital reprocessors is appropriate because:

- The health risk associated with reprocessing SUDs varies with each device.
- It may avoid any unintended and unpredictable consequences, such as potential shortages, in certain hospitals.
- Establishments such as hospitals may be unfamiliar with FDA regulations and a phased-in approach will allow those facilities time to learn about the requirements.
- The agency’s limited resources do not permit immediate enforcement of all regulatory requirements.

FDA stresses, however, that nothing in the new policy, including the phased-in enforcement approach, precludes the agency from taking immediate action against any particular product that is causing harm.

The primary goal of the new policy is to ensure a program for regulating device reprocessing and reuse that is based on good science and that protects the public health, while ensuring that its regulatory requirements are fair to all parties. ■

New Dietary Guidelines

Give Practical Advice for Healthier Living

By Linda Bren

"...Those desiring to lose weight should perform hard work before food. They should take their meals after exertion and while still panting from fatigue...They should, moreover, eat only once a day and take no baths and sleep on a hard bed and walk naked as long as possible."

—Hippocrates, the father of medicine, on his philosophy about dieting

Theories on the weight-loss benefits of walking around naked and not bathing have not proved out, but Hippocrates' other dietary advice isn't completely off the wall. While perhaps not the healthiest advice, Hippocrates' recommendations do show that even 2,400 years ago, the relationship between food intake and energy expenditure was recognized.

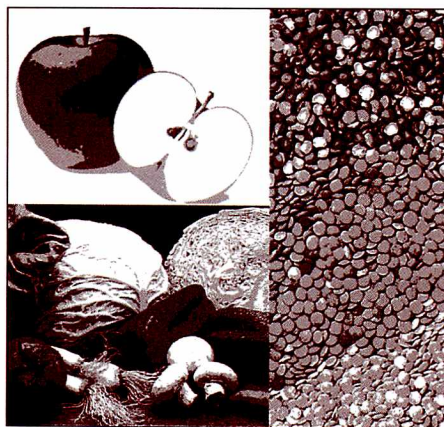
Today, insight into the relationship between eating and exercise still plays a significant role in determining dietary recommendations. The new "Dietary Guidelines for Americans," which President Clinton first announced in his radio address to the nation in the spring, rely on current knowledge about weight, nutrition and physical activity. Calling them the "gold standard of nutritional information," Clinton said the guidelines are part of the federal government's efforts to "empower Americans with the latest and best information on food and nutrition."

The President's speech kicked off the release of the new dietary guidelines, the 5th edition, at the National Nutrition Summit held in Washington, D.C., on May 30 and 31. The first national nutrition meeting in more than 30 years, the summit was co-sponsored by the two federal departments that produced the guidelines: the Department of Health and Human Services and the Department of Agriculture.

DHHS Secretary Donna E. Shalala, Ph.D., said the new guidelines "offer

more practical advice and scientific information than ever before to help American consumers make the smartest possible decisions when it comes to what we eat."

The Food and Drug Administration is a major user of the guidelines, according to Elizabeth Yetley, Ph.D., lead scientist in FDA's Center for Food Safety and Applied Nutrition. "We use them to address food labeling issues as well as to develop FDA's nutrition policies and guidelines."



The guidelines give 10 recommendations, compared to seven in past editions. For ease of understanding, the recommendations are grouped within three areas that the guidelines call the ABCs of good health:

- Aim for fitness
- Build a healthy base, and
- Choose sensibly.

The new guidelines place more emphasis than in previous editions on being physically active and maintaining a healthy weight. At the nutrition summit, Shalala stated that nearly 55 percent of all adults and 10 percent of all children in America are overweight. Being overweight increases a person's risk for many chronic conditions and diseases, including heart disease, stroke, diabetes, arthritis, breathing problems, high blood pressure, and certain types of cancer.

The current guidelines contain a Body Mass Index (BMI) chart, which replaces the weight-for-height chart found in pre-

vious editions. A calculation based on weight and height, BMI is used by health professionals to help determine if a patient is overweight, obese, or at a healthy weight.

For the first time ever, the guidelines address food safety, particularly the need to store and prepare foods safely in the home. FDA works in concert with USDA and other federal agencies to combat foodborne illness, an important public health concern.

As in previous editions, the guidelines continue to emphasize balance, moderation, and variety in food choices. They recommend eating whole grains, fruits and vegetables, and choosing a diet low in saturated fat, cholesterol and salt. They also advise moderating sugar and total fat intake. The guidelines give specific examples of foods that provide certain nutrients, and include choices for vegetarians.

First published in 1980 and revised every five years by law, the guidelines are based on the recommendations of a scientific advisory group of 11 non-government experts. The guidelines are used by federal agencies to determine, among other things, standards for the nutritional content of the lunches served every day in school to 26 million children.

The dietary guidelines give consumers the information they need to select the right kinds and amounts of food. But, ultimately, it is up to consumers to take action and follow the guidelines' advice. "Government can shine the spotlight and direct resources to solving the problems of obesity and poor nutrition," says USDA Secretary Daniel Glickman, "but only individuals can commit themselves to good nutrition and good health."

Consumers can download the "Dietary Guidelines for Americans" from the Internet at www.health.gov/dietaryguidelines. For a printed copy, send your name, address and 50 cents by check or money order to: Consumer Information Center, Department 378-C, Pueblo, CO 81009. ■

Precision In Public Health Protection

A Woman's Life's Work In Radiation

By Linda Bren

You sit tensely in the dentist's chair, trying not to flinch as the technician points the x-ray machine at your cheek. You may be thinking root canal, or periodontal disease, or worse. You're worrying about the possible pain and assured expense about to befall you, but chances are you aren't worrying about the danger of radiation from the x-ray machine. And for that piece of mind, you have Elizabeth Rodgers to thank.

Rodgers is one of three technicians in the Food and Drug Administration's Center for Devices and Radiological Health who calibrate the equipment used to test medical and dental x-ray machines throughout the United States for compliance with federal regulations. It's this exacting calibration and mathematical precision that help protect patients from overexposure to radiation.

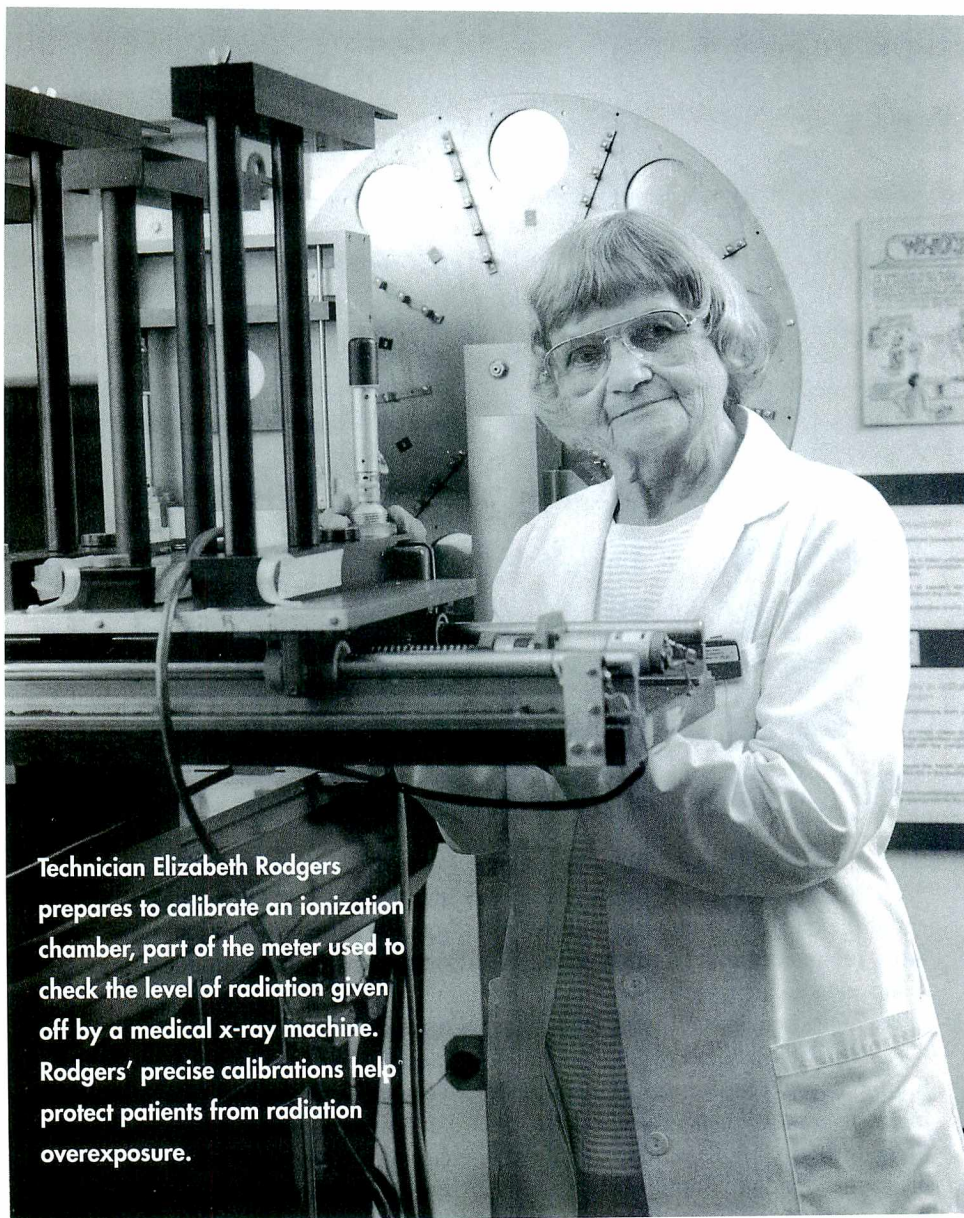
Radiation has always been a part of Rodgers' 37-year federal career—and it's been a large part of her life.

* * *

The year is 1951. In the barren Nevada desert, atomic energy explodes into the sky. A plume of black smoke drifts through the air for hundreds of miles, raining down toxic radioactive dust onto the land and into the streams.

Thirteen years later, Rodgers hunches over columns of numbers, tallying the cases of thyroid cancer in Utah residents. These victims were downwind of the Nevada Test Site, where more than 100 nuclear weapons were detonated between 1951 and 1962. No one knew at the time that these tests would contaminate the food supply and cause a potentially fatal disease.

"We've come a long way since then," says Rodgers, who also remembers the



Technician Elizabeth Rodgers prepares to calibrate an ionization chamber, part of the meter used to check the level of radiation given off by a medical x-ray machine. Rodgers' precise calibrations help protect patients from radiation overexposure.

days when radiation from x-ray machines was considered harmless. She recalls walking into a shoe store that had one of the x-ray machines used for shoe-fitting that were a common sight in the late 1940s and early 1950s. Rodgers thought it was exciting to slip her feet clad in new shoes under the x-ray machine to "see the bones."

Rodgers' career has taught her how radiation can both kill and save lives. Overexposure—whether from an atomic explosion or an x-ray machine—can be

deadly, but the right amount of x-ray radiation can be crucial for locating tumors, broken bones, and other malformations. The correct dose of radiation can eradicate cancer, but excessive radiation can cause it.

Rodgers has first-hand experience with the radiation-cancer connection. She developed thyroid cancer 20 years after working as a technician in a chiropractor's office. "The chiropractor had me stay in the room at the same time the x-ray was taken to make sure



Shoe-fitting x-ray units were a common sales promotion novelty in shoe stores in the late 1940s and early 1950s. Radiation aimed at the foot revealed the bone structure, which was viewed through the ports at the top of the cabinet. The units were later discontinued when their radiation hazards became known.

the patient didn't move," Rodgers says. "At that time, they didn't know much about the dangers of x-ray radiation." After removal of part of her thyroid gland and treatment with the right amount of radiation, her cancer is gone now.

Rodgers went from keeping ledgers of thyroid cancer cases in an office to reading instrument gauges in a laboratory. Since the early 1970s, it has been the job of Rodgers and the Public Health Service bureau that became FDA's Center for Devices and Radiological Health to protect patients from the diseases caused by over-irradiation from x-ray machines. And, today, the 70 percent of Americans who get a medical or dental x-ray each year are protected from dangerous levels of radiation because of Rodgers' exacting calibrations.

By law, each x-ray machine must conform to FDA performance standards. A large sample of all the installed machines is inspected and tested annually to assure safety and reliability. Inspectors

in all 50 states and the territories of Puerto Rico and Guam rely on Rodgers to furnish them with accurately calibrated instruments and the supplies they need to inspect and test the machines. She controls an inventory of over 2,000 pieces of equipment from her workstation in Rockville, Md.

"Any time they have a problem with equipment, they call Elizabeth," says Frank Cerra, acting chief of the Radiation Metrology Branch and Rodgers' supervisor. "She gives them what they need and does it in an efficient way. She is very good in dealing with people."

Ed Gloor can attest to that. As an x-ray inspection program quality assurance coordinator at the California Department of Health in Sacramento, Gloor has dealt with Rodgers for 20 years. "She's my lifeline," he says. "Calibration testing of x-ray equipment is very important. If we issue a cease-and-desist order that shuts a facility down because the x-ray equipment appears to be out of

compliance—and we later find out it's our error due to defective test equipment—patient care suffers, the facility loses revenue, and litigation may result."

When she started working in FDA's calibration laboratory nearly 30 years ago, Rodgers supplied about 60 inspectors with equipment. "Now there are 236 just to inspect the mammography machines," she says. Under the Mammography Quality Standards Act of 1992, FDA regulates and annually inspects all mammography facilities in the United States. Since the inspection program began in 1995, nearly 50,000 inspections have been conducted, and Rodgers has been responsible for making sure each inspector had an accurately calibrated radiation meter when needed.

John L. McCrohan Jr., director of FDA's Division of Mammography Quality and Radiation Programs, stresses the importance of Rodgers' relationship with inspectors. "She's on the front line interfacing with them when they have a problem. She handles emergencies, and when a piece of equipment doesn't work, she makes sure a replacement is delivered overnight." Rodgers' dedication earned her an award this spring for meritorious service from the Conference of Radiation Control Program Directors, an organization that promotes the highest standards of quality in radiation protection.

"Danger" and "high voltage" signs plaster the walls of the laboratory where the 5-foot-1-inch Rodgers hoists, mounts, and hauls around heavy test equipment. She has a lot of work to finish up before her "extended vacation" of two weeks. "I've never taken two whole weeks off before," she says. She confesses she is giving out her phone number at the beach where she is vacationing, and where she also plans to spend more time when she retires this year at the age of 78.

This is sad news for Charles Ditmer, an environmental health manager at the Bureau of Radiological Health in South Carolina. "We grew up with Ms. Rodgers," Ditmer says, speaking for himself and his fellow inspectors. "She is the one person we can always count on. They won't find anybody to fill her shoes." ■

MAKE NO MISTAKE!



Medical Errors Can Be Deadly Serious

By Tamar Nordenberg

Two months after a double bypass heart operation that was supposed to save his life, comedian and former Saturday Night Live cast member Dana Carvey got some disheartening news: the cardiac surgeon had bypassed the wrong artery. It took another emergency operation to clear the blockage that was threatening to kill the 45-year-old funnyman and father of two young kids.

Responding to a \$7.5 million lawsuit Carvey brought against him, the surgeon said he'd made an honest mistake because Carvey's artery was unusually situated in his heart. But Carvey didn't see it that way: "It's like removing the wrong kidney. It's that big a mistake," the entertainer told *People* magazine.

Based on a recent report on medical mistakes from the National Academy of Sciences' Institute of Medicine, Carvey might fairly be characterized as one of the lucky survivors. In its report, *To Err Is Human: Building a Safer Health System*, the IOM estimates that 44,000 to 98,000 Americans die each year not from the medical conditions they

edge. People in the hospital are just a small proportion of those at risk. Doctors' offices, clinics, and outpatient surgical centers treat thousands of patients each day; retail pharmacies fill countless prescriptions; and nursing homes and other institutional settings serve vulnerable patient populations.

