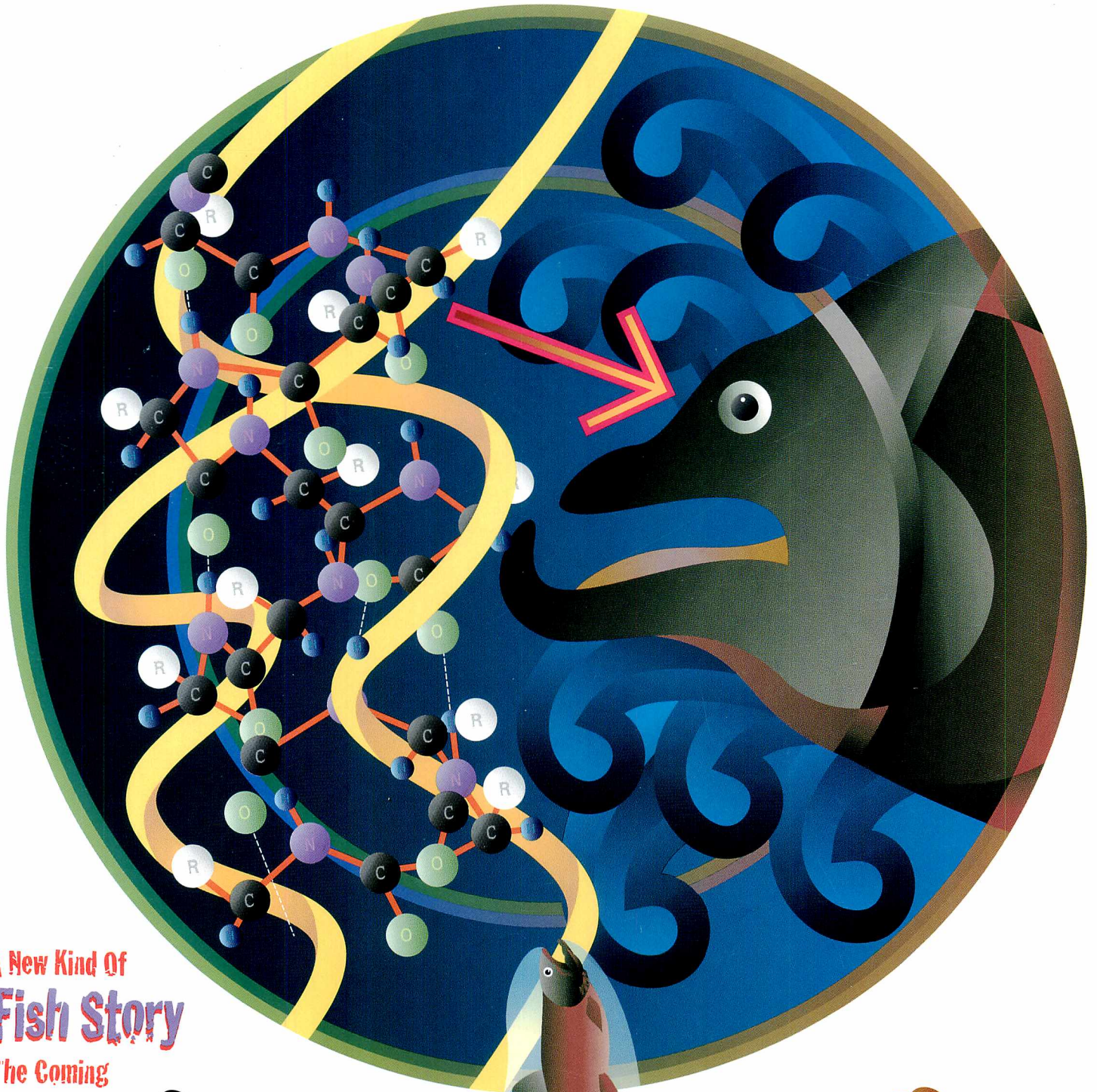


FDA *Consumer*

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

January–February 2001 • Vol. 35 No. 1



A New Kind Of **Fish Story**

The Coming
Of Biotech
Animals





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Consumer safety officers Matthew M. Henciak (left) and A. Dean Cook, members of FDA's Office of Regulatory Affairs' Baltimore District import operations group, walk the dock at the Dundalk Marine Terminal on the Chesapeake Bay to begin a day of inspections. For more about FDA's role in international food safety, see page 25.

OBSERVATIONS

When John W. Hinckley Jr. shot President Ronald Reagan on March 30, 1981, Secretary of State Alexander M. Haig Jr. rushed into the White House press room and declared that he was “in control here.” It wasn’t a coup. Secretary Haig was just trying to reassure the nation and the world that the government of the United States would go on if the president died from his wounds.

Secretary Haig was criticized, and then long teased, for acting prematurely: After all, Vice President George Bush was unharmed, safely flying back to Washington and available to assume his constitutional responsibility. Secretary Haig was fourth in line, after the vice president, the House’s speaker and the Senate’s president pro tempore. The laws dictating an order of succession were in place and the government’s leaders stood ready to follow them. Fortunately, the president didn’t die and the nation—and the government—did continue with little interruption.

America thrives because it is a nation of laws and the laws transcend any individual. We can see that again with the current presidential election. As I write this at the beginning of December, the election is still unresolved, but everyone knows it will be. There is no panic in the streets, no tanks on the corner. The rules that regulate the electoral process rest on the Constitution, are watched over by the courts, and have been honored by everyone involved.

Meanwhile, the government continues to do its work.

That impresses me. This is my first tour of government duty. I’ve been at the Food and Drug Administration a few years now, and I’ve come to appreciate two things: FDA’s actions are based on a solid foundation of laws, and the people who



Larry Thompson, Editor

work here, who give the agency its heart, care deeply about the public they serve.

The nation’s food and drug laws reach all the way back to President Theodore Roosevelt, who signed the original Pure Food and Drugs Act. In just five years, the nation will mark the Act’s 100th anniversary. FDA’s legal mandates increased dramatically over the decades.

Moreover, the agency’s professionals—doctors, nurses, pharmacists, many types of scientists and lawyers—directed by these laws and using the best science available, make reasoned decisions about the safety and effectiveness of the therapeutic products and the foods now on the market. I experience the commitment of my colleagues every time we discuss an article in this magazine. Their knowledge, caring and commitment gives this publication its credibility.

And I see that FDA’s work goes on, no matter what the uncertainty in the nation’s political life. The agency continues to review and approve new drugs, anticipates changing technologies that create new products (see the cover story on transgenic animals), considers global issues (see the story on international food safety) and even worries about issues close to home (see the story on hair-care products).

The business of government also goes on. Since Election Day, the Government Printing Office, which prints this magazine, notified FDA that the magazine’s subscription price would be going up—a lot. After careful—and gracious—discussions with Superintendent of Documents Francis J. Buckley Jr., GPO agreed to keep the price hike to a minimum, \$1.50. *FDA Consumer* is GPO’s most popular consumer publication, and Mr. Buckley added his considerable support to its growth. So for the next year, this magazine will cost \$13.50. With the recent improvements in the magazine—more articles, shorter articles, and more color—it’s still a bargain. I hope you stay with us to see what comes next.

TO THE EDITOR

Medical Errors

Medical Errors are errors we would all like to avoid—health-care practitioners and consumers alike (“Make No Mistake: Medical Errors Can Be Deadly Serious,” September–October 2000 *FDA Consumer*). But do you know that there is a dedicated group of professionals whose life work it is to protect the consumer from error-prone or negligent health-care providers? Certified credentialing professionals are valued members of the health-care team and work in most managed care plans, many IPAs, group practices, and hospitals. We write certification exams and participate in ongoing education to retain our certi-

fication. What are we paid to do? We are paid to snoop. We are trained where to look, what resources to use, and how to document our findings. Both the Joint Commission on Accreditation of Healthcare Organizations and the National Committee for Quality Assurance require that our services be utilized by any health-care facility desiring certification. Visit the Web site of the National Association of Medical Staff Services (www.namss.org) or contact your state association to learn more.