Despite the recent focus on the IOM statistics, experts assure that the health system in the United States is safe. But its safety record is a far cry from the enviable record of the similarly complex aviation industry, which is being held up as an example for the medical world. A person would have to fly nonstop for 438 years before expecting to be in-

tive, to how they'll be used in the real world."

Medication Mistakes

Even the seemingly simple process of giving a patient medicine—the right drug, in the right dose, to the right patient, at the right time—is, in reality, teeming with opportunities for error. The IOM estimates that preventable medication errors result in more than 7,000 deaths each year in hospitals alone, and tens of thousands more in outpatient facilities. (See "Most-Made Mistakes" on page 18.)

Name confusion is among the most common causes of drug-related errors,

Medical errors have been ranked as the eighth leading cause of death among Americans.

checked in with, but from preventable medical errors.

A medical error, under the report's definition, could mean a health-care provider chose an inappropriate method of care, such as giving a patient a certain asthma drug without knowing that he or she was allergic to it. Or it could mean the health provider chose the right course of care but carried it out incorrectly, such as intending to infuse a patient with diluted potassium chloride—a potassium supplement—but inadvertently giving the patient a concentrated, lethal overdose.

The Institute of Medicine (IOM) estimates that fully half of adverse reactions to medicines are the result of medical errors. Other adverse reactions—those that are unexpected and not preventable—are not considered errors. (See "When Is a Medical Product Too Risky?" in the September-October 1999 *FDA Consumer*.)

The statistics in the IOM report, which were based on two large studies, suggest that medical errors are the eighth leading cause of death among Americans, with error-caused deaths each year in hospitals alone exceeding those from motor vehicle accidents (43,458), breast cancer (42,297), or AIDS (16,516).

But the numbers in the report don't tell the whole story, its authors acknowl-

ed in a deadly airplane crash, based on recent airline accident statistics. That, IOM says, places health-care at least a decade behind aviation in safeguarding consumers' lives and health.

The report is a self-described "call to action" for the health-care system. "Whether a person is sick or just trying to stay healthy, he or she should not have to worry about being harmed by the health system itself," its authors say.

In response to IOM's call, President Clinton has proposed a plan to halve the number of medical errors over five years. "If we do the right things," President Clinton said while announcing the White House plan, "we can dramatically reduce the times when the wrong drug is dispensed, a blood transfusion is mismatched, or a surgery goes awry."

Clinton's plan includes the creation of a new Center for Quality Improvement in Patient Safety, with a \$20 million budget, and the installation of patient safety programs to reduce medical errors in each of the 6,000 hospitals participating in Medicare.

For its part, the Food and Drug Administration will take a "much-enhanced" role in error prevention, says Janet Woodcock, M.D., the head of FDA's Center for Drug Evaluation and Research. "We'll be taking a much harder look at medical products—beyond just whether they're safe and effec-

says Peter Honig, M.D., an FDA expert on drug risk-assessment. A recent example: the sound-alike names for the antiepileptic drug Lamictal and the antifungal drug Lamisil. The volume of dispensing errors involving these two drugs prompted the manufacturer of Lamictal, Glaxo Wellcome Inc. of Research Triangle Park, N.C., to launch a campaign warning pharmacists of the potential confusion. The possible consequences of prescribing the wrong drug are grave: Epileptic patients receiving the antifungal drug Lamisil by mistake could experience continuous seizures. Patients erroneously receiving the antiepileptic drug Lamictal might experience a serious rash, blood pressure changes, or other side effects.

Errors also have occurred in prescribing the arthritis drug Celebrex, the anti-convulsant Cerebyx, and the antidepressant Celexa. There have been well over 100 reports of confusion among the three drugs, none of which has resulted in serious harm to a patient.

In one case, a physician wrote a prescription for "Celexa 200 mg." Since the antidepressant drug is available in only 20 and 40 milligram doses, the doctor was called, and he corrected his prescription to the intended Celebrex 200 mg. In response to such reports, the co-marketers of Celebrex, G.D. Searle & Co., Chicago, Ill., and Pfizer Inc., New

York, have undertaken an educational ad campaign to alert health professionals to the possible mix-ups.

Under FDA's authority to regulate drug labeling, the agency's new Office of Postmarketing Drug Risk Assessment evaluates medicines' brand names in an attempt to avoid sound-alike and look-alike names. If FDA considers the name of a new medical product to be potentially confusing to health professionals, the agency works with the drug company to change the product's name. FDA is developing new standards to prevent such name mix-ups, as well as to prevent confusion between similar-looking drug packaging.

Also, the agency is developing new label standards to highlight common interactions between drugs so that doctors

are less likely to mistakenly prescribe dangerous combinations. And even after a drug is approved, FDA monitors its use to see if unexpected adverse events occur and whether any labeling changes are required to help avoid medication mishaps.

So where does FDA's responsibility end and the health professionals' judgment take over? "FDA must do everything within its authority to maximize the likelihood that approved products will be used correctly in the real world," says Honig. But, he notes, "We don't regulate the practice of medicine, such as the sloppy handwriting when prescribing a drug."

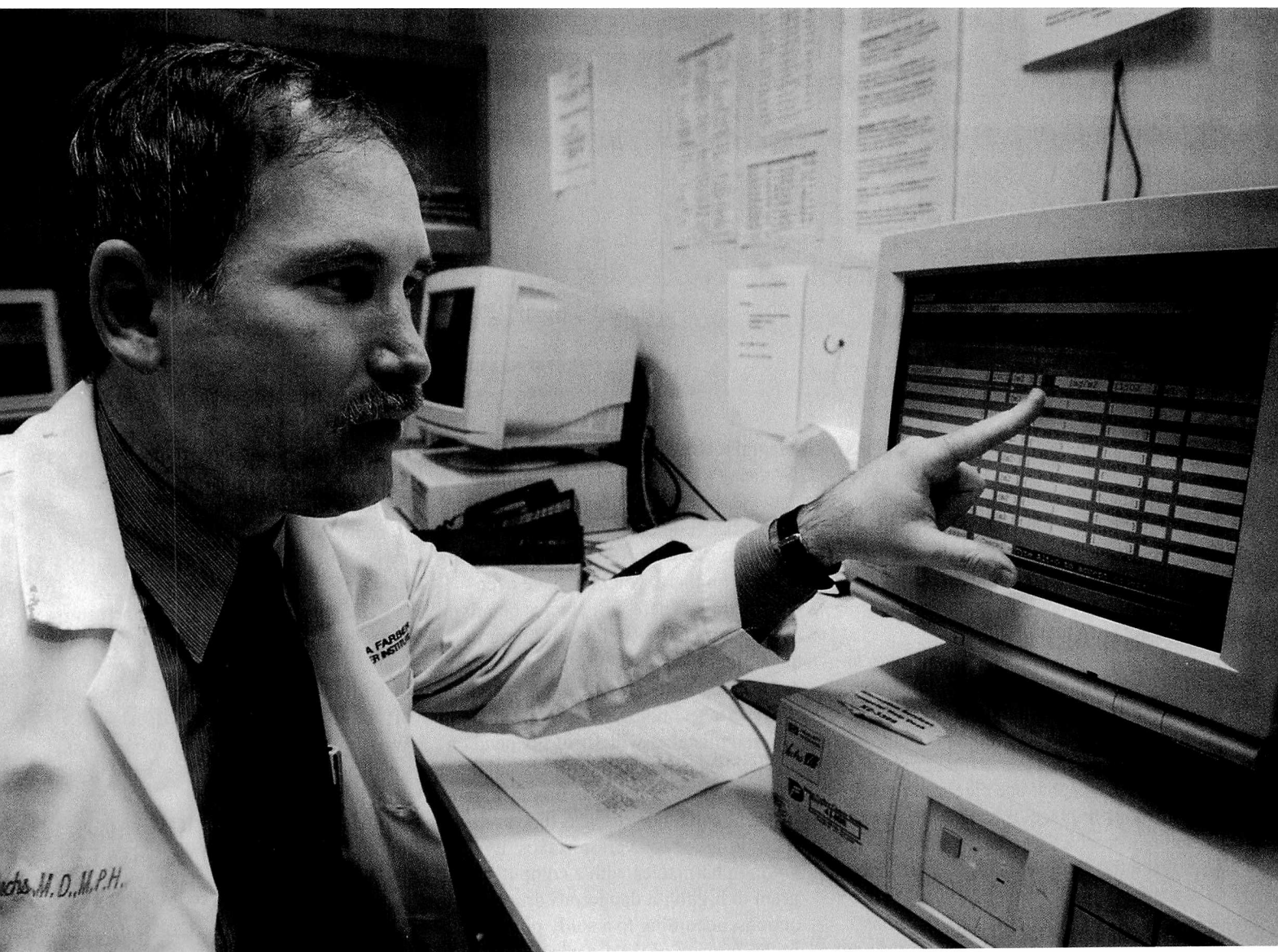
The real-world practice of medicine occurs within an intricate system, says Woodcock. "It's that complexity," she

says, "coupled with the limitations of humans, that makes avoiding mistakes a consuming task."

Human Limitations

As its title—*To Err Is Human*—suggests, the IOM report supports moving away from the traditional culture of "naming, shaming, and blaming" individual health providers who make mistakes. Instead, the institute believes that preventing future errors is best achieved by designing a safer overall system.

Woodcock supports that view. Most health-care practitioners are competent professionals who are vulnerable to error simply by virtue of being human, she says. The professionalism model—"If we train people enough, they won't make a mistake, and we'll punish them



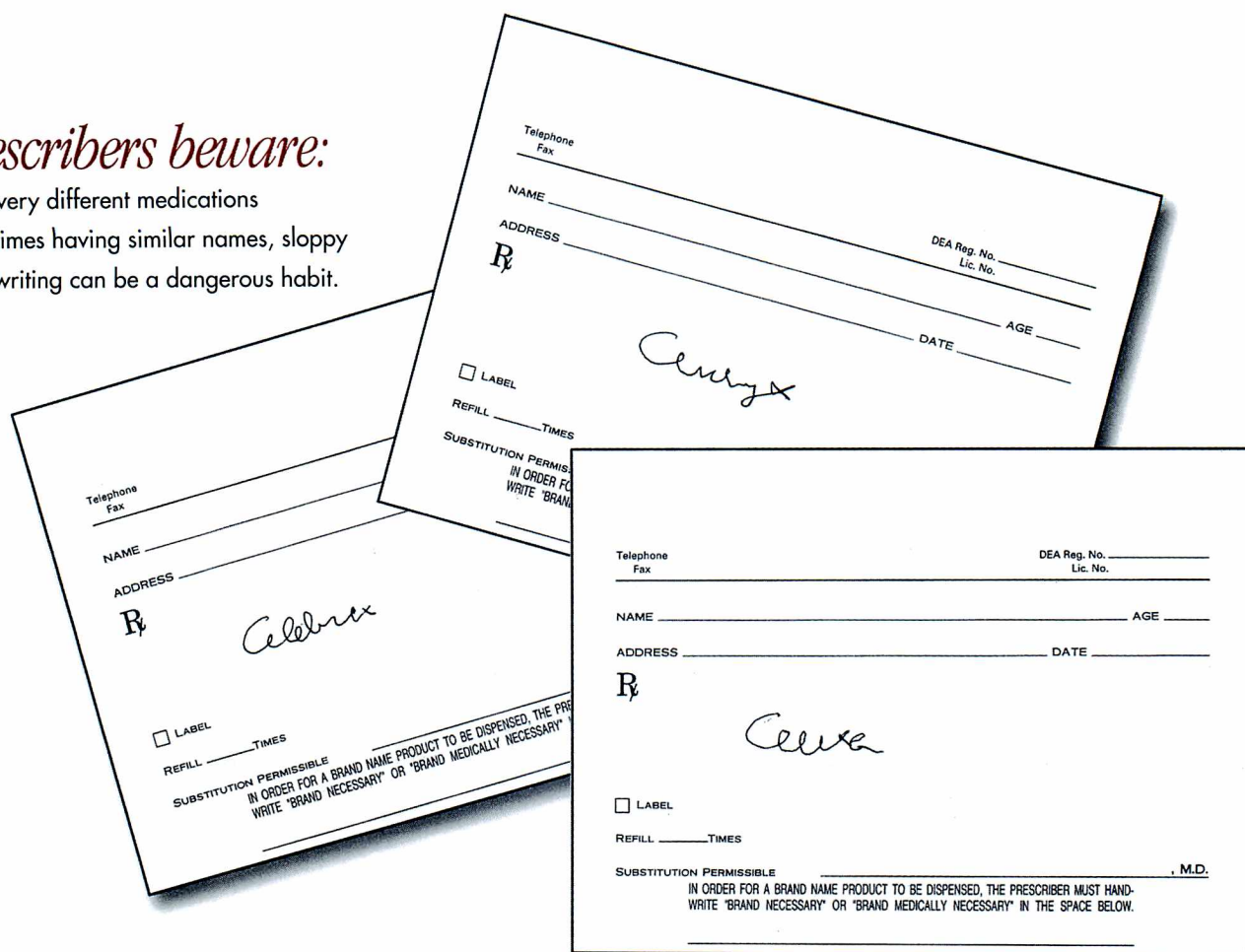
Even a simple computer system can provide a lifesaving check of doctors' prescribed treatments.

Photograph by Steven Gilbert, StudioFlex Productions

Name confusion is among the most common causes of drug-related errors.

Prescribers beware:

With very different medications sometimes having similar names, sloppy handwriting can be a dangerous habit.



if they do”—has outlived its usefulness, according to Woodcock. “People have made mistakes and been drummed out of their professions. They were the ones unfortunate enough to administer the lethal dose, but the systems were not in place to adequately support them in preventing such an error.”

Some medical centers have begun using computer programs and other system supports to curtail medical mishaps by double-checking the care decisions doctors and nurses make. Even simple computer systems that use electronic prescriptions in place of handwritten ones have in some cases already paid off with substantial error reductions. (See “Lessons Learned,” on page 17.)

But systems, too, can fail, cautions Raymond L. Woosley, M.D., a professor and chairman of pharmacology at

Georgetown University Medical Center. Woosley’s example: “It’s true that if you have a prescription drug with an electronic bar code on it—the right code—it can help prevent errors. But if the wrong code is on there, you may have even more errors. There will always be mistakes, though they will be different mistakes as the systems change. You’ve got to be ready to handle them.”

Despite technological advances, preventing mistakes will always depend on the vigilance of health professionals, Woosley says. Otherwise, human carelessness can render useless the very systems designed to avert mistakes. Even among pharmacies with a computer program to highlight dangerous drug interactions, according to a study published in the *Journal of the American Medical Association*, one-third of pharmacists

nevertheless continued to fill prescriptions for a known killer combination: the prescription antihistamine Seldane (terfenadine) with the antibiotic erythromycin. (Seldane has since been removed from the market.)

“The pharmacists would get the computer warnings and zip right on by them,” Woosley says. “Or they would turn off the program entirely.” Why turn off the computer program? Because, Woosley explains, it was slowing down the pharmacists when they wanted to print labels.

Health professionals “are trained to memorize everything and are rewarded for it,” says the pharmacology professor. “The medical student who says, ‘I don’t know; I’ve got to look it up’ is likely to fail an exam, yet that’s the one who is less likely to make an er-

Lessons Learned

Nineteenth-century essayist William Ellery Channing defined error as “the discipline through which we advance.” Some medical institutions have turned tragic patient safety failures into life-saving lessons.

Department of Veterans Affairs

The VA health-care system is held up in the Institute of Medicine’s report on medical errors as a shining success story. The VA has the largest health-care system in the country, by one estimate serving more than 3 million veterans a year at its 172 hospitals and its 1,000-plus outpatient clinics, nursing homes, counseling centers, and other health programs.

The VA counted almost 3,000 errors—some 700 deaths among them—within its health network between June 1997 and December 1998.