Debi Hansen, Education Chair
Washington Association of
Medical Staff Services

My wife was ill [recently] and lost three days of skiing because our pharmacy gave us the wrong medicine. They misread the writing and did not check with the medical doctor who wrote it. Whitney A. Brown’s letter to you (November–December 2000 *FDA Consumer*) suggested the use of numbers. A world-wide adopted system of numbers for all the medicines and chemicals is in use and available. A system of naming new drug entities is also in place once the entity has been published in a journal which is reviewed by The Chemical Abstracts Service (CAS). They are called Chemistry Abstract Registry Numbers. The US Pharmacopeia publishes the



Glaxo Wellcome Withdraws Irritable Bowel Syndrome Medication

Glaxo Wellcome of Research Triangle Park, N.C., recently informed the Food and Drug Administration that it will voluntarily withdraw Lotronex (alosetron hydrochloride) tablets from the market. Lotronex is a prescription medication approved to treat irritable bowel syndrome in women. FDA is advising patients taking Lotronex to contact their health-care providers to discuss treatment alternatives.

FDA analyzed post-marketing reports of serious adverse events, which included five reports of death, in patients taking Lotronex. Specifically, FDA has been concerned about reported cases of intestinal damage resulting from reduced blood flow to the intestine (ischemic colitis) and severely obstructed or ruptured bowels (complications of severe constipation).

As of Nov. 10, 2000, FDA had received and reviewed 70 cases of serious post-marketing adverse events, including 49 cases of ischemic colitis and 21 cases of severe constipation. Of the 70 cases, 34 resulted in hospitalization without surgery, 10 resulted in surgical procedures, and three resulted in death. FDA received two additional reports of death, but the association with the use of Lotronex remained uncertain.

Prior to approval of the drug on Feb. 9, 2000, four cases of ischemic colitis were observed in clinical studies and were discussed at a November 1999 meeting of FDA's Gastrointestinal Drugs Advisory Committee. These symptoms were tran-

sient, mild-to-moderate in nature, and reversible upon discontinuation of the drug.

Between approval and June 1, 2000, FDA received seven post-marketing reports of serious complications of constipation. This resulted in the hospitalization of six patients, three of whom required surgery. During the same time period, FDA received eight post-marketing reports of ischemic colitis. This resulted in four hospitalizations, four endoscopic procedures, and no surgeries.

Risk management options in response to the serious adverse event reports were discussed at a public advisory committee meeting convened by FDA on June 27, 2000. No deaths were reported up to that date. Following the meeting, FDA updated the health-care professional labeling for Lotronex and required Glaxo Wellcome to distribute a Medication Guide that warned patients directly about risks associated with the drug. At the request of FDA, Glaxo Wellcome also issued letters to health-care professionals and pharmacists about the drug's risks.

FDA continued to receive severe adverse event reports of ischemic colitis and complications of constipation associated with Lotronex. In addition, FDA received reports of death and more serious complications of ischemic colitis requiring a blood transfusion or surgery.

Glaxo Wellcome's action to voluntarily withdraw Lotronex followed a meeting on Nov. 28, 2000, where the company and FDA discussed risk management options that included restricting the distribution of the drug and marketing withdrawal.

TO THE EDITOR (continued)

USAN (United States Approved Names) and Dictionary of Approved Names and uses this system already. If physicians somehow can place numbers on the prescription more accurately (like sticky labels) than writing the names of medicines, the drug-related errors may be reduced. As an aside, I have read the *FDA Consumer* for 30 years for my own education. No one else tells me the difficult health questions as well as you do.

Walter R. Benson, PhD
Bethesda, Md.

Dr. Benson, now retired, was formerly director of FDA's Division of Drug Chemistry.

Insulin Pump User Support

You might want to refer your readers to this resource: www.insulin-pumpers.org ("Overcoming Juvenile Diabetes With a Little Planning And High-Tech Tools," July–August 2000 *FDA Consumer*). The Insulin Pumpers Web site and mail list is the largest support forum in the world for the users of insulin pumps. Its members include many doctors, certified diabetes educators, RNs, over 300 pumping kids ages 13 months through teens (or their parents), and more than 2,400 adult pumpers.

Michael Robinton, Executive Director
Insulin Pumpers

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 an address and telephone number for verification. The editor reserves the right to edit letters for space and appropriateness.

Drug Helps Delay Progression of Multiple Sclerosis

The first anti-cancer drug to be proven effective in treating patients with advanced or chronic multiple sclerosis (MS) was approved for this new use by the Food and Drug Administration in October. Novantrone (mitoxantrone hydrochloride), which is administered intravenously by a doctor, reduces the frequency of flare-ups and helps keep mobility in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting MS. These are all forms of MS in which patients become significantly worse between relapses and over time. The drug is not, however, approved for treating primary progressive MS, one form in which the patient's neurologic condition deteriorates over time without specific relapses.

MS is a highly debilitating autoimmune disease that attacks the nervous system and can cause weakness, impaired vision, loss of balance, and poor muscle coordination. The disease can have different patterns, sometimes leaving patients relatively well after episodes of acute worsening, and other times leading to progressive disability that persists after episodes of worsening. In the worst cases, MS can lead to paralysis. According to the Multiple Sclerosis Foundation, more than 300,000 Americans are diagnosed with MS today.

FDA cautions that some patients treated with Novantrone may develop serious heart problems. The risk of congestive heart failure increases with the cumulative dose, and patients with MS should ordinarily not receive more than eight to 12 doses administered over two to three years. FDA advises having the heart and blood tested regularly to help avoid serious side effects. Less severe side effects include nausea, hair thinning, loss of menstrual periods, bladder infections, and mouth sores.

Novantrone is manufactured for Immunex Corporation, of Seattle, by Lederle Labs.

Arsenic-Based Therapy Benefits Leukemia Patients

A new arsenic-based drug may benefit some leukemia patients for whom standard therapy has failed. The Food and Drug Administration approved Trisenox (arsenic trioxide) to treat patients with acute promyelocytic leukemia (APL) who have not responded to, or have relapsed after the use of, trans-retinoic acid and anthracycline-based chemotherapy, which is considered the first-line therapy. Trisenox was approved for marketing only three years after the study of the drug first started in the United States—the fastest development of any cancer therapy.

APL is a cancer in which abnormal white blood cells in bone marrow and blood accumulate quickly, resulting in anemia (a reduction in red blood cells), susceptibility to infections, and bleeding. About 1,500 new cases of APL are diagnosed each year and an estimated 400 of those patients will not respond to or will relapse from first-line therapy.

Trisenox offers a new alternative. Arsenic trioxide changes immature cancerous white blood cells into normal white blood cells. The result can be a sudden increase in the white blood cell count. In a multi-center clinical study of 40 patients who received arsenic trioxide infusions, 28 patients (70 percent) had a remission of their leukemia.

In some cases, the increase in the white blood cell count is accompanied by the "APL differentiation syndrome," a potentially fatal condition characterized by inflammation and fluid accumulation, particularly in the lining of the heart and lungs. The usual treatment is to temporarily stop the leukemia therapy and treat with high-dose steroids. This syndrome appeared in eight of the 40 patients (20 percent), but no cases were severe enough to require interrupting the arsenic trioxide therapy.

Trisenox can also cause changes in the heart's function, revealed by an increase in what is termed the Q-T interval, a part of the measurement on an electrocardiogram. This condition can sometimes lead to irregular heart rhythms that can be fatal. Significant increases of the Q-T interval appeared in 16 of the 40 patients (40 percent). No serious abnormal rhythm developed in those patients, but the risk of the effect required close monitoring of the patients and their electrocardiograms.

Other adverse effects of Trisenox are abdominal discomfort, nausea, vomiting, headache, fatigue, skin changes, and fluid accumulation. Most of the adverse effects were considered mild and resolved after therapy was completed.

Interest in arsenic-based therapy—used more than 100 years ago in the United States to treat leukemia and infections before being replaced by modern chemotherapy and antibiotics—has resurfaced due to reports of anti-leukemic activity of traditional Chinese preparations containing arsenic trioxide.

Cell Therapeutics, Inc., of Seattle will market the drug.

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, available from the FDA Web site or by calling the toll-free number below.
- 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 Web site for further assistance.

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

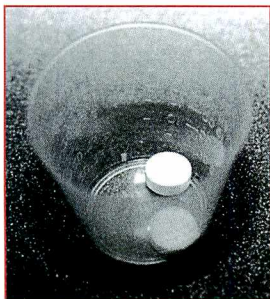
Combination Drug Approved to Treat HIV

In September, the Food and Drug Administration gave accelerated approval for a new treatment that combines two drugs to fight human immunodeficiency virus (HIV) infection. Called Kaletra, the new therapy relies on the antiviral properties of lopinavir, a drug that inhibits a critical HIV enzyme called protease, combined with a low dose of ritonavir, a drug that slows down the rate at which the body metabolizes lopinavir. This results in blood levels of lopinavir that enhance its effectiveness against HIV.

FDA approved Kaletra for adults and children older than six months. It is used with other anti-HIV drugs and should be taken with food to increase absorption into the blood stream. Kaletra was studied in six controlled clinical trials and one expanded access trial. Side effects include diarrhea, fatigue, headache, and nausea. The drug also increases blood lipid levels (cholesterol and triglycerides), which may require treatment for some patients. People with high levels of triglycerides in the blood can be at risk for pancreatitis. Infrequent cases of pancreatitis have been observed among patients receiving antiretroviral regimens that included Kaletra.

Like other protease inhibitors, Kaletra may be associated with other significant or serious adverse events, including increases in blood glucose, redistribution of body fat, and potentially serious or life-threatening drug interactions. To prevent such drug interactions and potential loss of drug effectiveness, health-care providers and patients should find out about drugs that should not be used with Kaletra and other antiretrovirals.

Abbott Laboratories in North Chicago, Ill., manufactures Kaletra.



New Uses for Old Drug: Reducing Risk of Heart Attacks and Strokes

A large international study has shown that a drug approved nearly 10 years ago to treat high blood pressure can also reduce the risk of heart attacks, strokes, and even death. Because of the new findings, the Food and Drug Administration gave the manufacturer approval in October to market the drug—ramipril—for these new uses.

The Heart Outcomes Prevention Evaluation (HOPE) study took place in 19 countries in North and South America and Europe. Of the more than 9,000 patients enrolled in the study, approximately 4,600 received ramipril and the rest a placebo.

Patients in the study were 55 years or older and were considered at high risk for cardiovascular events because they had a history of coronary artery disease, stroke, or peripheral vascular disease. In addition, diabetic patients were eligible to participate if they had at least one other risk factor for heart disease, such as hypertension, high total cholesterol, or cigarette smoking.

The study participants treated with ramipril showed a 22 percent reduction, compared with placebo, in the risk of heart attack, stroke, or death from cardiovascular or other causes over a five-year follow-

up period. Complications related to diabetes also decreased substantially among the patients who took ramipril.

“These results indicate that if ramipril is used widely in appropriate patients, over one million premature deaths, heart attacks and strokes would be prevented each year [worldwide],” says Salim Yusuf, MD, HOPE study chairman and professor of medicine at McMaster University, Hamilton, Ontario. The results of the HOPE study were published in the *New England Journal of Medicine*, January 20, 2000, and can be found on the journal’s Web site at www.nejm.org.

Another arm of the HOPE study, continuing for several more years, is examining the effects of vitamin E versus placebo on heart disease and cancer.

Side effects of ramipril include headaches, dizziness, fatigue and dry cough. As with all angiotensin-converting enzyme (ACE) inhibitors, the drug should not be taken by pregnant women.

Ramipril is manufactured under the brand name Altace by Aventis Pharmaceuticals, Kansas City, Mo., and distributed by Monarch Pharmaceuticals, Bristol, Tenn., a wholly owned subsidiary of King Pharmaceuticals, Inc.

Monthly Injection Provides New Contraceptive Choice

Women now have one more way to prevent pregnancy. In October, the Food and Drug Administration approved Lunelle, a once-a-month injection that combines the hormones progesterin and estrogen to inhibit ovulation. The injection contains medoxyprogesterone acetate and estradiol cypionate as its active ingredients.

The intramuscular injections are given by a health-care provider every 28 to 30 days, and no longer than 33 days apart. To ensure that Lunelle is not accidentally given to a pregnant woman, the first injection should be given during the first five days of the menstrual period. The effects of Lunelle are reversible, and women can begin ovulating again two to four months after discontinuing the injections.

Several clinical trials of Lunelle’s safety and effectiveness have reported failure rates of less than 1 percent. Most women experience changes in their menstrual cycle. In the U.S. trial, weight gain was the most common adverse event leading to discontinuation of Lunelle. Out of 782 women using Lunelle for up to 15 cycles, nearly 6 percent of participants stopped using the drug because of weight gain.

Doctors and consumers should be aware that there are some groups of women who should not use Lunelle, including women known or suspected to be pregnant, heavy smokers (more than 15 cigarettes per day) who are over the age of 35, and women with severe hypertension.

Pharmacia Corporation in Peapack, N.J., manufactures Lunelle.

Survey Shows Parents Need to Measure Children's Medicine More Accurately

"Take 1 tsp. 3 times a day."

A parent reads these familiar dosage directions on her child's prescription medicine. She reaches into her kitchen silverware drawer and selects a small spoon, then carefully pours the liquid and gives the tot the correct dose. Right?

Probably not.

Almost three-quarters of caregivers surveyed in a recent study use standard flatware spoons to measure medicines at least some of the time. But typical household teaspoons hold from 2 to 10 milliliters of liquid, so chances are this mom gave something other than the prescribed 5 milliliter dose—the equivalent of one measuring teaspoon.

Even though the American Academy of Pediatrics has been recommending for 25 years that more accurate dosing devices be used, there have been few studies that look at how often or how well these devices—including oral dosing sy-

ringes, medicine cups, and calibrated medicine droppers and spoons—are actually used by parents. So physicians Diane J. Madlon-Kay and Frederick S. Mosch of Regions Hospital in St. Paul, Minn., and the University of Minnesota

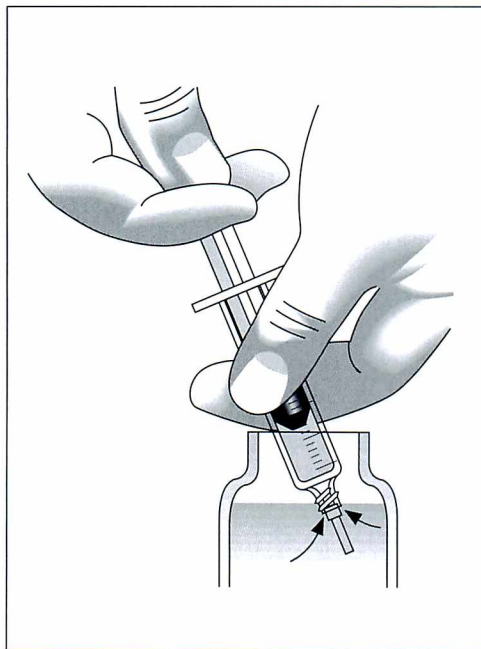
Medical School in Minneapolis designed a study to find out. They surveyed patients at three primary care clinics in St. Paul, Minn., to see what dosing devices caregivers use and how accurately they are measuring their medications.

Seventy-three percent of the 130 patients surveyed reported using a

household teaspoon for measuring medicines, but most could also use more accurate devices correctly. The participants were able to measure the proper amount of liquid using an oral dosing syringe more than 90 percent of the time. When interpreting dosing instructions, survey

participants usually were correct when instructions called for taking medicine three or four times a day. But in many cases, they misinterpreted instructions calling for a dose every six hours, assuming that medicine should be given in six-hour intervals while awake, resulting in three daily doses, rather than the prescribed four a day.

Based on these survey results, the researchers encourage clinicians to promote the use of accurate dosing implements, especially oral dosing syringes. They also suggest that medication instructions should indicate the dosing interval by number of doses per day, rather than hours between doses. (*The Journal of Family Practice*, August 2000)



For more on how to give medicines properly, see "Avoiding Problems:

Liquid Medication and Dosing Devices," October 1994 *FDA Consumer*, and "How to Give Medicine to Children," January–February 1996 *FDA Consumer*. Both are available on FDA's Web site, at www.fda.gov/fdac/fdacindex.html. To request a printed copy of the 1996 article, write to FDA (HFD-210), 5600 Fishers Lane, Rockville, MD 20857.

New Glue Approved to Reduce Blood Flow During Brain Surgery

A new glue offers another option for reducing blood loss in a rare form of brain surgery. The Food and Drug Administration approved the Trufill n-BCA Liquid Embolic System for use in patients at risk of hemorrhaging and dying from a cerebral arteriovenous malformation (AVM). An AVM consists of abnormally connected arteries and veins that may rupture and cause a stroke. Typically, surgery is performed to remove the AVM and reduce the risk of serious complications. Approximately 4,000 cerebral AVM

procedures are performed each year.