Among the major steps the VA has taken to improve its safety record is a new bar-coding system to prevent and track medical errors. Generally, the bar-coding system works this way: ID strips are worn by nurses and patients and attached to medications. Before giving a patient a drug, a nurse scans all three ID strips into a computer, which verifies that the drug is being given correctly and will not cause drug interactions. If the program identifies a potential problem, it flashes a warning. Otherwise, it just

keeps a record of the activity.

In a test of the bar-coding technology at two VA hospitals in Kansas, the medication error rate dropped 70 percent over a five-year period.

Other changes at VA facilities include:

- Storing concentrated potassium chloride and other such hazardous medications away from patient care areas, and
- Encouraging cooperation and a focus on correcting the system rather than placing blame on individuals unless they perform negligently or incompetently.

Dana-Farber Cancer Institute

In November 1994, two women got poisonous doses of chemotherapy while being treated for recurrent breast cancer at the prestigious Dana-Farber Cancer Institute in Boston. Boston Globe medical reporter Betsy Lehman, age 39 at the time, died as a result of the error, and the second patient, Maureen Bateman, suffered permanent heart damage and died from cancer several months after the mistake.

Instead of prescribing the daily dose of the powerful anticancer drug cyclophosphamide to be given on each of four days, as planned, the doctor ordered the drug’s combined four-day dose so that the total was given to the patients each day.

Since the fatal miscommunication, Dana-Farber has updated its systems to avoid errors. For one thing, the institute

has installed a \$1.7 million computer system to take over many tasks. Doctors don’t hand-write prescriptions anymore, but instead fill out an electronic form with the patient’s personal information, as well as the name of the drug, the dose, and the number of days for which the medicine is to be given. The information goes into the institute’s computer system, which compares the information with upper dose limits for the drug and other pre-programmed guidelines. If the doctor seems to have made a mistake, the computer signals the error.

Secondly, a nurse checks the information in the computer before ordering the drug from the pharmacy. The pharmacist conducts yet another computerized review for potential drug interactions with other drugs, foods, or the patient’s allergies.

After being prepared at the pharmacy, the drug goes next to the nurses’ station, where two nurses check the drug’s label and the patient’s wristband to make sure the right person gets the drug.

Additionally, the cancer center began a system of non-punitive error reporting to encourage open discussion of medical mistakes. The change effectively brought about what the institute has described as a “dramatic increase” in error reporting. ■

—T.N.

ror.” Woosley hopes medical students will be taught to accept their limitations and admit their mistakes. Under the current system, however, some people call that goal pie-in-the-sky.

Culture of Secrecy

Neonatologist Margaret Donahue, M.D., says the fear of being sued suppresses discussions about medical errors. “Even if a procedure is done with the best intention and skill, and it doesn’t turn out the way it was supposed to, the doctor often still ends up having to pay the patient a huge settlement. It’s

that culture—the feeling they’re going to lose no matter what they do—that keeps physicians closed among themselves.”

Historically, people have looked for someone to blame when medical accidents happen, according to FDA’s Woodcock. For victims and their relatives, she says, there may be some satisfaction in that. But from the perspective of fixing the problem, the secrecy that results keeps the medical community from learning what happened and how to correct the problem.

Most experts agree that mandating medical error reporting, in itself, will not

surmount the hesitancy of doctors. More than 20 states currently have mandatory reporting systems, yet state officials say that underreporting persists.

FDA, too, faces the problem of “tremendous underreporting,” according to Susan Gardner, Ph.D., deputy director of the Office of Surveillance and Biometrics in the agency’s Center for Devices and Radiological Health.

Hospitals, nursing homes, and other facilities that use medical devices are required to report to FDA all deaths caused or possibly caused by devices. “Guess what? They don’t report,”

“It’s unfortunate that people research buying a car better than they research health-care decisions.”

—Peter Honig, M.D., FDA risk-assessment expert

says Gardner, whose office gets only about 4,000 reports a year from the 40,000 to 50,000 facilities covered by the reporting requirement.

Gardner thinks that simply assuring facilities of confidentiality of reports could go far to increase compliance with the reporting requirement. “If you give incentives to report, they’ll report. In many cases, that might simply mean good feedback so they can improve their systems.” A published list of previously reported device problems in FDA’s database, Gardner says, would enable facilities to benchmark their own experiences. Newsletters could discuss important medical device issues. And strategies could be suggested to avoid potential pitfalls in using a medical device.

With devices, more than with drugs, it can be difficult to determine if an adverse event was a preventable error or an unexpected reaction, Gardner says. Devices sometimes require specific knowledge and training to use the product correctly.

It’s the interface between the device and the user, referred to as “human factors,” that can complicate an investigation into why something went wrong. The problem usually isn’t that the device itself broke, Gardner says, but rather that it wasn’t intuitively user-friendly, or the user didn’t have instruc-

tions on hand or didn’t know about a change in the way the device was to be used in a certain setting.

In the agency’s Center for Biologics Evaluation and Research, the lack of reporting is characterized by consumer safety officer Sharon O’Callaghan as one of the biggest problems where medical errors are concerned. She says that while manufacturers of biological products, such as blood components and vaccines, must report to FDA certain errors that occur during manufacturing, companies are not sufficiently aware of reporting requirements.

For biological products, manufacturing errors can lead to mistakes in treatment that are potentially serious and even deadly. In blood banks, for example, a blood product that is mislabeled can present a serious threat to a patient if the wrong type of blood is transfused.

“Things happen that we might not hear about,” O’Callaghan says. “We want to increase reporting so we can assess what’s happening in the industry.” To increase reporting of manufacturing glitches, the agency has proposed a rule that would increase the number of facilities that must report errors and other adverse events.

Clinton’s proposal to reduce medical errors contains a nationwide, state-based system of reporting medical errors that

would include mandatory reporting of mistakes that result in death or serious injury and voluntary reporting of other medical mistakes, including so-called “close calls” or “near misses.” Clinton also expressed support for legislation that protects provider and patient confidentiality, while safeguarding the legal remedies of those whose health is harmed.

To Improve Is Human

Woodcock encourages consumers to help prevent errors by being vigilant about their health-care—understanding their treatment, keeping organized records of what doctors they see and what medications they take, and asking questions when things don’t seem right. For example, “If your pills look different than they have in the past, they might be the right medication, and they might not. But raise the issue.”

Honig calls consumer education the “secret weapon” in the war against medical errors. “It’s unfortunate that people research buying a car better than they research health-care decisions. They’re willing to tolerate more uncertainty with their health-care than their mode of transportation.” He encourages patients to feel comfortable asking more questions about their medical care.

With everyone from pharmaceutical manufacturers to consumers playing a role in improving the safety of the health system, Woodcock believes that the already “very safe” medical system in the United States will become even safer. “There are fixes,” she says. “We know that from other industries.”

The spotlight on the health system’s problems might be just what the system needed to transform itself, says Woodcock. After all, as the IOM report notes, “It may be part of human nature to err, but it is also part of human nature to create solutions, find better alternatives, and meet the challenges ahead.” ■

Tamar Nordenberg is a staff writer for FDA Consumer.

Most-Made Mistakes

The American Hospital Association lists these as some common types of medication errors:

- **Incomplete patient information** (not knowing about patients’ allergies, other medicines they are taking, previous diagnoses, and lab results, for example)
- **Unavailable drug information** (such as lack of up-to-date warnings)
- **Miscommunication of drug orders**, which can involve poor handwriting, confusion between drugs with similar names, misuse of zeroes and decimal points, confusion of metric and other dosing units, and inappropriate abbreviations
- **Lack of appropriate labeling** as a drug is prepared and repackaged into smaller units
- **Environmental factors**, such as lighting, heat, noise, and interruptions, that can distract health professionals from their medical tasks ■

—T.N.

HUMAN GENE THERAPY

By Larry Thompson

Harsh Lessons, High Hopes



Ashanti DeSilva (on bed), then 4 years old, receives her own genetically treated white blood cells from NIH researcher Kenneth W. Culver, M.D., while study leaders W. French Anderson, M.D., and R. Michael Blaese, M.D., watch the proceedings with an unidentified nurse. The pioneering treatment took place in the NIH Clinical Center on Sept. 14, 1990.



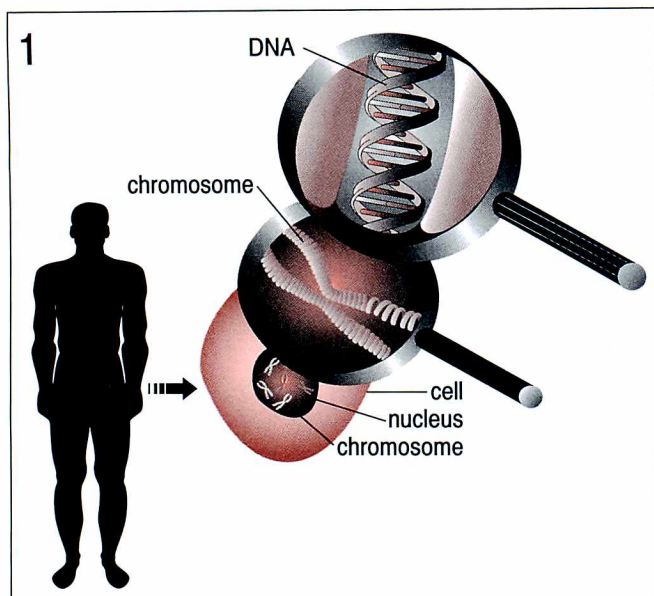
four-year-old girl named Ashanthi DeSilva from the suburbs of Cleveland lay on crisp white hospital

sheets with a needle stuck in a vein. She didn't mind; this happened all the time in her chronically sick childhood. At the other end of the intravenous hookup hung a clear plastic bag of very special cells: her own white blood cells, genetically altered to fix a defect she inherited at birth.

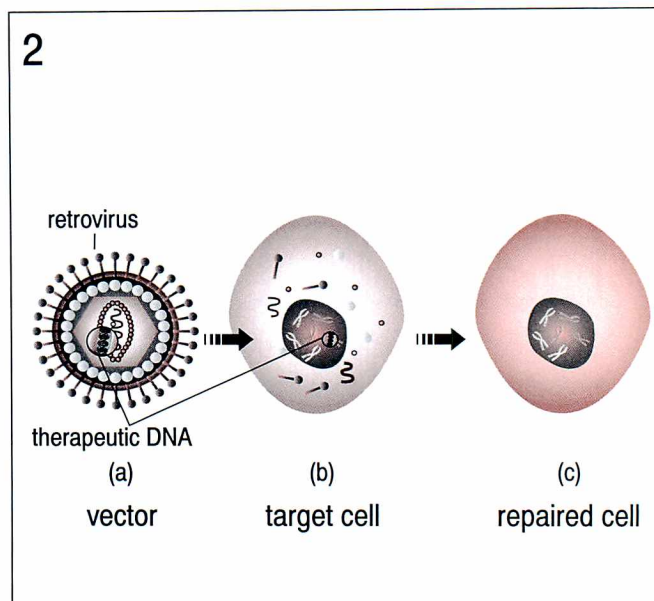
A strikingly thin middle-aged doctor stared anxiously at the tiny figure. W. French Anderson, M.D., and his colleagues R. Michael Blaese, M.D., and Kenneth Culver, M.D., all then working at the National Institutes of Health, crossed a symbolic threshold with Ashanthi DeSilva that day, becoming the first group to begin a clinical trial in the new frontier of medical treatment: human gene therapy.

See related commentary in The Last Word, page 40

Fundamentals Of Gene Therapy



You look a little like your mother and a little like your father because of the genes they gave to you. Genes, those conceptual units composed of deoxyribonucleic acid—DNA, carry the information needed to make proteins, the building blocks of our bodies. The body buries genes deep in the heart of every cell, the nucleus, and organizes them in the chromosomes that hold the DNA. But when your DNA is damaged, it no longer makes all the needed proteins and disease results.



To reverse disease caused by genetic damage, researchers isolate normal DNA and package it into a vector (a), a molecular delivery truck usually made from a disabled virus. Doctors then infect a target cell (b)—usually from a tissue affected by the illness, such as liver or lung cells—with the vector. The vector unloads its DNA cargo, which then begins producing the missing protein and restores the cell to normal (c).

The reason for the excitement was simple: Most diseases have a genetic component and gene therapy holds the hope of curing, not merely treating, a broad range of ailments, including inherited diseases like cystic fibrosis and even chronic conditions like cancer and infectious diseases like AIDS.

At least, that's the theory.

In the 10 years since that first genetic treatment on Sept. 14, 1990, the hyperbole has exceeded the results. Worldwide, researchers launched more than 400 clinical trials to test gene therapy against a wide array of illnesses. Surprisingly, cancer has dominated the re-

search. Even more surprising, little has worked.

"There was initially a great burst of enthusiasm that lasted three, four years where a couple of hundred trials got started all over the world," says Anderson, now at the University of Southern California in Los Angeles. "Then we came to realize that nothing was really working at the clinical level."

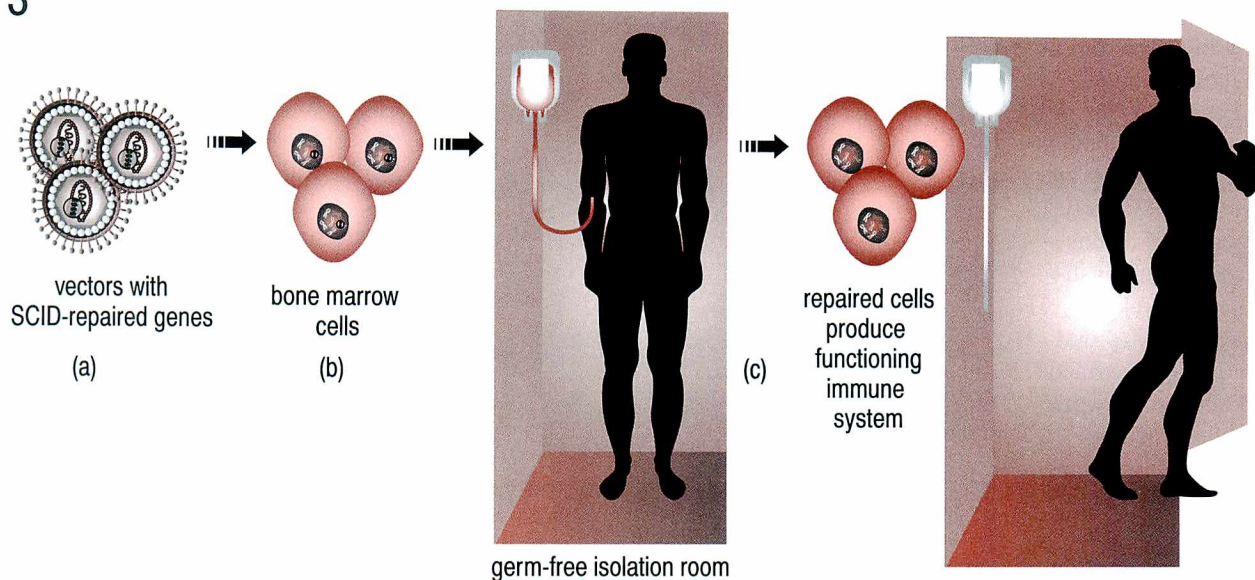
Abbey S. Meyers, president of the National Organization for Rare Disorders Inc., an umbrella organization of patients' groups, is much more blunt. "We haven't even taken one baby step beyond that first clinical experiment,"

Meyers says. "It has hardly gotten anywhere. Over the last 10 years, I have been very disappointed."

And then things got worse.

In September 1999, a patient died from a reaction to a gene therapy treatment at the University of Pennsylvania's Institute of Human Gene Therapy in Philadelphia. Jesse Gelsinger, an exuberant 18-year-old from Tucson, Arizona, suffered from a broken gene that causes one of those puzzling metabolic diseases of genetic medicine. An optimistic, altruistic Gelsinger went to Philadelphia to help advance the science that might eventually cure his type of illness.

3



Infographic by Renée Gordon

Recently, French researchers reported dramatic results in treating a disease called severe combined immune deficiency (SCID), the disorder suffered by David, The Boy in the Bubble. A broken gene eliminates the production of an enzyme essential for the development of a normal immune system. Scientists isolated the normal copy of the gene and packaged it into a vector (a). In the laboratory, they then used the vector to transport the gene into the patient's own bone marrow cells (b). Bone marrow cells create the immune system. The treated bone marrow cells are then given back to the patient (c) where they reconstitute a normal, functioning immune system, freeing the patient from the need to remain in isolation.

Instead, the experiment killed him.

In the aftermath of his death, there has been a flurry of activity to minimize the chance of future accidental deaths. The Food and Drug Administration, along with the National Institutes of Health, launched several investigations of the University of Pennsylvania studies and others. The inquiries provided disappointing news: Gene therapy researchers were not following all of the federal rules requiring them to report unexpected adverse events associated with the gene therapy trials; worse, some scientists were asking that problems not be made public. And then came the alle-

gations that there were other unreported deaths attributed to genetic treatments, at least six in all.

"Probably the clearest evidence of the system [to protect research subjects] not working is that only 35 to 37 of 970 serious adverse events from [a common type of gene therapy trial] were reported to the NIH" as required, says LeRoy Walters, the recently retired head of the Kennedy Institute of Ethics at Georgetown University and former chairman of NIH's Recombinant DNA Advisory Committee. "That is fewer than 5 percent of the serious adverse events."

The news hit the clinical trial commu-

nity like a thunderclap. The consequences have been immediate and wide-ranging, and may threaten future research.

"Participation in gene therapy trials is way down because the public is not sure what to make of this," says Philip Noguchi, M.D., director of the Cellular and Genetic Therapy Division in FDA's Center for Biologic Evaluation and Research (CBER). "They want to know what the government is doing to help restore the confidence in this field."

Responding to the Crisis

The federal government moved

“You can’t be sloppy when you are dealing with a human. Everything matters.”

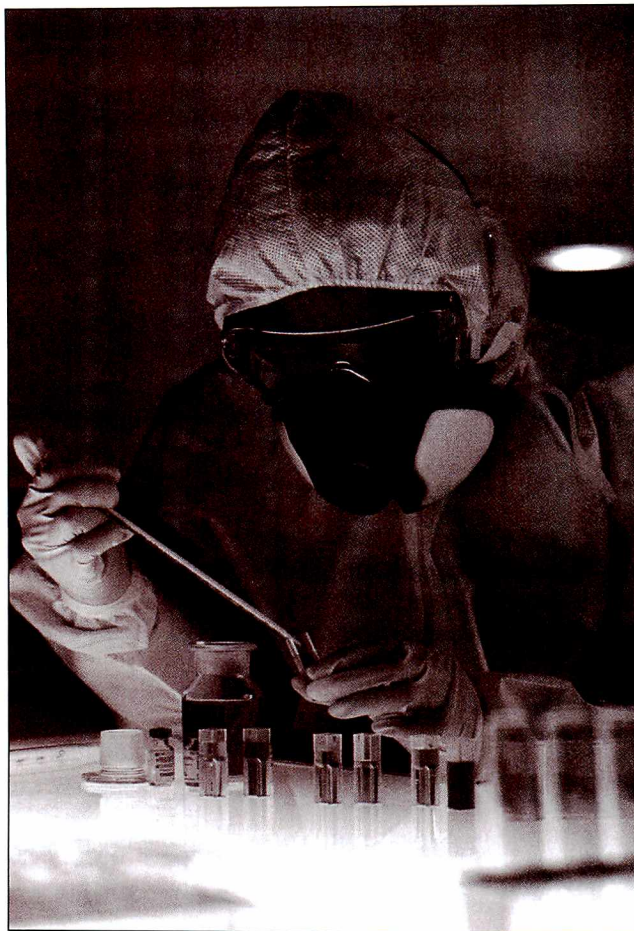
—Philip Noguchi, M.D., FDA gene therapy expert

quickly to do just that. FDA immediately shut down the trial in which Gelsinger had volunteered, and all clinical gene transfer trials at the University of Pennsylvania in January. The university went on to severely restrict the research of its once-high-flying gene therapy institute director James Wilson, M.D., announcing in May that all his work would be confined to animal and laboratory experiments and that he would be barred from conducting studies in people.

FDA also suspended gene therapy trials at St. Elizabeth’s Medical Center in Boston, a major teaching affiliate of Tufts University School of Medicine, which sought to use gene therapy to reverse heart disease, because scientists there failed to follow protocols and may have contributed to at least one patient death. FDA also temporarily suspended two liver cancer studies sponsored by the Schering-Plough Corporation because of technical similarities to the University of Pennsylvania study.

Moreover, as nervousness spread through the field in the months after revelations about Gelsinger’s death, some research groups voluntarily suspended gene therapy studies, including two experiments sponsored by the Cystic Fibrosis Foundation and studies at Beth Israel Deaconess Medical Center in Boston aimed at hemophilia. The scientists paused to review their studies and make sure they learned from the mistakes made at the University of Pennsylvania.

In March, the Department of Health and Human Services announced two initiatives by FDA and NIH. The Gene Therapy Clinical Trial Monitoring Plan is designed to ratchet up the level of scrutiny with additional reporting requirements for study sponsors. A se-



ries of Gene Transfer Safety Symposia was designed to get researchers to talk to each other, to share their results about unexpected problems and to make sure that everyone knows the rules.

In addition, FDA launched random inspections of 70 clinical trials in more than two dozen gene therapy programs nationwide and instituted new reporting requirements. “We see the need to get the concept across that this is for keeps,” says FDA’s Noguchi. “You can be sloppy when you are dealing with a scientific paper, but you can’t be sloppy when you are dealing with a human. Everything matters.”

So far, the inspections only suggest that one other program appears to be in trouble, he says, but by the fall, “We should be able to say accurately [what is] the state of the art of gene therapy and where it needs to improve.”

Meanwhile, President Clinton an-

nounced more “new actions designed to ensure that individuals are adequately informed about the potential risks and benefits of participating in research ... and steps designed to address the potential financial conflicts of interest faced by researchers.” In addition, the President said in May, “We are also sending the Congress a new legislative proposal to authorize civil monetary penalties for researchers and institutions found to be in violation of regulations governing human clinical trials.” If the legislation passes, FDA will, for the first time for drugs and biologics, have the power to essentially fine researchers and their institutions, up to \$250,000 and \$1 million respectively.

“This is a clear message,” HHS Secretary Donna E. Shalala, Ph.D., said in May, “that we intend to get serious.”

A History of Special Concern

Genetic engineering has always worried the general public.

When scientists first learned to clone genes in the mid-1970s, public reaction ranged from antipathy to hostility. Opponents, fearing that genetically engineered bacteria might escape from a laboratory, shut down the research at Harvard University and the Massachusetts Institute of Technology for months. Twenty-five years ago, in response to public concern, American scientists organized a voluntary moratorium on certain types of gene engineering experiments until safety questions could be resolved.

To help assuage public concern, NIH created its Recombinant DNA Advisory Committee, the RAC—which most simply call the “rack”—to provide a forum for genetic engineering debates to take place in public. As a result, the general opposition subsided.

Ethical issues aside, the bigger problem for gene therapy has been basic biology.

But the RAC could do little if scientists didn't follow the rules. The promise of gene therapy, the glory of being the first to cure human ills, led at least one very smart scientist to make a very questionable decision. In 1980, an ambitious hematologist at the University of California at Los Angeles tested his gene therapy ideas on patients in Israel and Italy after being denied permission to perform the tests in Los Angeles. The experiments, conducted by Martin Cline, M.D., failed to help his subjects, and they violated federal rules designed to protect research subjects, leading to severe censure of the California scientist.

Ethical issues aside, the bigger problem for gene therapy has been basic biology. It's difficult to get new genes into billions of target cells within the body. Once inserted, the new genes need to function. Frequently, the body suppresses gene expression, essentially turning the new genes off, or destroys the transplanted genes. Although techniques have improved, today's scientists still face these challenges. To solve the problems, independent researchers have sometimes devised their own remedies of unknown safety. FDA began paying careful attention to these laboratory constructs when researchers began to request permission to test them in people under Investigational New Drug applications.

"Early investigators were more mom and pop operations," Noguchi says. "They were individual investigators making their own products ... Almost all of them went on clinical hold because there was a lack of product information." Before FDA could allow them to proceed, technical questions about safety had to be answered, and that took time.

Typically, scientific questions are answered in laboratory and animal studies,



but, with gene therapy, clinicians have been anxious to test their ideas in people. Once the NIH physicians treated their tiny patient in 1990, researchers rushed to get into the game with human trials. At the halfway point in the decade, the field was not progressing well. Then-NIH Director Harold Varmus, M.D., himself critical of the gene therapy trials in people, created a committee to review NIH's investment in the field. Varmus wanted to know whether NIH should continue to invest so heavily in the new technology.

The committee's conclusions were bleak:

"While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 ... approved

protocols," concluded the *ad hoc* committee co-chairmen Stuart H. Orkin, M.D., of Harvard Medical School and Arno G. Motulsky, M.D., of the University of Washington in Seattle in December 1995. While they saw promise, they also saw challenges. "Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host."

To transfer a repair gene into a patient, the researchers must go through several steps (see "Fundamentals of Gene Therapy" on page 20). First, they must isolate the disease-related gene. Then it must be packaged in a vector, usually a disabled virus that cannot reproduce and cause disease, but that can act like a delivery truck to transport the gene inside the patient's cells. Once inside the body's cells, the new gene can begin to function and restore health.

But building an effective delivery truck hasn't been easy. Scientists started by using a type of mouse virus as a vector, engineered so that it cannot replicate itself, that easily infects human cells and integrates the new genes into the cell's chromosomes (structures in the cell that hold the genes). These mouse vectors, however, only infect dividing cells, so researchers switched to adenovirus, a type of human virus that causes the common cold. Because the adenovirus's own genes to reproduce itself have been removed, the remaining viral container is unable to cause an illness.

At least, that's the idea.

The Gelsinger Case

When Orkin and Motulsky reported on the technical limitations of gene transfer techniques five years ago, they

virtually predicted problems in the clinic. During that same December meeting at which Orkin and Motulsky made their disheartening report, the RAC approved the University of Pennsylvania gene therapy trial for ornithine transcarboxylase deficiency (OTCD). FDA, too, allowed the study to proceed.

The treatment idea was fairly straightforward. OTCD occurs when a baby inherits a broken gene that prevents the liver from making an enzyme needed to break down ammonia. With the OTCD gene isolated, the University of Pennsylvania researchers packaged it in a replication-defective adenovirus. To reach the target cells in the liver, the Philadelphia scientists wanted to inject the adenovirus directly into the hepatic artery that leads to that organ. Some members of the NIH RAC objected, fearing that direct delivery to the liver was dangerous. Nonetheless, after a vigorous public discussion with the University of Pennsylvania researchers, the RAC voted for approval of the study.

At age 18, Jesse Gelsinger was in good health, but was not truly a healthy teenager. He had a rare form of OTCD that appeared not to be linked to his parents, but the genetic defect arose spontaneously in his body after birth. During his youth, he had many episodes of hospitalization, including an incident just a year before the OTCD trial in which he nearly died from a coma induced by liver failure. But a strict diet that allowed only a few grams of protein per day and a pile of pills controlled his disease to the point where he appeared to be a normally active teenager. With the encouragement of his father, Paul Gelsinger, Jesse volunteered for the study, and when he was initially evaluated, his medical condition qualified him to participate.

Gelsinger received the experimental treatment in September 1999. Four days later, he was dead. No one is really sure exactly why the gene therapy treatment caused his death, but it appears that his immune system launched a raging attack on the adenovirus carrier. Then an overwhelming cascade of organ failures occurred, starting with jaundice, and progressing to a blood-clotting disorder, kidney failure, lung

failure and ultimately brain death.

In its investigation, FDA found a series of serious deficiencies in the way that the University of Pennsylvania conducted the OTCD gene therapy trial, some more serious than others. For example, researchers entered Gelsinger into the trial as a substitute for another volunteer who dropped out, but Gelsinger's high ammonia levels at the time of the treatment should have excluded him from the study. Moreover, the university failed to immediately report that two patients had experienced serious side effects from the gene therapy, as required in the study design, and the deaths of monkeys given a similar treatment were never included in the informed consent discussion.

FDA's discussions with the university remain ongoing.

Signs of Progress

Not all the news about gene therapy is bad. It's true that dramatic cures have not been seen to date, but there are tantalizing signs that important advances may be just around the corner.

Ashanthi DeSilva, the girl who received the first credible gene therapy, continues to do well a decade later. She suffered a type of inherited immune disorder called Severe Combined Immune Deficiency, or SCID (pronounced skid), that left her susceptible to every passing microorganism. Without gene therapy, DeSilva would be living like David, the Boy in the Bubble, who had a similar disorder. Instead, the NIH researchers inserted a normal copy of the broken gene into some of her white blood cells, healing them, helping them function normally to restore her immune system. Cynthia Cutshall, the second child to receive gene therapy for the same disorder as DeSilva, also continues to do well.

Scientists, however, have discounted the benefit of the first gene therapies because the girls began receiving a new drug treatment that replaces the missing enzyme just before receiving the genetic therapy. And they continue to receive the drug after the genetic treatment, though gene therapy pioneer Anderson argues that since the drug dose has remained the same while their bodies have grown substantially over the decade, it makes a negli-

gible contribution to their well being.

In April, French scientists reported convincing evidence that they successfully treated a different form of SCID (X-linked severe combined immune deficiency, the type suffered by the boy in the bubble) with gene therapy. Four of the first five babies treated by Alain Fischer, M.D., of the Necker children's hospital in Paris have had "a complete or near complete recovery" of their immune systems after the treatment.

Meanwhile, researchers at Children's Hospital of Philadelphia, Stanford University and Avigen, Inc., a biotech company in Alameda, Calif., have reported promising results in hemophilia B patients. The team packaged a gene for Factor IX, a blood clotting protein, in a defective adeno-associated virus (AAV). They then used the AAV to insert the gene into patients who suffered abnormal blood clotting because they lack Factor IX. Normally, these hemophilia patients needed to inject Factor IX to prevent uncontrolled bleeding. In June, the researchers reported treating six patients with the Factor IX gene therapy. Even though the dose of the gene therapy was so low that no one expected it to help, it reduced the number of injections of Factor IX that these patients used on an *ad hoc* basis.

"The hemophilia studies are looking promising," says FDA's Noguchi, "but will need further study to know whether it is an effective product."

These two studies suggest the power of genetic treatments.

"We do seem to have turned the corner," says Anderson, "and there are a number of clinical trials that are starting to show success."

Even as FDA increases its scrutiny of the field to ensure patient safety, there is a sense of advancement. "There is good progress being made," Noguchi says. "FDA thinks that gene therapy will work, but we don't know for which disease. The recent events in France show that if you have the right disease, and can insert the right gene, you can obtain good results." ■

Larry Thompson is the editor of FDA Consumer.

User Fees

For Faster Drug Reviews

Are They Helping Or Hurting The Public Health?

By Larry Thompson

A DECADE AGO, the Food and Drug Administration was an obstacle to the delivery of novel drugs to patients because its drug review activities were under-funded and the staff couldn't review products in a timely way. The review of New Drug Applications, the so-called NDAs that companies file on all new pharmaceuticals they want to market, took unacceptably long to process—about two-and-a-half years.

Today, FDA staff review applications for new drug products in a year and as quickly as six months or less for priority drugs. The review staff increased by some 600. Better information and management systems were put in place to ensure uniformity in the quality and sophistication of the analytical reviews across the divisions that handle the different types of pharmaceuticals and biologics.

The difference: user fees.