Cordis Neurovascular Inc., of Miami Lakes, Fla., makes the glue, which reduces blood flow to the surgical site in the brain before the procedure begins. Surgeons inject the glue into the AVM prior to its removal. The glue is infused into blood vessels through a catheter that is inserted into the leg and threaded up to the brain. Later, the glue is removed during surgery.

The company's multi-center study of 104 patients showed the glue was as ef-

fective in blocking blood flow as the standard treatment with poly-vinyl alcohol particles. Half the patients in the study were treated with glue and half with poly-vinyl alcohol particles. Both groups had about the same rate of complications.

FDA based approval of the product on a review of Cordis' pre-clinical and clinical studies of safety and effectiveness, and on the recommendation of the Neurological Devices Panel of FDA's Medical Devices Advisory Committee.

Electronic Brain Implant Helps Patients Regain Hearing After Cranial Nerve Surgery

There's new hope for patients with a rare neurological disease who lose their hearing after undergoing surgery to remove tumors growing on cranial nerves. A newly approved implanted device restores some of the hearing lost when the auditory nerves that transmit sounds to the brain are severed.

The auditory brain stem implant, approved for marketing in October by the Food and Drug Administration, is the first of its kind. Part of the electronic device is surgically implanted into the brain, where it stimulates the area that normally receives electrical signals from the ear. The patient wears a pocket-sized speech processor that picks up sound and changes it into electrical pulses that

are transmitted to the implant.

The implant was approved for use in teenagers and adults who have a rare disease called Neurofibromatosis Type 2 (NF2). People with the disease eventually need surgery to remove tumors on cranial nerves. When this surgery severs the auditory nerve, the patient will have a total loss of hearing that cannot be helped by external hearing aids or cochlear implants (devices that aid hearing by stimulating the cochlea, a structure of the inner ear).

In studies conducted to establish its safety and effectiveness, the device was implanted in about 90 people during surgery for NF2. When patients were evaluated after six months, most were able to

perceive at least some sounds. More than 80 percent of the people who were evaluated after receiving the implant could detect certain familiar sounds, such as honking horns and ringing doorbells, and could understand conversation with the aid of lip reading. And 12 percent of those evaluated could hear well enough to use a telephone. However, 18 percent of all patients studied were not able to hear any sound at all, because the implant was either placed incorrectly or it moved after surgery.

The device, called the Nucleus 24 Multichannel Auditory Brainstem Implant, is manufactured by Cochlear Corporation of Englewood, Colo.

Device Delivers Shock Waves to Help Ease Heel Pain Caused by Plantar Fasciitis

The same shock wave treatment that has been used for years to break up kidney stones without surgery is now helping to relieve chronic heel pain. The Food and Drug Administration has approved the OssaTron device to treat chronic proximal plantar fasciitis, a condition that causes severe pain in the heel of the foot, for use on adults who have been unsuccessful with other treatments.

Plantar fasciitis is usually caused by an inflammation of the ligament that runs from the heel to the ball of the foot, and is typically treated with physical therapy, pain relievers, cortisone injections, heel-cushions, and in severe cases, with surgery.

The shock used in the treatment is created by a spark-plug-like device that's enclosed in a soft plastic dome filled with water. During treatment, the dome is placed closely against the heel so that the shock waves pass through the dome to the heel. One theory for the mechanism of action is that the shock wave-induced damage causes new blood vessels to form, in turn healing

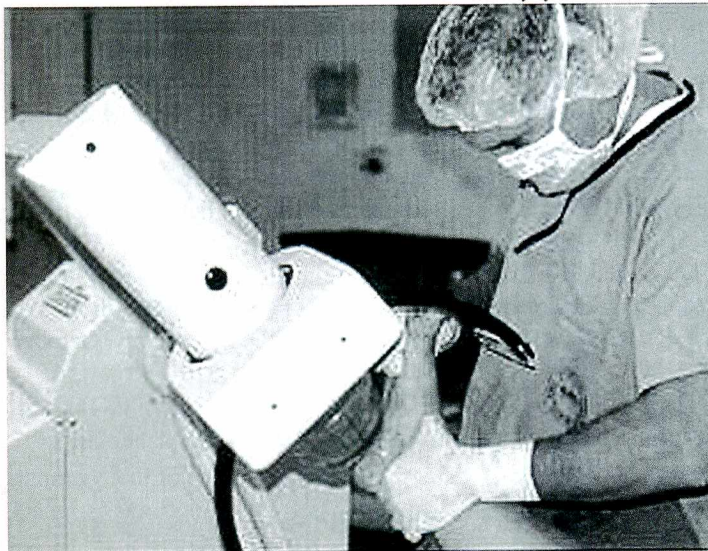
cells that grow new, healthy tissue. A total of 1,500 shocks are usually delivered, and treatment is performed as an outpatient procedure.

FDA approval was granted based on the results of a multi-center, randomized, placebo-controlled study of about 300 patients. Approximately 60 percent of patients were completely relieved of symptoms following a single OssaTron treatment, and 80 percent experienced

significant relief.

The OssaTron's side effects include mild neurological symptoms and tears in the tissue on the bottom of the foot. As a condition of approval in October, FDA is requiring the manufacturer, HealthTronics, Inc., of Marietta, Ga., to conduct another study to evaluate further the problems of neurological symptoms and plantar fascial ruptures.

Photo courtesy of Richard Alvarez, MD



Richard Alvarez, MD, applies shock wave treatment to a patient with heel spurs during the OssaTron's phase 1 FDA trials at Memorial Hospital, Chattanooga, Tenn.

Head Injury Linked to Increased Risk of Alzheimer's Disease

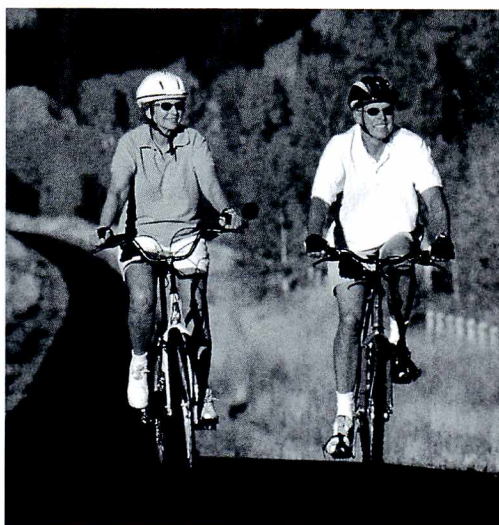
There may be one more reason to wear that bike helmet now, says epidemiologist Richard Havlik, MD, of the National Institute on Aging in Bethesda, Md. Serious head injury in early adulthood may be linked to developing Alzheimer's disease (AD) and other forms of dementia later in life, according to Havlik and a team of researchers at NIA and Duke University Medical Center in Durham, N.C.

The researchers studied the records of more than 7,000 World War II male veterans who were sent to military hospitals with head injuries or unrelated conditions. They then tracked down 1,776 veterans who were eligible for the study—548 of whom had suffered a head injury. The remaining 1,228 without head injuries made up the control group. Telephone interviews with the veterans or a family member were used to determine the current cognitive and functional abilities of the men.

Study results suggested that the more severe the head injury, the greater the risk of developing AD or other forms of dementia. The risk was doubled for individuals with moderate head injury, and men with severe head injuries had a four-fold greater risk. Moderate injury was defined as a skull fracture, or amnesia or loss of consciousness for more than 30 minutes but less than 24 hours. Severe injury was amnesia or loss of consciousness for 24 hours or more. Results for participants who had mild injury—loss of consciousness or amnesia for less than 30 minutes—were inconclusive.

Previous studies have suggested a relationship between head injuries and dementia, but were thought to be influenced by “recall errors” because they relied on patient and family memories of injuries that may have occurred decades earlier. Havlik cautions that the new findings do not show a direct cause-and-effect relationship between head injury and dementia but do show an association that warrants further study. “We now need to hone in on what’s behind these findings, especially what may be happening biologically,” he says.