In 1992, Congress, with the support of the administration, industry, and patient groups, passed a law that gave FDA the authority to collect user fees from manufacturers seeking marketing approval. Any time a company wants to submit a new drug or biologic to the agency so the product can go on the market, the company must pay a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. Previously, taxpayers alone paid for product reviews through budgets provided by Congress. In the new program, industry provides the cash in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness.

Companies supported the legislation because they wanted more predictable and faster reviews. While FDA's review standards remained unchanged, companies could get their products on the market faster if they met FDA's benchmarks. Patients supported it because they would get access to needed new medications faster. Congress supported the experiment because it could be undertaken without costing additional appropriations. And FDA's review divisions finally received the help they needed to do their job efficiently and effectively.

The user fee program worked so well that Congress renewed it in 1997 for another five years. Now, with expiration on the horizon, FDA wants to publicly evaluate a program that, after eight years, has reached a certain maturity but also has generated controversy. On Sept. 15, 2000, the agency will begin a public discussion to consider the changes that may be needed in any renewal of the Prescription Drug

User Fee Act. The act, frequently referred to as PDUFA (pronounced pah DEW fah), created the user fee program. (For the specifics about the public meeting and other opportunities to comment, see "The PDUFA Public Meeting" on page 27.)

"We want to understand from all of our constituents what they think about user fees," says FDA Commissioner Jane E. Henney, M.D.

Most observers expect the discussion to be lively. While the agency believes that the program enjoys support by many constituencies, FDA's leaders recognize that the program has raised sensitive questions and believe that, as constructed, it has some shortfalls. Views on the value and appropriateness of indus-

try funding of the agency's review function vary widely, from strong industry support to complete rejection by some critics.

"By and large, our experience with PDUFA has been quite positive," says Alan Goldhammer, Ph.D., associate vice president of science and regulatory affairs at Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, D.C. PhRMA is a trade organization representing the nation's major pharmaceutical companies. "The time to approval in the review process has been coming down markedly since we instituted the program in 1992," he says. "At that time, it was like 30 months, incredibly long. Now, it is down on average to about 11 months to get a

new drug through the process."

Some consumer groups, however, have been less dazzled by PDUFA's success in speeding up drug reviews. "It's a terrible system," says Sidney Wolfe, M.D., director of Public Citizen's Health Research Group in Washington, D.C. "The review of new drugs turns out to be too important to leave to user fees." He compares the industry's financial support for FDA's review system to charging criminals user fees to pay for the police department.

Not surprisingly, FDA's leadership falls somewhere in between. "Everyone is impressed with the speed of new drug reviews," Commissioner Henney says, "but the truth is, the program is barely surviving because of the way it was designed. We don't have the resources to do the things we believe are essential, such as adverse event reporting, because they were not part of the process" supported by PDUFA funds.

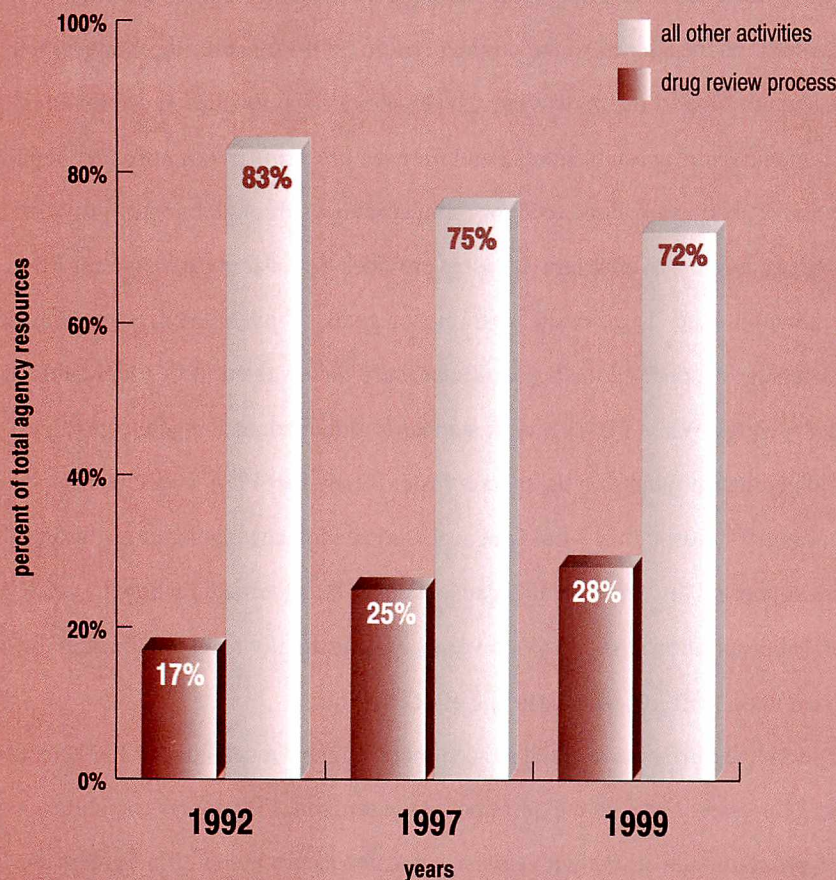
While everyone agrees PDUFA has fulfilled the initial intent of improving the timeliness of drug and biologic reviews, nearly everyone has complaints or concerns about some aspect of the program. For its part, the agency needs to preserve the level of resources provided by user fees. Yet FDA believes it's time to add critical activities, such as adverse event reporting and discussions with companies before applications are filed, to the functions supported by user fees. The growing debate means the public will have plenty to consider and discuss during the public meeting.

An Independent Review

A major concern focuses on the perceived impact of industry money, and there are some who express apprehension about the arrangement. In its report from the Government Performance Project in March 2000, the Maxwell School of Public Administration at Syracuse University concluded that the "emphasis on speed of industry-funded drug reviews raises concerns."

Some critics have publicly worried that making the agency dependent on company funding diminishes the agency's independence and objectivity. In short, they think FDA is in the industry's pocket. Wolfe's group, for example, argued before Congress that

How Funding Changes Functions FDA Now More Focused on Drug Evaluation



As industry user fees have gone up, the percentage of total FDA resources devoted to human drug review has increased relative to all other FDA regulatory functions, including food safety, medical devices, blood products and inspections.

Infographic by Renée Gordon

The PDUFA Public Meeting

FDA's public discussion of the Prescription Drug User Fee Act will take place at 9:00 a.m. on September 15, 2000.

Location:

U. S. Department of Labor Auditorium
200 Constitution Ave. N.W. (3rd and C
Street entrance), Washington, D.C.

Written comments may be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rockville, MD 20852.

Look for more information on how to comment, how to request time to speak at the public meeting, and other aspects of PDUFA and the public meeting on FDA's Website at www.fda.gov/oc/pdufa2/meeting2000.html.

Or call 301-827-3409, fax 301-594-6777. ■

—L.T.

funding FDA's drug reviews with industry money has "lowered U.S. drug safety standards, arguably once considered the world's best, to pre-1938 levels [before] the Food, Drug and Cosmetic Act was passed."

FDA does not believe that review criteria have been compromised, but understands that this is a perception problem, one it hopes to confront at the September meeting.

No matter what the perception about the funding source, the agency believes it has made the drug and biologics review process more efficient without lowering drug review standards. But that claim, too, has been controversial. In the 10 months between September 1997 and June 1998, FDA directed the withdrawal of five approved pharmaceuticals from the market because of unexpected, severe adverse events. The withdrawn drugs included a diet drug combination, a calcium channel blocker for treating hypertension and chronic stable angina,

a non-steroidal anti-inflammatory drug, and a once-widely used antihistamine. Some of these were approved before user fees.

Agency critics point to this spate of drug withdrawals as evidence that the accelerated reviews under the user fee program have led to sloppy analyses and increased risk to the public. To determine whether the agency was "maintaining adequate quality control over its premarketing review decisions," Henney established a task force in 1999 to investigate the concern. By comparing a General Accounting Office study of drugs approved before 1990 with new pharmaceuticals approved under the user fee system between 1994 and 1997, the task force concluded "that there has been no increase in the rate of drug withdrawals in the United States" since the user fee program began.

As much as anything, the need to remove some drugs from the market after

they go into widespread use reflects the limitations of the clinical studies on which drug approvals are based. Typically, new pharmaceuticals are tested in less than 5,000 human volunteers during development. That provides enough information to identify fairly common side effects, but does not turn up the rare, but sometimes severe, adverse effects seen only when millions of people use the drug. The agency relies on its post-market surveillance system to identify these uncommon side effects. When a problem is discovered, FDA can take a wide range of actions to protect the public health, from notifying health-care professionals about the problem or changing the instructions on how the drug should be used, to, in very serious cases, removing it from the market.

A Balanced Budget

Congress created FDA's user fee program to help solve the agency's chronic



The sheer volume of technical information associated with a manufacturer's request to market a new drug can be overwhelming. This is a single New Drug Application that FDA must review by agreed-to deadlines set by the Prescription Drug User Fee Act.

resource shortages. In the 1992 version of the act, neither Congress nor the industry envisioned user fees becoming the principal source of funding for the FDA drug-review program. In fiscal year 2000, for the first time, that may change: user fees and appropriated dollars are approaching equilibrium, and that concerns Commissioner Henney.

"There is a feeling that the public will not tolerate having the drug review program more than 50 percent user fee-funded," Henney says. "Others say that the fact that industry funds any of it is bad."

Part of the problem has been overall congressional appropriations: they haven't kept pace. "FDA is not receiving appropriated dollars to balance PDUFA dollars," says Robert Byrd, FDA's

deputy commissioner for management and systems. "Congress has increased agency funding amounts, but only for specific initiatives. FDA has lost roughly \$200 million over the past six years because of having to absorb inflation and pay raises that have not been funded." Because funding failed to keep up, the agency has actually lost people because it was forced to reduce some of its staffing to cut costs.

"We share a concern with FDA about the current balance between the user fee portion and the appropriated portion of the review process," PhRMA's Goldhammer says. As industry funding approaches half of the review budget, "it has led to a perceptual issue that industry is paying for the review process and that the American public, through its tax

moneys, is not. We would hope that can be dealt with in some way because we don't want there to be the perception that this is an industry-driven program."

Wolfe's solution to the perception problem is simple: Eliminate user fees. "If industry really wants FDA to have an adequate budget," he says, "it should lobby hard for a greatly expanded FDA budget through the normal congressional appropriations process."

Balancing revenue streams between public and private sources, however, does not cause everyone heartburn. In some other countries, all drug regulation costs are funded by industry. And in the United States, regulatory agencies as diverse as the Nuclear Regulatory Commission, the U.S. Patent and Trademark Office, and the Securities and Exchange Commission receive all, or nearly all, of their funding from regulated industries.

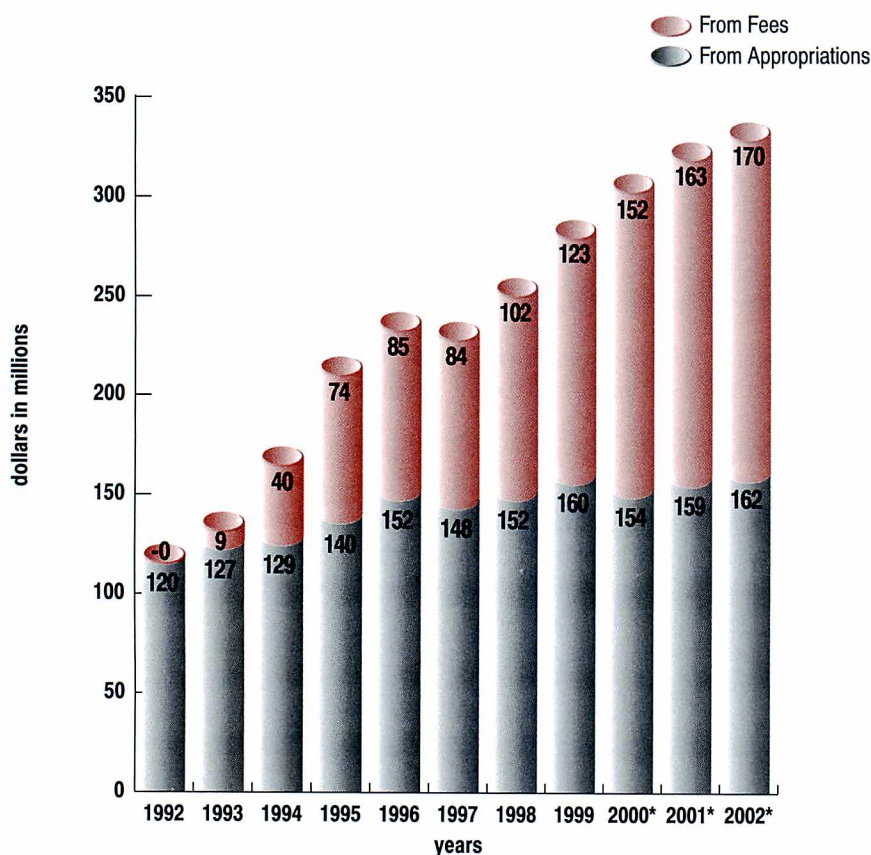
"We are not the only government agency that relies on user fees," says FDA Senior Associate Commissioner Linda Suydam, D.P.A. "But the question is, does that in any way jeopardize FDA's integrity and independence? We have no evidence of this, but we are using the public meeting to make sure it doesn't. We want everyone to engage in the public debate."

For FDA, another problem is the sense of "haves and have-nots" within the agency. The review programs supported by user fees have more resources, while other parts of FDA, divisions with important public health missions, often go without.

"User fees distort the distribution of labor at the FDA in that it piles up a large amount of funds for reviewing new drug applications," Wolfe says, "but does not provide funds for other essential public health functions like reviewing drug advertising, except at the beginning, or adequate funds for the increased load in post-market surveillance."

FDA's budgetary statistics show that as user fees flowed into the agency, appropriations to support other activities have remained unchanged or have declined. As a result, the percentage of FDA activities and resources devoted to drug reviews has increased from 17 percent before Congress passed PDUFA to 28 percent in fiscal year 1999. Mean-

Growth of User Fees to Support Drug Review



Since the program's creation in 1992, industry funding through user fees has grown steadily while congressional appropriations have risen more slowly. In the current fiscal year, approximately half of FDA's funding for human drug reviews comes from industry. In future years, more than half of FDA funding for drug reviews will come from industry.

* projected figures

Infographic by Renée Gordon



Photograph By Ronald Usery /Duke University

FDA's leadership discusses ways to work cooperatively with industry and academia during a recent public meeting at Duke University.

while, funding for other programs, from color additives in foods to post-market surveillance to manufacturer and import inspections, has drifted downward.

Balancing Benefits and Costs

Even in user fee-funded operations, the additional resources have come at a cost. Industry insisted on performance goals and standards that resulted in increased pressure to meet deadlines, increased tracking and reporting requirements and a sense of micro-management. For the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, the agency's primary review centers for drugs and biological products, PDUFA has been a Faustian bargain.

On one hand, says CDER director Janet Woodcock, M.D., the user fee program provides enough staff to meet the performance deadlines and more scrutiny during drug development, but the intense schedules "create a sweatshop environment that's causing high staffing turnover." Highly trained scientists and experts want to do more with their careers than crank out reviews, so many leave within three years, preventing the agency from building an institutional memory of previous reviews.

Staff turnover can be disruptive for the industry as well. "When your technical reviewer changes," Suydam says, "it

throws the process into a tizzy."

In addition to the current impacts of the user fee program on FDA's activities, Suydam worries about the future. Several recent studies by the University of California at San Diego, Anderson Consulting and PriceWaterhouseCoopers have tried to look into the future and predict how the drug development process will evolve and how FDA will need to respond.

The studies predict that the pharmaceutical industry will quadruple the annual output of new drugs while reducing development time to market by one-third. They also project a 65 percent increase by 2008 in the number of so-called new molecular entities (NMEs) moving into early clinical development. NMEs are chemically unique drugs that are completely different than any other drug on the market. These compounds require additional scrutiny since there are no similar drugs to which they can be compared.