Each year, an estimated 1.5 to 2 million individuals in the United States suffer a significant head injury, according to the National Institutes of Health. It is estimated that up to 4 million Americans currently have AD. (*Neurology*, October 24, 2000)



For further information on Alzheimer's disease, contact the Alzheimer's Disease Education and Referral (ADEAR) Center, a service of the National Institute on Aging, at PO Box 8250, Silver Spring, MD 20907-8250, toll-free telephone 1-800-438-4380, Web site www.alzheimers.org/.

Ask FDA ...

Call the Food and Drug Administration's toll-free information lines for answers to your questions about FDA-regulated products.

For all FDA topics:

1-888-INFO-FDA
(1-888-463-6332)

For foods, food safety, and cosmetics:

Food Safety Information Service
1-888-SAFEFOOD
(1-888-723-3366)

*Staffed by information specialists
10 a.m. to 4 p.m. weekdays; extensive library of recorded messages all other times*

Food Safety Recorded Message Hotline:

1-877-727-FOOD
(1-877-727-3663)

Recorded message about timely topics, such as recalls or public health promotions

Or call the public affairs specialist in your local FDA field office (check the blue pages of the phone book under “U.S. Government/Food and Drug Administration”).

FDA Issues Public Health Advisory On Phenylpropanolamine In Drug Products

By Michelle Meadows

On November 6, the Food and Drug Administration issued a public health advisory alerting consumers to stop using over-the-counter (OTC) and prescription drug products containing phenylpropanolamine because this ingredient has been associated with an increased risk of hemorrhagic stroke (bleeding in the brain).

Phenylpropanolamine is commonly used as a decongestant in OTC and prescription cough and cold medications and as an appetite suppressant in OTC weight loss products. FDA recommends that consumers check labels of OTC drugs for phenylpropanolamine and stop using products that contain this ingredient.

Those using a prescription decongestant or cough-cold product should ask their pharmacists and health providers if it contains phenylpropanolamine. A commonly used alternative decongestant is pseudoephedrine, and most manufacturers will reformulate cough and cold products using this ingredient, says Robert Sherman, a biologist with FDA's Center for Drug Evaluation and Research (CDER). "Although it is in the same drug class as phenylpropanolamine and is effective as a nasal decongestant, we do not have the same concerns with pseudoephedrine," he says. As for using phenylpropanolamine as an OTC appetite suppressant, there is no alternative OTC drug product.

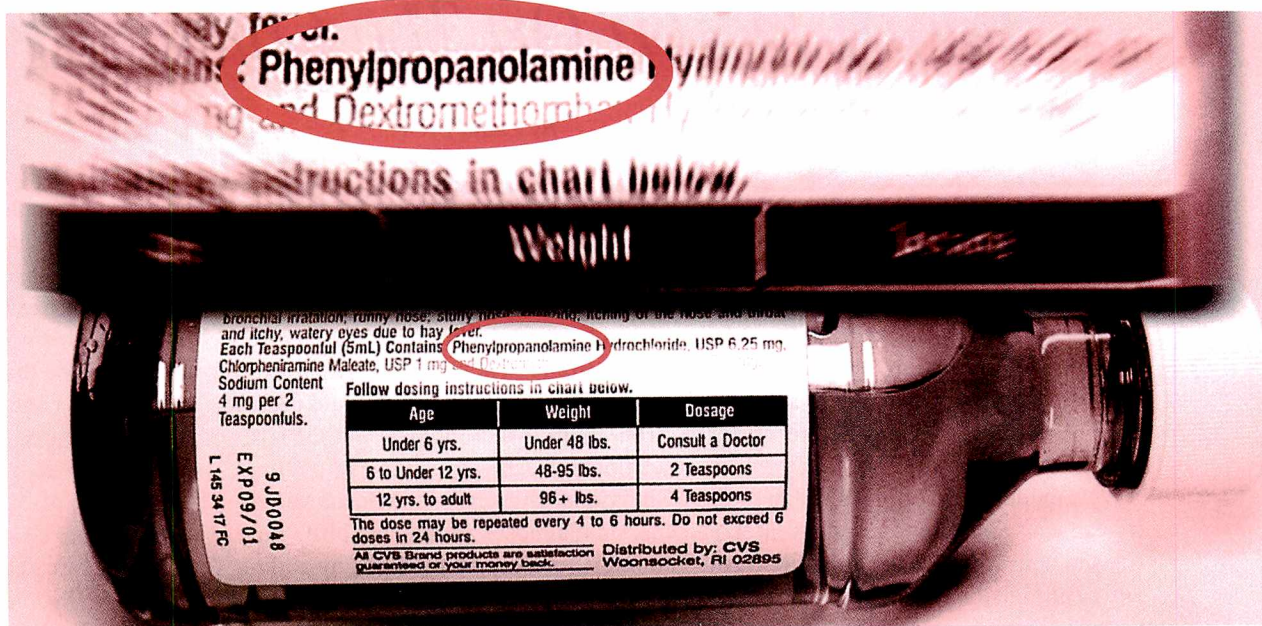
FDA intends to proceed with the public rulemaking process that will propose the removal of phenylpropanolamine from OTC products. CDER sent letters to drug manufacturers, repackers, and distributors, requesting that they voluntarily discontinue marketing products containing phenylpropanolamine. This interim measure aims to protect the public's health while FDA moves forward with rulemaking to classify phenylpropanolamine as "not generally recognized as safe and effective."

About 10,000 hemorrhagic strokes occur each year among people aged 18 to 49 in the United States, and an estimated 200–500 could be associated with phenylpropanolamine, says CDER director Janet Woodcock, MD. "Though the risk of

stroke is low," she says, "FDA is concerned because of the seriousness of the adverse event and advises consumers to stop taking products with phenylpropanolamine."

In October 2000, FDA's Nonprescription Drugs Advisory Committee voted that phenylpropanolamine should not be considered safe after it evaluated several reports, including a recent epidemiological study conducted by scientists at Yale University's School of Medicine.

The study enrolled 702 men and women ages 18 to 49 who



were hospitalized because of hemorrhagic stroke and 1,376 control subjects who did not have strokes. Researchers found an association between phenylpropanolamine use and hemorrhagic stroke in women. Because so few men in the study were exposed to the drug, researchers couldn't determine if their risk is different from women's. So while the risk of stroke was found mostly in women, men may also be at risk.

FDA requested the Yale study because of previous reports of a potential association between phenylpropanolamine and hemorrhagic stroke. In 1976, an expert panel recommended that the ingredient be generally recognized as safe and effective as a nasal decongestant, and another expert panel made the same recommendation for weight control in 1982. FDA hadn't finalized phenylpropanolamine's safe and effective status because of concerns over occasional reports of stroke associated with the drug.

FDA encourages health professionals and consumers to report serious adverse reactions to phenylpropanolamine to MedWatch, 1-800-FDA-1088; www.fda.gov/medwatch. ■



Antibiotic Resistance

From Down On The Chicken Farm

By Linda Bren

Chicken wings and turkey drumsticks are almost as ingrained in American culture as apple pie and baseball. But the lip-smackin', finger-lickin' good taste is less palatable when the poultry makes people sick. Even harder to swallow are germs that don't respond to drugs that may be prescribed to fight the sickness.

New evidence that drugs used in poultry can cause antibiotic-resistant infections in consumers spurred the Food and Drug Administration's Center for Veterinary Medicine (CVM) to take action. On October 31, CVM proposed to withdraw the approval of an antibacterial, Baytril (enrofloxacin), used to treat disease in chickens and turkeys. CVM approved Baytril in 1996. Made by the Bayer Corporation of Shawnee Mission, Kan., Baytril belongs to a class of antibacterials called fluoroquinolones, which have been used in humans since 1986.

Shortly prior to CVM's announcement, Abbott Laboratories of North Chicago, Ill., requested withdrawal of the approvals for its poultry fluoroquinolone products. This means that Abbott will voluntarily remove these products, trade name SaraFlox, from the market.

The Bayer Corporation has requested a hearing to present safety data to try to keep Baytril on the market. The com-

pany must submit all data and analysis to support consideration for a hearing by January 2, 2001.

Poultry growers use fluoroquinolone drugs to keep chickens and turkeys from dying from *Escherichia coli* (*E. coli*) infection, a disease that they could pick up from their own droppings. But the size of flocks precludes testing and treating individual chickens—so when a veterinarian diagnoses an infected bird, the farmers treat the whole flock by adding the drug to its drinking water. While the drug may cure the *E. coli* bacteria in the poultry, another kind of bacteria—*Campylobacter*—may build up resistance to these drugs. And that's the root of the problem.