Once an NME is approved, companies will create "fast-followers" with related compounds that try to target different patient segments. For example, a fast-follower might have a similar therapeutic effect but reduced side effects.

Computer technologies will improve the predictive modeling of new drugs, and computer simulations will optimize clinical trial design and increase the amount of

clinical information collected. Finally, information technologies will streamline electronic submissions to the agency.

To handle these changes, FDA "regulators will assume an expanded role as knowledge integrators exerting increased influence on every phase of new product development," according to the studies. To make this work, FDA reviewers will need to spend more time advising companies about protocol design and making themselves available for an ongoing dialogue throughout the drug development process.

In addition, the studies concluded, "regulators face major challenges in staying current with scientific advances, managing ever-increasing information and communicating more effectively." FDA's staff will need "new strategies to seamlessly manage growing information on a product over its life cycle."

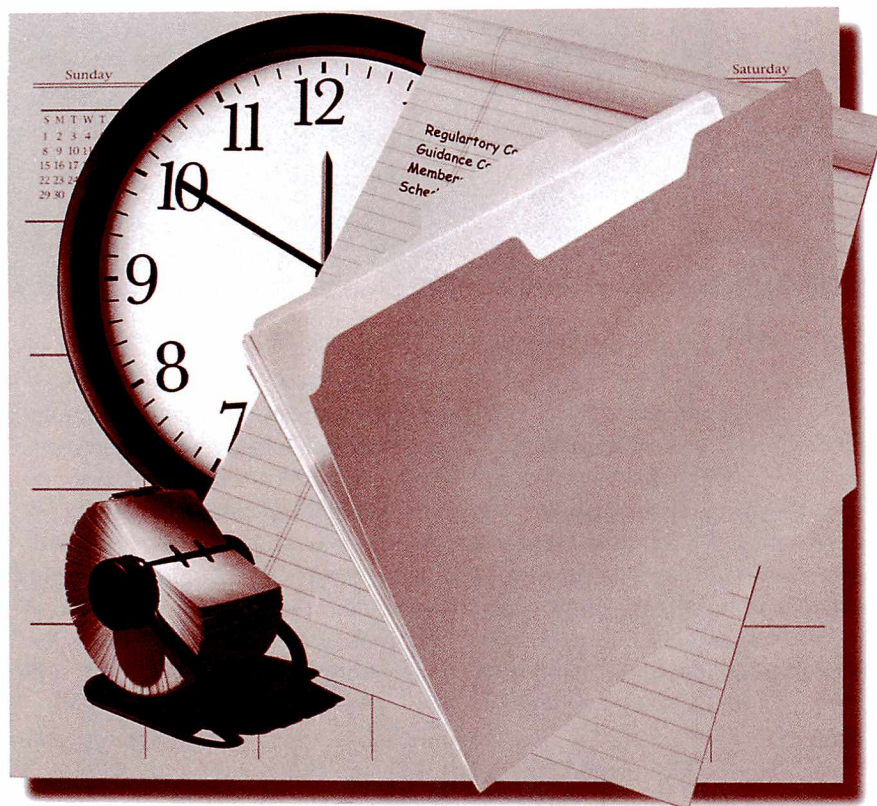
FDA's management sees serious challenges ahead, especially if budgetary resources remain inadequate. "What these studies have envisioned for FDA," Suydam says, "is nowhere near anything we can do now."

Whether user fees will play a part in addressing these future problems remains unclear. ■

Larry Thompson is the editor of FDA Consumer.

Advisory Committees

By Carol Lewis



Should the latest drug to treat AIDS be allowed on the market or will it put patients at risk? One member of the committee evaluating products for the Food and Drug Administration has difficulty casting her vote. She is not a doctor, not a scientist, not even a health-care provider, but her opinion counts. And she faces a complicated choice. On the one hand, not enough multicultural studies have been done to her liking to determine the drug's overall safety and effectiveness. On the other, the desperate patient whose life the medication may save sits silently pleading beside her.

"There were nights I didn't sleep because I wondered if I'd made the right decision," says Susan Cohen, one of many individuals grappling with the complex, science-based issues related to FDA's public health responsibilities.

Cohen serves on a committee of outside experts and consultants who advise FDA in its evaluation of regulated products and help the agency make sound decisions based on the reasonable application of good science. It may seem unnecessary to seek outside advice, given the full complement of scientific specialists the agency employs, but as scientific advances in the many areas that FDA regulates become more specialized, the agency sometimes looks to the critical expertise that exists at major research institutions for a more balanced evaluation. Consumer representatives like Cohen contribute to the scientific debate by ensuring that the health-care concerns of specialized groups, such as the elderly, minorities, and the disabled, are adequately represented on FDA's 32 advisory committees.

Although Cohen, who recently served

on FDA's Antiviral Drugs Advisory Committee, eventually voted to recommend approval of the AIDS drug, these decisions, she says, are never made without lingering doubt.

"The United States is made up of so many different cultures and you need to include data on all these groups when you're considering marketing a drug that's going to help a lot of people," she says. At the same time, while trying to stay objective about the criteria she uses for making a judgment, the consumer advocate is also aware that sometimes there's a personal side to the issue. "When you're voting, you are very conscious of the person sitting next to you because he represents that immediate segment of society that needs the help."

But do these outside opinions really make a difference? FDA thinks so.

"Advisory committees are among the most important FDA institutions where representatives of the public have a place at the table," says Sharon Smith Holston, FDA's Deputy Commissioner for International and Constituent Relations. "And because of them, various public sectors have gained a better understanding of the frequently complex reasons why new products are—or are not—allowed on the market."

FDA's advisory committees provide independent, expert scientific and medical advice to the agency on the safety, effectiveness, and appropriate use of products under its jurisdiction. The committees consist of individuals with recognized expertise and judgment in a specific field, and who have the training and experience necessary to evaluate information objectively, often under controversial circumstances. The advisory committee process encourages public interaction with the agency in arriving at decisions, and members of the public are encouraged to appear before the com-

FDA's Primary Stakeholders Have A Say

As scientific advances in the many areas that FDA regulates become more specialized, the agency sometimes looks to the critical expertise that exists at major research institutions for a more balanced evaluation.

mittee during the open part of each meeting.

Public Policy Defined

Historically, FDA made regulatory decisions concerning new and investigational products with only occasional assistance from the outside. Independent advice was limited to difficult issues on an as-needed basis and only to compensate for a lack of specific expertise within the agency. But over the last 50 years, FDA found that it could best protect the public health if the people it served better understood its strengths and limitations, and if they partnered with the agency in a common enterprise. In short, the traditional relationship between FDA and the public had to change.

One telling example occurred shortly after World War II, when the agency, through a series of public meetings, consulted the lay public in its development of standards of identity for certain food staples. To find out what ingredients Americans wanted—or didn't want—in white bread, FDA asked for the views of not only nutritionists and manufacturers of bread, but also of consumer organizations representing the nation's proverbial man in the street. Based on consumers' concerns, FDA made sure the adopted standards reflected the public's wishes and recommendations.

Encouraged by this experience, the agency took the next step by hiring part-time consumer consultants to work on other food standards and similar issues. These earlier successes eventually evolved into a full-scale public-partici-

pation program that would later include patient and consumer representatives like Cohen.

In 1972, Congress passed the Federal Advisory Committee Act to promote the formal use of advisory committees in all of the federal government, just as FDA's public participation system was evolving into more extensive use.

But the big advance came in 1976 when Congress amended the Federal Food, Drug, and Cosmetic Act and made FDA responsible for evaluating and approving medical devices. At the same time, the law mandated that the interests of the general public would now be represented on medical device advisory committees by non-voting consumer members. President Carter acknowledged the growing importance of public representation in 1978, when he formally called on all federal agencies to "provide adequate opportunity for consumer participation in the decision-making process."

Consumers Cast Their Vote

Today, the charter of each advisory committee provides for at least one voting or non-voting member to represent the consumer perspective. Consumer representatives raise concerns that might not otherwise be addressed before products come to the marketplace, while other committee members focus on these issues from the scientists' and clinicians' perspectives.

Typically, and depending on the focus of the particular committee, consumer representatives who have served in the past haven't exactly been lay people.

They have included consumer advocates, college professors, consumer lawyers, nurses, physicians, microbiologists, engineers and veterinarians. Most have ties to consumer- and community-based organizations. Although they are not necessarily experts in their fields, like their counterparts, consumer representatives must be able to analyze data, understand research design, discuss benefits and risks, and evaluate the safety and effectiveness of the products under committee review—but from the consumer perspective.

"A consumer member on one of the FDA panels needs to recognize that she or he is always in the minority, thus placing her or him at a disadvantage," says Diony Young, consumer representative for FDA's Obstetrics/Gynecology Devices Panel. But even though she doesn't have the expertise that other panel members have, Young emphasizes that consumer representatives must be strong advocates on behalf of the public, and that they "must not be intimidated or coerced by physicians and others with higher professional credentials."

Although consumer representatives must be technically qualified to serve on advisory committees, FDA's Acting Associate Commissioner for Consumer Affairs, Patricia M. Kuntze, says their role isn't always understood by other committee members.

"We provide information and training, and actively participate in orientation sessions so that other committee members are aware of the role of the consumer representative on any given

Public participation at FDA has become a two-way process through which the agency communicates priority health information to the public and the public in turn expresses its views, attitudes, reactions and knowledge to FDA.

committee,” Kuntze says. “However, sometimes it takes the experience—and I can guarantee that after one or two meetings, no one on the committee has any questions or reservations about the added value of the consumer representative.”

Consumer representative Abbey Meyers adds, “I only know that when I read the background materials, and when I listen to the scientific presentations, I must never forget the patients.” President of the National Organization for Rare Disorders in Connecticut and consumer representative for the Biologi-

cal Response Modifiers Advisory Committee, Meyers feels, “If my allegiance is to them, and if I always focus on their welfare, I will have served them well even if the rest of the committee disagrees with me.”

Barbara Loe Fisher, on the other hand, was surprised when FDA wanted to appoint her to the Vaccines and Related Biological Products Advisory Committee, which is responsible for evaluating the quality of scientific data presented by manufacturers applying for licenses for new vaccines. A nationally known critic of the mass vaccination system,

Fisher has spent the last 18 years publicly calling for the institution of vaccine safety and informed consent reforms.

“This was not a passive appointment where I could sit quietly and just listen,” Fisher says. “It became clear to me early in that first meeting that the contribution I uniquely could make, and had to make, was to be the voice that had rarely been heard there before.” But Kuntze says that’s just what the agency is looking for—those who represent the different points of view that balance the information committee members have to weigh.

“There’s synergy in the panel as a



Over the last 50 years, FDA has found it could best protect the public health if the people it served better understood its strengths and limitations, and if they partnered with the agency in a common enterprise.

result of the type of people who are on it," says committee member and former chairman of the Clinical Chemistry/Clinical Toxicology Devices Panel, Henry C. Nipper, Ph.D. "We all help each other out, we all learn from each other, and I believe the panel is stronger because of this good mix of backgrounds and interests."

FDA formalized a selection process, called the Consumer Consortium, that involves consumers in the recruitment, nomination, and recommendation of consumer representatives to serve on FDA committees. The consortium may

involve 10 to 15 members representing consumer and patient advocacy groups, such as the National Women's Health Network (NWHN) in Washington, D.C., who serve a diverse range of constituencies. FDA's Office of Consumer Affairs (OCA) is responsible for coordinating the nomination and selection process, and facilitates consortium discussions so that consumers can evaluate candidates for consumer representative vacancies on advisory committees. At least nine months in advance of a vacancy, OCA consults with the agency's manager of the committee (the executive secretary) to determine the scientific or technical expertise that is required.

"It makes certain seats hard to fill," says Cynthia Pearson, Executive Director of NWHN, a current consortium member. "Having a consumer representative at the table is essential, yet consumers don't always have enough science at hand to fill the role." Others, she says, are masters at their craft. "Candidly, it's a mixed bag, but we've seen that consumer representatives can and do sway opinion."

Additionally, OCA conducts extensive recruitment efforts through a host of other channels, including self-nomination, current and former consumer representatives, and outreach efforts to key consumers.

Putting a Face on the Disease

In order to learn the views of people who were intimately familiar with the devastating effects of such raging epidemics as HIV infection and AIDS, the

agency created a new category of public participation—patient representatives—and added them to the advisory panels that dealt with various aspects of the diseases. Prompted by both the valuable contributions that consumers were making on regulatory issues not readily apparent to the legal experts and scientists, and the shock of the 1980s AIDS epidemic, FDA believed that the process of including consumer representatives could serve as a model.

In the fall of 1988, activists of an organization called ACT UP (AIDS Coalition to Unleash Power), consisting mostly of young men with AIDS and their friends and relatives, stormed FDA headquarters, demanding immediate access to unapproved therapies to fight AIDS and the HIV virus. Protestors accused the agency of being too slow in reviewing AIDS drugs and of conducting business "as usual" while *they* were dying. Some of the demonstrators were dressed like corpses in a morgue and carried signs that said, "I died for the sins of FDA," "Time isn't the only thing the FDA is killing," and "Killed by the System."

"The entire demonstration, genuine as it was in its intent, was predicated on wrong assumptions," says Deputy Commissioner Holston, who was trapped inside the building behind police protection during the rally. She says that FDA was not barring access to promising new antiviral drugs, and that the agency, in fact, was far from slow in processing AIDS applications for therapies, to the extent that there were any to process.

Zidovudine, or AZT—the only drug against AIDS then in existence—had been approved by the agency in March 1987 in three and a half months, she says. Prior to that, it had been given to 4,000 people with AIDS in a study that FDA authorized in just four days. According to Holston, the ACT UP protest turned out to be a distortion of truth, but an experience that actually inspired the agency to examine public participation with a new sense of urgency.

This 1988 ACT UP (AIDS Coalition to Unleash Power) demonstration outside FDA headquarters in Rockville, Md., became a watershed event in the agency's changing perception of how to best accomplish its traditional mission of protecting consumers and promoting the public health.



How To Participate

To find out more about becoming a patient or consumer representative on an FDA advisory committee, send a résumé to one of the following offices:

For Consumer Representatives:

Food and Drug Administration
Office of Consumer Affairs (HFE-40)
Advisory Committees Desk
5600 Fishers Lane
Rockville, MD 20857

For additional information on consumer representation, call 301-827-5006.

For Patient Representatives:

Patient Representative Program
Office of Special Health Issues (HF-12)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

For additional information on the patient representation program, call 301-827-4460.



The later appointment of patient representatives enabled FDA to conduct far-reaching and thorough consultations on how to confront the AIDS epidemic and mitigate its enormous suffering, while tackling the overwhelming scientific and medical problems associated with the disease. Although there was some initial resistance by committee members to include patient representatives on the panels, FDA found that their opinions paid significant benefits. For example, some of the activists understood the scientific problems faced by the agency in reviewing new antiviral drugs, and this was a very important added benefit—they were very successful not only in presenting the AIDS community's views to FDA, but also in explaining FDA's positions to people with AIDS. In addition, AIDS patients could judge better than anyone what drug side effects were acceptable in return for possible health benefits.

"We see that more and more patients with serious and life-threatening diseases are actively involved in their own treatment," says Theresa Toigo, Associate Commissioner for Special Health Issues. "Our informal evaluation tells us that this initiative has not only been ac-

cepted but is endorsed by scientists, FDA staff, and the pharmaceutical industry."

In fact, the success of AIDS patient representatives stimulated a similar initiative for cancer patients and their advocates. In the early 1990s, following discussions with representatives of the cancer patient community, FDA established a cancer liaison program within its Office of Special Health Issues to work closely with these patients. And because there are too many types of cancers for a single patient to represent the entire field, public participation took another step forward in March 1996 when President Clinton announced a new policy that provides for voting patient representatives on all FDA advisory committees dealing with cancer-related issues. This program has included over 26 patient representatives on 16 advisory committees to review 40 cancer-related therapies. One patient representative has served five times.

Patient representatives often have a history with the disease for which a new treatment will be discussed. In some cases, a caregiver or representative of a patient group might be chosen to serve. As with consumer representatives, a

background as a scientist or researcher is not necessary, as long as the representative can comprehend the scientific data presented and effectively communicate patient concerns. More importantly, their experience as a patient enables them to bring a unique perspective to FDA advisory committees.

"Patients can offer a point of view that no one else on the committee can provide because we've had the experience to share what they haven't," says patient representative Martha Solonche, a five-year survivor of both uterine and ovarian cancer. Solonche believes that the "emotionally charged" nature of some of the issues is "all the more reason for someone with the disease to argue a point."

"One of the biggest hurdles at a committee meeting," says Sallie Forman, a patient representative who suffers from colon cancer, "is convincing the rest of the panel that the approval of a drug that may buy me three or four more years may also take away my quality of life. In other words, a drug that is so toxic to the system, but gives one more week of life, isn't worth it."

Solonche agrees. "No one on the panel could understand this. Only someone who's lived through constant side effects, every time they take a certain drug, can know what that's like."

Partnership and Satisfaction

Public participation at FDA has become a two-way process through which the agency communicates priority health information to the public and the public in turn expresses its views, attitudes, reactions and knowledge to FDA.

"Together, this team of advisors delivers a valuable external viewpoint about difficult issues that face the agency," says FDA Commissioner Jane E. Henney, M.D. And its growing emphasis, she says, clearly demonstrates that consumer and patient contributions to the advisory committees are significant. As a result, communications have improved between FDA officials and committee experts, and the public has begun to feel more involved in the agency's decision-making process. ■

Carol Lewis is a staff writer for FDA Consumer.



Hot spots and cool links on FDA's Website and beyond.

By John Henkel



'Thermometer' Promotes Thorough Food Cooking

Many people think they can tell when food is completely cooked just by eyeballing it. But food safety experts tell us this system is flawed. One out of four hamburgers, for example, turns brown—appearing fully cooked—before it's cooked to a temperature high enough to destroy harmful bacteria. According to the U.S. Department of Agriculture, the best way to ensure meat,

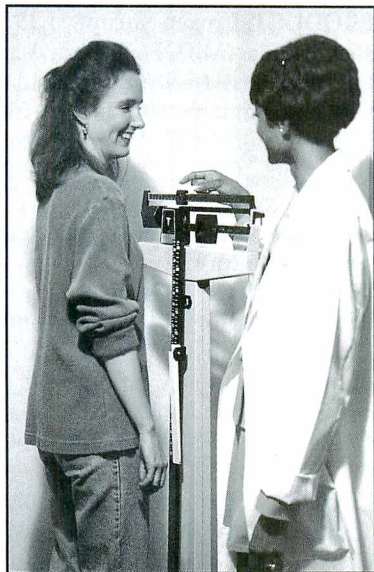
poultry and egg products are "done" is by using a food thermometer. However, a 1998 federal study showed that less than half of the population owned a thermometer and only 3 percent used it when cooking hamburgers. To help promote wider thermometer use, USDA created "Thermometer," a cartoon character being displayed with food-safety messages on posters and literature in grocery

stores nationwide. Thermometer also has a Website, www.fsis.usda.gov/thermy/, which has games and educational materials for kids and a chart showing safe minimum cooking temperatures for various foods. The site includes links to other helpful information on food safety, such as how to keep food safe when camping or hiking.

Weighing In On Diet Choices

Losing weight. It can be pretty tough. Even harder is keeping off the pounds once they've been shed. Many experts agree that the key to losing weight and maintaining a healthy weight is setting sensible goals and expectations. On its Website at

www.consumer.gov/weightloss/, the Partnership for Healthy Weight Management has some good advice on starting a weight-loss program and sticking with it. The site promotes gradual weight loss—no more than two pounds a week—as opposed to a "crash" diet where much weight is taken off in a short period. A consumer guide available on the site, "Finding a Weight Loss Program That Works for You," includes a checklist of various weight-loss plans that allows consumers to tailor their own program. The site also has helpful information on avoiding weight-loss products advertised with extravagant, and often bogus, claims. The Federal Trade Commission manages the site as part of a coalition of scientific, academic, health-care, government, commercial, and public health members.



Cancer 'Tools' Page Opens

Consumers and patients can learn more about different types of cancer and their treatments on a new FDA Website called "Oncology Tools." At www.fda.gov/cder/cancer/, users can search for information by specific cancer type and by approved drug therapies. Documents are available on cancer drug labeling, approval summaries, and advisory committee transcripts. Health care professionals can use the site to get references for performing clinical studies and for information on calculating drug dose. And the page includes links to other FDA resources for cancer patients, including the latest on clinical trials and more on treatments and diagnostic tools.

'Access'-ing Government Publications

Looking for an item in the *Federal Register*? How about a figure from the U.S. budget from the last three years? Or maybe a chapter in the *U. S. Government Manual*?

Well, you could probably seek out hard copies of these documents, but a much easier way would be to go to the Government Printing Office's "GPO Access" site, where those and more than 100,000 other federal publications are a keystroke away. Split into categories such as legislative, executive, judicial, and regulatory, the site includes the *Congressional Record*, the *Code of Federal Regulations*, and *Ben's Guide to U. S. Government for Kids*, a resource for parents, teachers, and students kindergarten to 12th grade. GPO Access users can even check out the latest federal job openings. The site includes a running tally of new items added, and visitors can search for an item by topic, title, agency, or keyword within one database or across several. To access the site, go to www.access.gpo.gov.

John Henkel is a member of FDA's public affairs staff.

SUMMARIES OF COURT ACTIONS



Summaries of Court Actions are given pursuant to section 705 of the Federal Food, Drug, and Cosmetic Act. Summaries of Court Actions report cases involving seizure proceedings, criminal proceedings, and injunction proceedings. Seizure proceedings are civil actions taken against *goods* alleged to be in violation, and criminal and injunction proceedings are against *firms* or *individuals* charged to be responsible for violations. The cases generally involve foods, drugs, devices, or cosmetics alleged to be adulterated or misbranded or otherwise violative of the law when introduced into and while in interstate commerce or while held for sale after shipment in interstate commerce.

Summaries of Court Actions are prepared by the Office of the Chief Counsel, Food and Drug Administration.

Published by direction of the Secretary of Health and Human Services.

SEIZURE ACTIONS

Food/Contamination, Spoilage, Insanitary Handling

PRODUCT: Articles of Food, Dusting Starch, at Norfolk, Va. (E.D. Va.); Civil Action No. 2:99cv1130.

CHARGED 7-16-99: While held for sale after shipment in interstate commerce at Golden Fields Enterprises, Inc., Norfolk, Va., the articles of food were adulterated in that they had been prepared, packed, and held under insanitary conditions whereby they might have become contaminated with filth—402(a)(4).

DISPOSITION: Pursuant to Default Decree of Condemnation, Forfeiture, and Destruction, the articles of food were destroyed Dec. 17, 1999. (F.D.C. No. 67278; S. No. 48739 et al.; S.J. No. 1)

PRODUCT: Beef trachea, 3 cases, more or less, at Greeley, Colo. (D. Colo.); Civil Action No. 99-Z-2398.

CHARGED 12-16-99: While held for sale after shipment in interstate commerce at Old West Treat Company, in Greeley, Colo., the article of food was adulterated in that it bore or contained *Salmonella*, a poisonous and deleterious substance which might have rendered it injurious to health—402(a)(1). **DISPOSITION:** The article of food was destroyed. (F.D.C. No. 67296; S. No. 57883; S.J. No. 2)

PRODUCT: Canned mushrooms, 1000 cases more or less, at South San Francisco, Calif. (N.D. Calif.); Civil Action No. C-97-3234.

CHARGED 9-2-97: While held for sale after shipment in interstate commerce, at QFCO, Inc., doing business as Queensway Foods Co. Inc., in South San Francisco, Calif., the articles of food were misbranded in that their labeling was false and misleading because it contained a fictitious can code which falsely suggested that the mushrooms were packed by Gen Hong Foods Industrial Co. Ltd., and because it falsely represented and suggested that the mushrooms were grown in Taiwan—403(a)(1).

DISPOSITION: The articles were destroyed. (F.D.C. No. 67190; S. No. 97-753-988; S.J. No. 3)

PRODUCT: Extra Virgin Olive Oil, 618 cases more or less, at Riviera Beach, Fla. (S.D. Fla.); Civil Action No. 00-0014. **CHARGED** 1-4-00: While held for sale after shipment in interstate commerce at Cheney Brothers, Inc., stored to the account of LFI, Inc., Fairfield, N.J., the articles of food were adulterated in that sunflower oil had been substituted in whole or in part for extra virgin olive oil (618 case lots); soybean oil had been substituted in whole or in part for olive pomace oil (160 case lots); and sunflower oil had been substituted in part for olive oil (86 case lots)—402(b)(2). The articles of food were misbranded because their labels falsely represented them as extra virgin olive oil, olive pomace oil, and pure olive oil—403(a)(1). The articles were further misbranded in that these mixtures of oils were largely sunflower or soybean oil, but were unlawfully offered for sale under the name of another food, namely, extra virgin olive oil, olive pomace oil, and pure olive oil—403(b).

DISPOSITION: The articles were destroyed May 23, 2000 pursuant to a default judgment. (F.D.C. No. 67299; S. No. 54822 et al.; S.J. No. 4)

PRODUCT: Frozen Shrimp, 1,192 cases more or less, at Jacksonville, Fla. (M.D. Fla.); Civil Action No. 98-236-Civ-J-20B.

CHARGED 3-16-98: While held for sale after shipment in interstate commerce at Industrial Cold Storage, Inc. and stored to the account of King and Prince Seafood Corporation in Brunswick, Ga., the articles of food were all adulterated in that they consisted in whole or in part of a decomposed substance by reason of the presence therein of decomposed shrimp—402(a)(3).

DISPOSITION: Pursuant to an order amending the consent decree, a portion of the defendant lot of decomposed frozen shrimp was satisfactorily reconditioned. The rejected portion of the reconditioned product had been destroyed under the supervision of the United States Marshals Service. (F.D.C. No. 67224; S. No. 98-712-573; S.J. No. 5)

PRODUCT: Frozen shrimp, 302 cases, more or less, at Tampa, Fla. (M.D. Fla.); Civil Action No. 98-476-CIV-T-17C.

CHARGED 3-4-98: While held for sale after shipment in interstate commerce at Americold Corporation, stored to the account of Central Seaway Company, Inc., in Tampa, Fla., all of the defendant shrimp were adulterated in that they consisted in whole or in part of a decomposed substance by reason of the presence therein of decomposed shrimp—402(a)(3). Furthermore, certain defendant shrimp (420 cases, more or less) were also adulterated in that they consisted in whole or in part of a filthy substance by reason of the presence therein of insect and bird filth—402(a)(3).

DISPOSITION: The condemned defendant shrimp was exported to Zhejiang Foreign Economic Relations and Trade Development Corporation, Hangzhou, China. (F.D.C. No. 67223; S. No. 98-768-226/228; S.J. No. 6)

PRODUCT: Preserved Turnip, 60 cases more or less, at Brooklyn, N.Y. (E.D. N.Y.); Civil Action No. 98-CV-0181.

CHARGED 1-14-98: While held for sale after shipment in interstate commerce at Yick Cheung Corporation, doing business as Goodworld Trading, in Brooklyn, N.Y., the articles of food were adulterated in that the articles (60 case lots of preserved turnips) consisted in part of a filthy substance, by reason of having been rodent-gnawed and by reason of the presence therein of rodent urine—402(a)(3). The articles were further adulterated in that they (all lots) had been held under insanitary conditions whereby they very likely became contaminated with filth—402(a)(4).

DISPOSITION: The condemned articles of food were successfully reconditioned. (F.D.C. No. 67222; S. No. 98-751-473; S.J. No. 7)

PRODUCT: **Soybeans and Mung Beans**, at San Lorenzo, Calif. (N.D. Calif.); Civil Action No. 99-4799.

CHARGED 11-1-99: While held for sale after shipment in interstate commerce at Dong Ling Sprout and Produce Co., in San Lorenzo, Calif., the articles of food were adulterated in that certain articles of food consisted in part of a filthy substance, including 350 50-pound bag lots of soybeans, by reason of being rodent gnawed; 720 55-pound bag lots of mung beans, by reason of the presence therein of insects and rodent excreta pellets; 1,190 110-pound bag lots of mung beans, by reason of the presence therein of rodent hairs; and 2,320 55-pound bag lots of mung beans, by reason of the presence therein of mammalian urine—402(a)(3). The articles were further adulterated in that all articles of food (all lots) had been held under insanitary conditions whereby they might have become contaminated with filth—402(a)(4).

DISPOSITION: The articles were destroyed. (F.D.C. No. 67290; S. No. 38938 et al.; S.J. No. 8)

PRODUCT: **Straw Mushrooms, 836 cases more or less**, at Brooklyn, N.Y. (E.D. N.Y.); Civil Action No. CV99-2475.

CHARGED 4-29-99: While held for sale after shipment in interstate commerce at S.D.J. Trading Corp., Brooklyn, N.Y., the article of food was misbranded in that its labeling was false and misleading because it contained a fictitious can code which falsely represented that the article was packed by the Zhang Zhou General Canned Food Factory, Zhang Zhou, People's Republic of China—403(a)(1).

DISPOSITION: The article was destroyed. (F.D.C. No. 67265; S. No. 42006; S.J. No. 9)

Drugs/Human Use

PRODUCT: **Liquid Oxygen**, at Manhattan, Kan. (D. Kansas); Civil Action No. 99-1269.

CHARGED 7-2-99: While held for sale after shipment of one or more of its components in interstate commerce, at Home-Ox of Kansas, Inc., the article of drug was adulterated in that the methods used in, and the facilities and controls used for, its manufacture, processing, packing and holding did not conform to, and were not operated and administered in conformity with, current good manufacturing practice (CGMP) re-

quirements—501(a)(2)(B). The article was misbranded in that it was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under 21 U.S.C. Section 360, and the article had not been listed as required by 21 U.S.C. Section 360(j)—502(o).

DISPOSITION: The article was reconditioned. (F.D.C. No. 67271; S. No. DOC 30295, 56568; S.J. No. 10)

PRODUCT: **Oxygen**, at Owings Mills, Md. (D. Md.); Civil Action No. L-99-1326.

CHARGED 5-7-99: While held for sale after shipment of one or more components in interstate commerce at Professional Respiratory Services, Inc., the articles of drug were adulterated in that the methods used in and the facilities and controls used for their manufacture, processing, packing and holding did not conform to, and were not operated and administered in conformity with, current good manufacturing practice requirements of the Food, Drug and Cosmetic Act—501(a)(2)(B). The article (cryogenic home units) was misbranded in that its label failed to bear the name and place of business of the manufacturer—502(b)(1). The article (cryogenic home units) was also misbranded in that its label failed to bear an accurate statement of the quantity of contents—502(b)(2). The article (cryogenic home units) was misbranded in that its label failed to bear adequate directions for use—502(f)(1). The articles were further misbranded in that their labels failed to bear, at a minimum, the symbol "Rx only"—353(b)(4)(A).

DISPOSITION: The articles were reconditioned. (F.D.C. No. 67264; S. No. DOC 19721/22; S.J. No. 11)

PRODUCT: **Oxygen**, at Shreveport, La. (W.D. La.); Civil Action No. CV99-0946.