People who consume chicken or turkey contaminated with fluoroquinolone-resistant *Campylobacter* are at risk of becoming infected with a bacteria that current drugs can't easily kill.

Campylobacter is the most common bacterial cause of diarrheal illness in the United States, according to the Centers for Disease Control and Prevention. It's estimated to affect over 2 million persons every year, or 1 percent of the population.

Commonly found in chickens, *Campylobacter* doesn't make the birds sick. But humans who eat the bacteria-

contaminated birds may develop fever, diarrhea, and abdominal cramps. In people with weakened immune systems, *Campylobacter* can be life-threatening. Eating undercooked chicken or turkey, or other food that has been contaminated from contact with raw poultry, is a frequent source of *Campylobacter* infection. Not washing utensils, countertops, cutting boards, sponges, or hands after coming into contact with raw poultry can also spread the bacteria and cause infection. People infected with *Campylobacter* may be prescribed a fluoroquinolone—which may or may not work.

But the damage doesn't stop there. "Cross-resistance occurs throughout this class of drugs," says Stephen F. Sundlof, DVM, PhD, director of CVM. "So resistance to one fluoroquinolone can compromise the effectiveness of all fluoroquinolone drugs."

Considered one of the most valuable drug classes available to treat human infections, fluoroquinolones are used to treat a wide range of diseases, including the gastrointestinal illness caused by *Campylobacter* infection.

The use of antibiotics in food animals has been a human health concern since the 1970s when FDA first called for restrictions on antibiotics used in animal

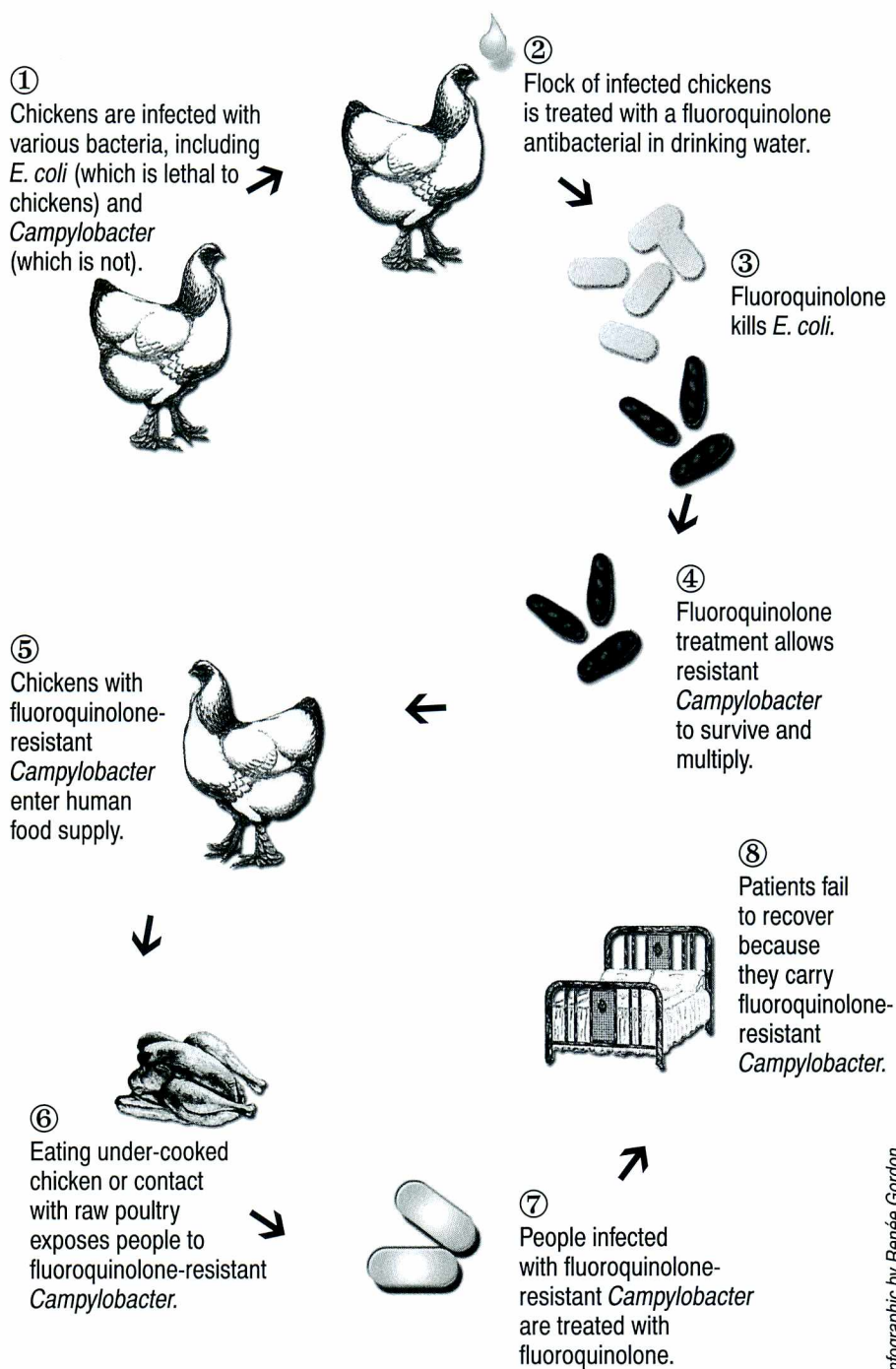
feed. Prior to 1995, when fluoroquinolones were first approved to treat poultry, very few fluoroquinolone-resistant *Campylobacter* were found in people with foodborne diseases in the United States. After the approval, however, many more fluoroquinolone-resistant bacteria were found in humans and in poultry from slaughter plants and retail stores.

The data to support these findings came from a study by the Minnesota Department of Health and a computerized system called NARMS—the National Antimicrobial Resistance Monitoring System. Created in 1996 as a joint effort by CVM, CDC, and the U.S. Department of Agriculture, NARMS monitors human and animal resistance to 17 antimicrobials. Antimicrobials include antibacterials, antivirals, antifungals, and antiparasitics.

Data provided by NARMS and other sources were used to develop a risk assessment. This assessment, along with other data, supported CVM's decision to propose the withdrawal of approval of Baytril for use in poultry. The risk assessment quantified, for the first time, the magnitude of the dangers to humans eating chicken contaminated with fluoroquinolone-resistant *Campylobacter*. It showed that the number of people infected with fluoroquinolone-resistant *Campylobacter* from eating chicken rose from an estimated 8,782 in 1998 to 11,477 in 1999.

The risk assessment, completed in October, is only one action CVM has taken to address the antimicrobial resistance problem over the years, says Sundlof. Another part of CVM's proactive program is its proposal to take a stronger regulatory approach when approving new antimicrobial drugs for use in food animals. A "framework document" lays out a plan for evaluating the safety of these drugs based on their importance to human health. If the plan is implemented, the drugs of highest importance—those used to treat a serious or life-threatening disease in humans for which there is no effective alternative treatment—would be subject to the strictest criteria for approval for animal use. Among the studies that would be required by drug sponsors are tests to show their product's potential to induce antibiotic resistance.

How People Get Antibiotic-Resistant Bacteria From Chickens



Infographic by Renée Gordon

CVM has invited input from outside experts on the principles in the framework document. Two public meetings have been held in the past year and a half, and a third is scheduled for January 22–24 to discuss establishing regulatory thresholds on antimicrobial resistance. The workshop will be held from 8:30 a.m. to 5:00 p.m. at the DoubleTree Hotel, 1750 Rockville Pike, Rockville, MD 20852. For more

details on the meeting and the framework document, see the CVM Home Page at www.fda.gov/cvm/.

"FDA and CVM will continue to work to put in place a regulatory system that addresses the dangers of antimicrobial resistance and offers better protection to public health," says Sundlof. "At the same time, CVM will strive to assure the safe use of antimicrobial drugs in food-producing animals." ■

Fighting The Flu

By Linda Bren

If you haven't gotten your flu shot yet, go get it. January is not too late to get a flu shot.

"Those getting vaccinated at any time will be better protected against the influenza (flu) virus," says Roland A. Levandowski, MD, a virologist in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER).

Delays in distribution of the vaccine to health-care providers have prevented some people from getting their shots in October and November—the usual time for vaccination. But the vaccine can be used in January and later with good effectiveness since the flu season lasts through March, says Levandowski.

Studies have shown the vaccine's effectiveness rate to be 70 to 90 percent in healthy young adults. In the elderly and in people with certain chronic illnesses, the vaccine sometimes doesn't prevent illness altogether, but does reduce its severity and the risk of serious complications and death.

The vaccine's most common side effect is soreness at the vaccination site for up to two days. Some people may experience post-shot fever, sore muscles and other symptoms resembling the flu that can last for one to two days. But the flu vaccine cannot actually cause flu because it contains only inactivated viruses.

The Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices strongly recommend vaccination for the following high-risk groups and their close contacts and health-care workers:

- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- Persons aged 65 years and older;
- Residents of nursing homes and other facilities that provide care for chronically ill persons;
- Adults and children who have certain underlying medical conditions that re-

quired hospitalization or regular doctor visits during the past year because of chronic disease including heart, lung or kidney disease, diabetes, asthma, anemia, or immunosuppression (for example, caused by medications or HIV infection);

- Children and teenagers (aged 6 months to 18 years) who must take aspirin regularly and therefore might be at risk for developing Reye syndrome if they get the flu; and
- Women who will be in the second or third trimester of pregnancy during the influenza season. (Pregnant women who have a high-risk condition should be immunized regardless of the stage of pregnancy.)

Some people—but not many—should avoid the flu shot. People who have had an allergic reaction to eggs or to a previous dose of influenza vaccine should consult a doctor before getting a flu shot if they plan to get the shot at a place other than their physician's office. And those with a high fever should not receive the vaccine until they feel better.

Flu Facts

Influenza, commonly called the flu, is an infection of the respiratory tract caused by the influenza virus. Signs of the flu include sudden onset of headache, chills, and feeling generally miserable. Respiratory symptoms like nasal congestion, cough and sore throat appear, and the flu sufferer often experiences extreme fatigue and muscle aches in the back and legs. Fever between 100 and 103 degrees Fahrenheit is typical in adults, and is often even higher in children.

Scientists have classified influenza viruses as types A, B and C. Type A is the most common and leads to the most serious epidemics. Type B can cause

epidemics, but usually produces a milder disease than type A. Type C viruses have usually been associated with symptoms suggesting a common cold.

Influenza rarely causes stomach upset; however, young children may have nausea and vomiting during the most severe phase of the flu. What is popularly called "stomach flu" is usually another malady: gastroenteritis. Bacteria, toxins, or viruses other than influenza are the usual causes of gastroenteritis.

Serious illnesses like strep throat, measles, and chickenpox sometimes have flu-like symptoms. It's important to see a doctor if symptoms persist, become severe or localized in the throat, stomach or lungs, or if other symptoms such as skin rash, vomiting or behavioral changes occur.

Influenza and other respiratory viruses can be transmitted in one of two ways: by inhaling infectious particles in the air (like respiratory secretions from a cough or sneeze), or by touching respiratory secretions, usually on the skin, of an already-infected person and then touching one's eyes or nose. Shaking hands, for example, with an infected person, or touching environmental surfaces (like doorknobs or handrails) that have been contaminated with flu virus particles and then touching your eyes or nose may transmit the virus.

"In addition to getting vaccinated, the single most important step people can take to help prevent getting the flu is to wash their hands," says Linda Lambert, PhD, influenza program officer with the National Institute of Allergy and Infectious Diseases. Hand washing is especially important after interacting with children, according to Lambert, since children are very susceptible to flu and are the primary spreaders of the virus in the community. Lambert also recommends disinfecting environmental surfaces in the home when someone is sick with the flu since the virus can live for several hours on these surfaces. Using virus-killing disinfectant on telephones, doorknobs, and computer keyboards, for example, can help prevent transmission to other family members. "And if you have the flu," says Lambert, "always use disposable tissues when coughing or sneezing and throw away the tissue immediately to help prevent infectious particles from spreading to someone else."

Other Flu Fighters

While the FDA-licensed vaccination is the chief method of preventing infection, one prescription medication, Tamiflu, can help prevent influenza types A and B.

FDA first approved Tamiflu (oseltamivir phosphate), a capsule, in 1999 to help lessen flu symptoms and duration in adults. Then in November 2000 the agency approved Tamiflu as an influenza prophylaxis (preventive) in adults and adolescents 13 years and older. To be effective in preventing influenza infection, the drug must be taken when a person is first exposed to others suffering from the flu. If someone in the home gets the flu, other family members can possibly avoid getting it by taking Tamiflu daily for at least seven days. The drug can be taken for up to six weeks by a person exposed to the flu because of an outbreak in the community.

Relenza (zanamivir), an inhaled powder, approved in 1999 for adults and children aged seven years and older, can also reduce the length and severity of the flu. Like Tamiflu, Relenza must be taken within the first two days after symptoms begin.

Relenza's labeling has been updated recently to emphasize the possibility of bronchospasm (wheezing) or serious breathing problems in some patients taking the drug. Because of the risk of these side effects, Relenza is not generally recommended for people with chronic respiratory disease, such as asthma, nor for those with chronic obstructive pulmonary disease. These conditions should be discussed with a health-care provider before taking the drug.

Two other drugs, Symmetrel (amantadine) and Flumadine (rimantadine), available in tablets or syrup, are approved to prevent and treat the symptoms of influenza A virus only. Symmetrel, approved in 1968, can be used to help prevent and treat influenza A virus in both adults and children. Flumadine, approved in 1993, can be used to prevent and treat influenza A virus in adults, and to prevent (but not to treat the symptoms of) influenza A virus in children. Both Symmetrel and Flumadine have the potential for causing serious central nervous system side effects. Although these drugs may be used by otherwise healthy people to prevent

and treat influenza A virus infections, both are usually reserved for use in more closely monitored situations, such as in nursing homes.

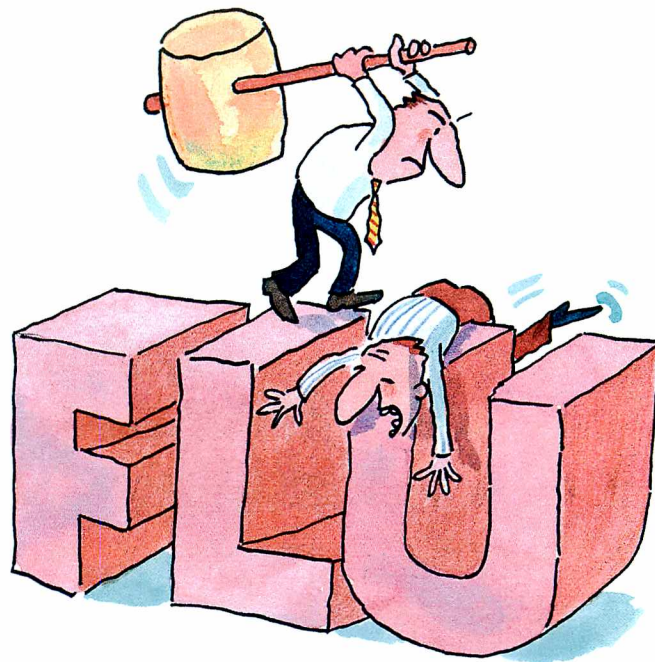
Treating Yourself

Flu sufferers should drink fluids, try to eat, and get plenty of rest, says Lambert. Your body is trying to attack the virus, and it takes energy to do that.

While fluids, nutrients, and rest are important elements to curing the flu, over-the-counter medications can help relieve some of the symptoms. "OTC cough-cold products can make you more comfortable," says Debbie Lumpkins, a microbiologist with FDA's division of over-the-counter drug products. "They are intended to treat the symptoms of minor conditions, not to treat the underlying illness."

There are many cough-cold products on the market that contain a variety of ingredients. It's important to check the ingredients listed on the label, says FDA, to make sure that the product does not contain phenylpropanolamine because researchers have found an association between phenylpropanolamine and hemorrhagic stroke. Although the risk of stroke is low, FDA believes that the conditions for which these products are used do not appear to warrant the risk for using this drug. (See article about the public health advisory on this ingredient on page 9.)

Children and teenagers with symp-



toms of flu or chickenpox should not take aspirin or products containing aspirin or other salicylates. Use of these products in young flu and chickenpox sufferers has been associated with Reye syndrome, a rare condition that can be fatal. Be sure to check the label of a product to make sure it doesn't contain aspirin or other salicylates.