CHARGED 5-27-99: While held for sale after shipment of one or more of their components in interstate commerce at Red Ball Oxygen Company, Inc., in Shreveport, La., the articles of drug were adulterated in that the methods used in and the facilities and controls used for their manufacture, processing, packing and holding did not conform to, and were not operated and administered in conformity with, current good manufacturing practice—501(a)(2)(B). Furthermore, the articles (Oxygen USP and Nitrogen UF in cryogenic vessels) were misbranded in that they failed to bear labels containing the name and place of business of the manufacturer—502(b)(1). DISPOSITION: The articles were reconditioned. (F.D.C. No. 67267; S. No. DOC 19131; S.J. No. 12)

PRODUCT: **Topical Products for Skin Diseases**, at Miami, Fla. (S.D. Fla.); Civil Action No. 99-2721.

CHARGED 10-18-99: While held for sale after shipment in interstate commerce at Ameritrade Beauty Care, Inc., in Miami, Fla., the articles of drug were misbranded in that their labeling failed to bear adequate directions for use and they were not exempt from such requirement under 21 C.F.R. Section 201.115, since the articles were unapproved new drugs—502(f)(1). The articles were also misbranded in that they had not been duly listed as required by 21 U.S.C. Section 360(j)—

502(o). The articles were further misbranded in that their labels failed to bear, at a minimum, the symbol "Rx only"—503(b)(4)(A).

DISPOSITION: The articles were destroyed. (F.D.C. No. 67288; S. No. 41344 et al.; S.J. No. 13)

PRODUCT: **Various topical products**, at Miami, Fla. (S.D. Fla.); Civil Action No. 99-2777.

CHARGED 10-18-99: While held for sale after shipment in interstate commerce at Victoria Beauty Supplies, in Miami, Fla., the articles of drug were misbranded in that their labeling failed to bear adequate directions for use and they were not exempt from such requirement under 21 C.F.R. Section 201.115, since the articles were unapproved new drugs—502(f)(1). The articles were also misbranded in that they had not been duly listed as required by 21 U.S.C. Section 360(j)—502(o). Moreover, the articles were misbranded in that their labels failed to bear, at a minimum, the symbol "Rx only"—503(b)(4)(A).

DISPOSITION: The articles were destroyed. (F.D.C. No. 67287; S. No. 52095 et al.; S.J. No. 14)

PRODUCT: **Various Topical Products for Skin Diseases**, at Miami, Fla. (S.D. Fla.); Civil Action No. 99-2779.

CHARGED 10-18-99: While held for sale after shipment in interstate commerce at Victoria Wholesale, Inc., in Miami, Fla., the articles of drug were misbranded in that their labeling failed to bear adequate directions for use and they were not exempt from such requirement under 21 C.F.R. Section 201.115, since the articles were unapproved new drugs—502(f)(1). The articles were also misbranded in that they had not been duly listed as required by 21 U.S.C. Section 360(j)—502(o). The articles were further misbranded in that their label failed to bear, at a minimum, the symbol "Rx only"—503(b)(4)(A).

DISPOSITION: The articles were destroyed. (F.D.C. 67286; S. No. 52095 et al.; S.J. No. 15)

Medical Devices

PRODUCT: **Surgical Sutures and Various Surgical Devices**, at Tampa, Fla. (M.D. Fla.); Civil Action No. 98-2363-Civ-T-26 (C).

CHARGED 11-18-98: While held for sale after shipment in interstate commerce at EcuAmerica International, in Tampa, Fla., the articles of devices were adulterated in that they were held under insanitary conditions whereby they might have become contaminated with filth or might have been rendered injurious to health—501(a)(2)(A). The articles were further adulterated in that their purity and quality fell below that which they purported and were represented to possess—501(c). The articles were misbranded in that they were in package form and their labels failed to bear the name and place of business of the company distributing the devices—502(b)(1). The articles were further misbranded in that their labeling was false and misleading because it failed to reveal the material facts that the manufacturer had inspected the devices and concluded that they had been rejected after undergoing a United States Surgical Corporation quality audit and that they

were not fit for use or sale under any circumstances—502(a). DISPOSITION: Pursuant to a default judgment entered 7-21-99, the articles were destroyed. (F.D.C. No. 67239; S. N. 98-800-025/9; S.J. No. 16)

CRIMINAL ACTIONS

DEFENDANT: **National Medical Care**, at Rockleigh, N.J. (D. N.J.); Civil Action No. 99-748.

CHARGED 12-22-99: On Dec. 22, 1999, the defendant, now a division of Fresenius Medical Care North America, appeared in the United States District Court for the District of New Jersey and pleaded guilty to two misdemeanor charges: (1) distribution in interstate commerce of devices that were adulterated because they were not manufactured in accordance with current good manufacturing practices; and (2) the failure to file medical device reports. NMC Medical Products admitted that from December 16, 1992, to Oct. 6, 1993, it released into interstate commerce adulterated bloodlines, the tubes that carry a dialysis patient's blood to and from the patient and a dialyzer (artificial kidney), even though its own tests showed the bloodlines were prone to develop potentially excessive levels of air bubbles as they carried the patients' blood. After it released the adulterated bloodlines, the company received four reports of serious injury caused by the devices, and 108 malfunctions during dialysis. The company also admitted that it failed to report in a timely manner 1,196 incidents in which its devices, such as dialyzers, bloodlines, and related products, may have caused or contributed to a death or serious injury or may have malfunctioned. The company admitted that it made those reports only after the company received a federal grand jury subpoena calling for their production.

DISPOSITION: The court ordered NMC Medical Products, Inc. to pay a fine of \$3,800,000, the highest fine ever imposed for a misdemeanor violation of the Federal Food, Drug, and Cosmetic Act. (Pros. No. 66868; S.J. No. 17)

INJUNCTION ACTIONS

DEFENDANT: **Cape Fear Valley Medical Center, Roy A. Weaver and John E. Strickland**, at Fayetteville, N.C. (E.D. N.C.); Civil Action No. 93-105-Civ-3-H.

CHARGED 11-17-93: While held for sale after shipment of one or more of their components in interstate commerce, the articles of drug, blood products, were adulterated in that the defendants failed to comply with the current good manufacturing practice (CGMP) regulations for drugs, 21 C.F.R. Parts 210 and 211, and the CGMP regulations for blood and blood products, 21 C.F.R. Part 606, in collecting, manufacturing, processing, testing, packing, labeling, holding, or distributing of such articles of drug—501(a)(2)(B).

DISPOSITION: The Court entered a consent decree of permanent injunction on Nov. 23, 1993. Defendant Cape Fear Valley operated under the consent decree for several years and made several corrections and changes to its operation. On Jan. 4, 2000, Defendants moved to vacate the injunction, and the government did not oppose the motion. On Jan. 11, 2000, the U.S. District Court (E.D. N.C.) issued an order vacating the injunction. (Inj. 1342; S. No. 93-696-712; S.J. No. 18)



FDA Lets Air Out Of Medical Gas Company

By Carol Lewis

It wasn't enough that a family-owned medical gas repacker had its products seized by the U.S. Marshals Service for failing to correct long-standing manufacturing violations. So, when the kinfolk from Nashville, Tenn. cut the yellow ribbons 'round the old gas cylinders and failed to hold onto the seized products, a federal judge held Mom in contempt.

Gayle Sensing, president of Medical Homecare Services Inc., was held in civil contempt on Oct. 6, 1999, by U.S. District Judge Thomas A. Higgins, and fined an amount conditional on the return of missing gas cylinders and cryogenic tanks, which had been tampered with and removed from the premises following seizure by U.S. Marshals in December 1998. Sensing was ordered to pay \$100 for every high-pressure oxygen gas cylinder that the firm failed to recover, and \$2,000 for each unreturned liquid oxygen cryogenic vessel. Twenty-two cylinders and one vessel were unaccounted for, resulting in a fine totaling \$4,200. In addition, Sensing was charged over \$1,000 for FDA inspections conducted to determine that the drug products had been moved from the location where they were seized, and nearly \$200 for related court fees.

Both the seizure and contempt actions followed the firm's 10-year violative history of FDA's current good manufacturing practice (CGMP) requirements, and subsequently, the firm's failure to correct the long-standing violations.

FDA was first alerted to Medical Homecare Services' repetitive violations following a routine inspection in January 1987. The agency sent the firm a Notice of Adverse Findings letter citing manufacturing violations, such as the failure to provide and follow written operating procedures. But a follow-up inspection in February 1988 resulted in a second Notice of Adverse Findings letter when FDA officials found that the deficiencies had not been corrected.

Subsequent inspections in 1990, 1993 and 1997 uncovered many of the same violations observed during earlier inspections, and FDA issued a Regulatory Letter and two Warning Letters to the firm.

In an attempt to help the firm comply with CGMPs, FDA officials met with Mrs. Sensing and her son Bradley in January 1998. When FDA brought the documented deviations to their attention, both pleaded ignorance to the regulations and requirements for oxygen transfilling, and asked for guidance. Mr. Sensing told FDA that he was not familiar with the term "CGMP." Mrs. Sensing admitted that she did not know anything about the medical gas business or how it was supposed to operate. Still, she promised to make corrections.

FDA reinspected the firm in May 1998, and found continuing deviations from CGMPs. Mrs. Sensing again admitted she knew nothing about the business, and said that she relied heavily on her son, who was also the pumper employee—one responsible for filling oxygen. But FDA officials were quick to note that Bradley Sensing knew very little about the medical gas industry, as well. He was unable to demonstrate how to "zero" the oxygen analyzer, nor could he calibrate it to the purity of the standard gas. Mr. Sensing also performed the odor

test for foreign gases after the cylinders were filled, instead of before, which could have resulted in an explosion.

FDA officials noted that the firm's standard operating procedures (SOPs) for transfilling oxygen lacked the required precautions and instructions. In addition, the high-pressure cylinders were misbranded because the labels failed to bear both an accurate statement of the quantity of the contents and the correct name and place of business of the manufacturer.

A reinspection in November 1998 revealed the same continuing CGMP violations as noted in May. Mrs. Sensing told FDA officials that she had turned the entire operation over to her son. Bradley Sensing told FDA investigators he had hired a pumper employee, but agency personnel discovered that the employee knew less about CGMPs than Mr. Sensing did. The pumper employee said that Brad Sensing had trained him on the job to fill oxygen, but that he was not told where the SOPs were located.

At the close of the inspection, Mrs. Sensing told FDA officials that it would do her no good to learn about the medical gas operations, of which she was in charge, because she would just forget them. She agreed that her family wanted to be in compliance, but was unsure of what the firm would do about it in the future.

Upon arrival at the firm to seize the products on Dec. 22, 1998, U.S. Marshals, accompanied by an FDA investigator, explained the reason for their visit and served the warrant for arrest of the products. The seized oxygen tanks were moved to an unoccupied corner of the business's storage room, and yellow tape marked "Restricted Area" was placed around the items, along with two "U.S. Marshal—No Trespassing" stickers. A copy of the warrant was posted on one of the seized cylinders. The Marshals advised Mrs. Sensing that the items were seized and were not to be touched, disturbed, or used until she was notified by the court.

Following the seizure, the parties involved began settlement negotiations on the consent decree for final disposition of the case. But the U.S. Attorney's Office said it had received earlier word from Medical Homecare Services' counsel that the cylinders and tanks seized in December had been moved and that some of the contents had been vented into the atmosphere. The U.S. Attorney's Office had also notified FDA officials, who began an investigation.

Based on an erroneous understanding from her attorney, Gayle Sensing said that she believed she had been given the "green light" to remove the U.S. Marshals tape and seals. But the Marshals contacted Mrs. Sensing after learning what she had done, and informed her that she needed to quickly recover the cylinders listed in the claim because by moving them, she had defied the original court order. A hearing on the charge of civil contempt was held on Sept. 30, 1999.

The types of CGMP violations found at Medical Homecare Services can result in medical gas that is contaminated and incorrectly identified. Injury and death of patients have occurred in the past due to similar CGMP problems at other facilities.

Gene Therapy Researchers React To Field's Pitfalls And Promises

By Savio L.C. Woo, Ph.D.

The possibility of correcting human genetic disorders by gene therapy caught the imagination of the scientific community as well as that of the public long before the first clinical gene transfer experiment was launched ten years ago. During the ensuing decade, however, the extraordinarily high level of expectation has proven to be grossly optimistic. This prompted Dr. Harold Varmus, then Director of the National Institutes of Health, to appoint two separate committees in the mid-1990s to evaluate the field of gene therapy. The committees independently concluded that clinical applications of gene transfer could not possibly succeed without adequate scientific and technological support, as well as sufficient preclinical studies in relevant animal models of human disease to validate treatment efficacy.

The scientific community has taken these constructive criticisms to heart during the past few years, and dramatic progress has been made in the basic science of viral and non-viral vector development used to transfer genes into patients. As a result, some approaches appear to be working. The Hemophilia B trial currently being conducted at the Children's Hospital of Philadelphia and Stanford University employs intramuscular delivery of the gene expressing human Factor IX, a protein involved in blood clotting. Patients in this trial have exhibited much improved whole blood clotting times for months after the gene treatment. Children in Paris with X-linked SCID, an inherited disorder that destroys the immune system, are able to live at home normally after genetic treatment of bone marrow stem cells. While both trials are in early phases, the encouraging results do provide proof of the scientific principle that human genetic disorders can be corrected by gene transfer.

In September 1999, clinical experiments in gene transfer research suffered their first patient loss as a direct consequence of the gene treatment itself. The patient was a 19-year-old male with a metabolic disorder who received a high dose of a genetic treatment directly into his liver at the University of Pennsylvania. He died from multi-organ failure induced by an adult respiratory distress syndrome secondary to a systemic inflammatory response to the method used to deliver the new gene.

Initial public response to the tragic incident was rather mild, as it is understood that medical research is not without risks. But public perception of clinical gene therapy took a precipitous turn for the worse after the FDA cited the University of

Pennsylvania investigators in December 1999 for multiple protocol violations in the trial. In addition, NIH revealed that only 6 percent of all serious adverse events observed in patients during past and current clinical gene transfer studies were reported to the NIH as required. These findings triggered a series of corrective actions by the relevant federal regulatory agencies including the FDA and the NIH, with the full cooperation and enthusiastic support of the American Society of Gene Therapy (ASGT). The Board of Directors of ASGT has accordingly adopted a policy that calls for all of its members to rigorously adhere to federal regulations and institutional guidelines in clinical gene transfer studies. This policy was published in the January issue of *Molecular Therapy*, the official scientific journal of the Society.

Another revelation that further shook the public's confidence in clinical gene transfer studies at its roots was that some investigators apparently have significant financial interests in the outcome of the clinical research they are conducting. To ensure the public that clinical gene transfer research will be performed with high ethical standards and without financial conflicts in the future, the ASGT Board of Directors adopted a second policy published in the May issue of *Molecular Therapy*. It prohibits investigators and team members from direct participation in the recruitment and clinical management of trial patients or in gaining participants' informed consent if they have financial interests in companies sponsoring the trial.

While the recent advances in clinical gene transfer to treat Hemophilia B and X-linked SCID show that gene therapy is indeed an immensely powerful technology that can be developed into novel treatments for a wide variety of human diseases, it is critically important for the scientific community to rise to the occasion and restore full confidence in the public's mind that clinical gene transfer research will be conducted by investigators in a responsible manner and free from financial conflicts. Only then can the full potential of using genes as medicines to treat human disease be realized, which will have a major impact on medicine and health in the 21st century.

Savio L.C. Woo, Ph.D., is the director of the Institute for Gene Therapy and Molecular Medicine at Mount Sinai School of Medicine in New York, where he is a professor, and is the immediate past president of the American Society of Gene Therapy.

Leveraging @FDA

The Food and Drug Administration protects the health of American consumers by regulating over \$1 trillion worth of products.

But we can't do it alone.

That's where our partners come in—public health organizations, scientific experts, other federal regulators, states, industry, and consumers.

We are continuously exploring new opportunities to work together with our partners to benefit the American public.

Visit FDA's leveraging Website to find out more about how FDA is collaborating with these partners to enhance research, new product review, safety monitoring, and consumer education.

Leveraging at FDA: www.fda.gov/oc/leveraging/