"In the future, consumers may have alternatives to the flu shot," says Lambert, "including needle-free vaccinations such as a nasal spray or a skin patch." Major pharmaceutical companies, in cooperation with scientists representing the National Institutes of Health, FDA's CBER, and academia, are continuing to investigate ways to make even more protective vaccines.

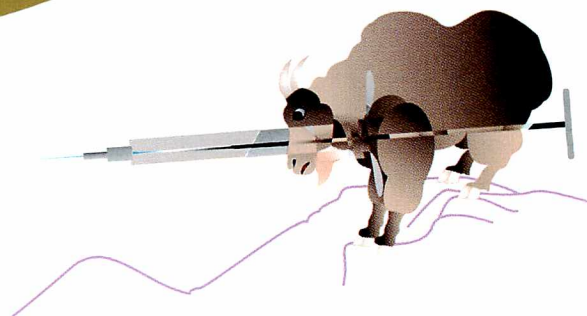
For further information on the flu and the influenza vaccine, see CBER's Web site at www.fda.gov/cber/flu/flu2000.htm. ■

Where to Get a Flu Shot

For individuals who are searching for a place to obtain an influenza vaccination, the Centers for Disease Control and Prevention (CDC) suggest the following:

- Contact your personal health-care provider.
- Call your local public health clinic or state health department immunization program. Most state health departments are listed on CDC's Web site at www.cdc.gov/nip/flu-vac-supply/FluStateList.htm. Or call the toll-free National Immunization Hotline at 1-800-232-2522 (English) or 1-800-232-0233 (Spanish).
- Check media outlets such as newspapers, radio stations, or other public information sources for specific clinics in your community.
- Check with your county medical society.

A New



Kind Of Fish Story

The Coming Of Biotech Animals

By Carol Lewis

Potatoes with built-in insecticide. Rice with extra vitamin A. Decaf coffee beans fresh off the tree. Just when Americans have begun to digest the idea of custom-built crops, along comes another major advance in biotechnology that could make an even bigger splash onto the dinner plate: genetically engineered fish.

Using the same type of gene transfer techniques that give plants new, more desirable traits, scientists have created a genetically engineered variety of Atlantic salmon that grows to market weight in about 18 months, compared to the 24 to 30 months that it normally takes for a fish to reach that size. For fish farmers, raising these so-called transgenic fish could be faster and cheaper because it takes less feed and about half the time to produce a crop they can send to market.

Transgenic animals are just another class of products developed through biotechnology that, it is hoped, will give renewed energy to the decades-old Green Revolution. Transgenic technology promises more and better crops and food animals to feed a continuously growing world population. Genetically engineered plant crops, such as corn and soybeans, have been on the market for several years. Now, geneti-

While it's still too soon to tell how quickly foods derived from transgenic animals will move to the market, FDA has already begun to focus on how it will ensure that they meet the same safety standards as traditional foods.

cally engineered animals may soon begin to make their way through the regulatory net, and ultimately to the dinner table—possibly starting with fast-growing fish that the sponsor promises will begin a “Blue Revolution.”

The potential benefits of transgenic animals, however, do not stop at food production. Scientists created the first transgenic animals to advance basic biomedical research, genetically modifying lab rats, mice, rabbits, and monkeys to give them characteristics that mimic human diseases. These research resources, for example, rapidly advanced the understanding of oncogenes—genes that have gone awry and are responsible for causing cancers.

Moreover, researchers now seek ways to genetically modify the organs of ani-

mals, such as pigs, for possible transplantation into humans.

And finally, transgenics can turn animals, such as cows, sheep and goats, into pharmaceutical factories that produce in their milk protein-based drugs such as alpha antitrypsin, a protein that can be used to treat cystic fibrosis.

Despite these benefits, genetic engineering of animals has met with some of the same resistance already aimed at designer crops. Critics cite ecological concerns, ethical objections and food-safety issues.

But no matter how transgenics is applied, the Food and Drug Administration will play a key role in regulating the products resulting from this rapidly emerging genetic technology. This means that any drug or biologic created through transgenic techniques will need to undergo

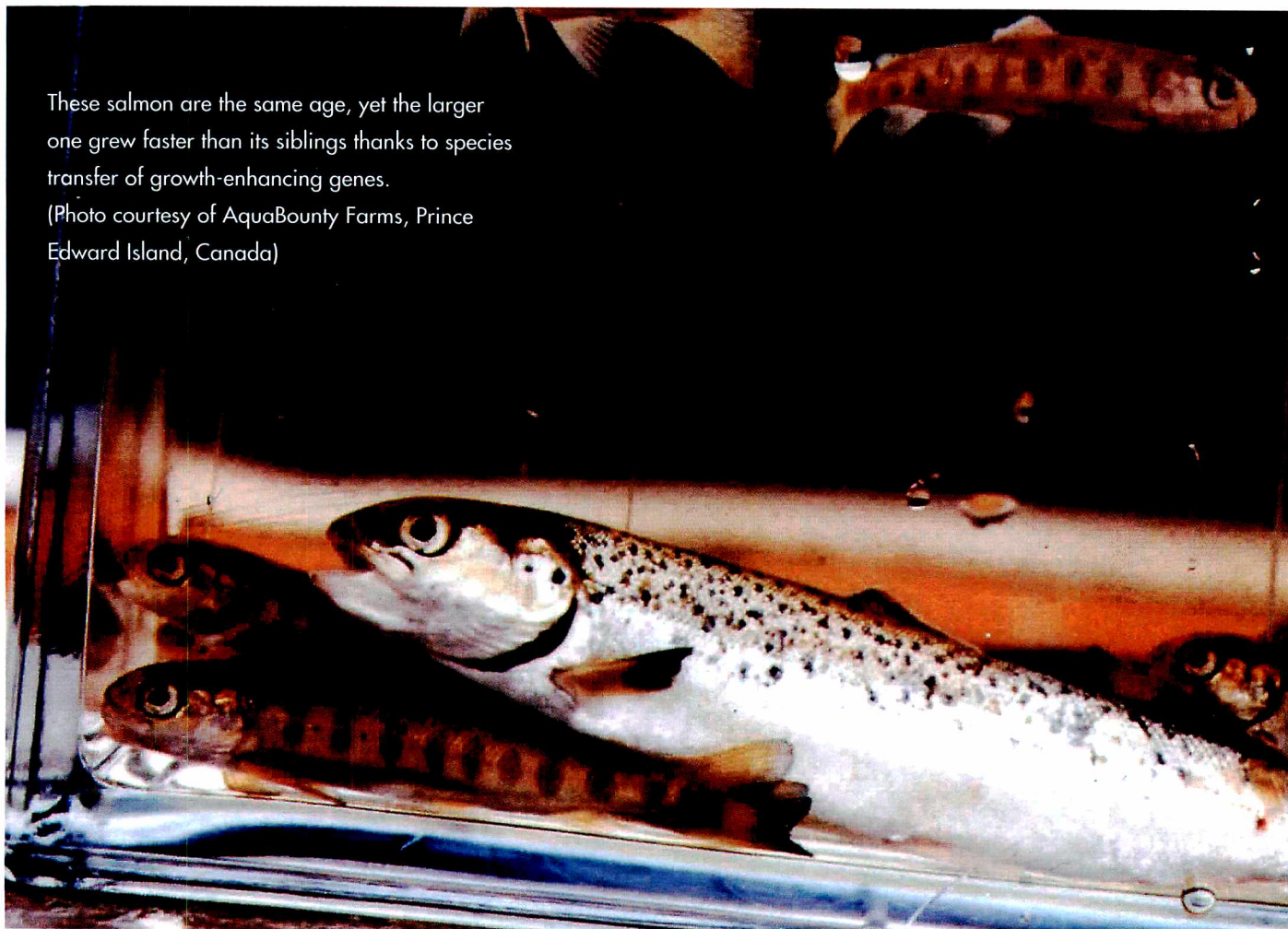
the same FDA scrutiny as any other treatment that a company wants to market, including clinical trials that demonstrate safety and effectiveness. And while it's still too soon to tell how quickly foods derived from transgenic animals will move to the market, FDA has already begun to focus on how it will ensure that they meet the same safety standards as traditional foods.

Making a Transgenic Animal

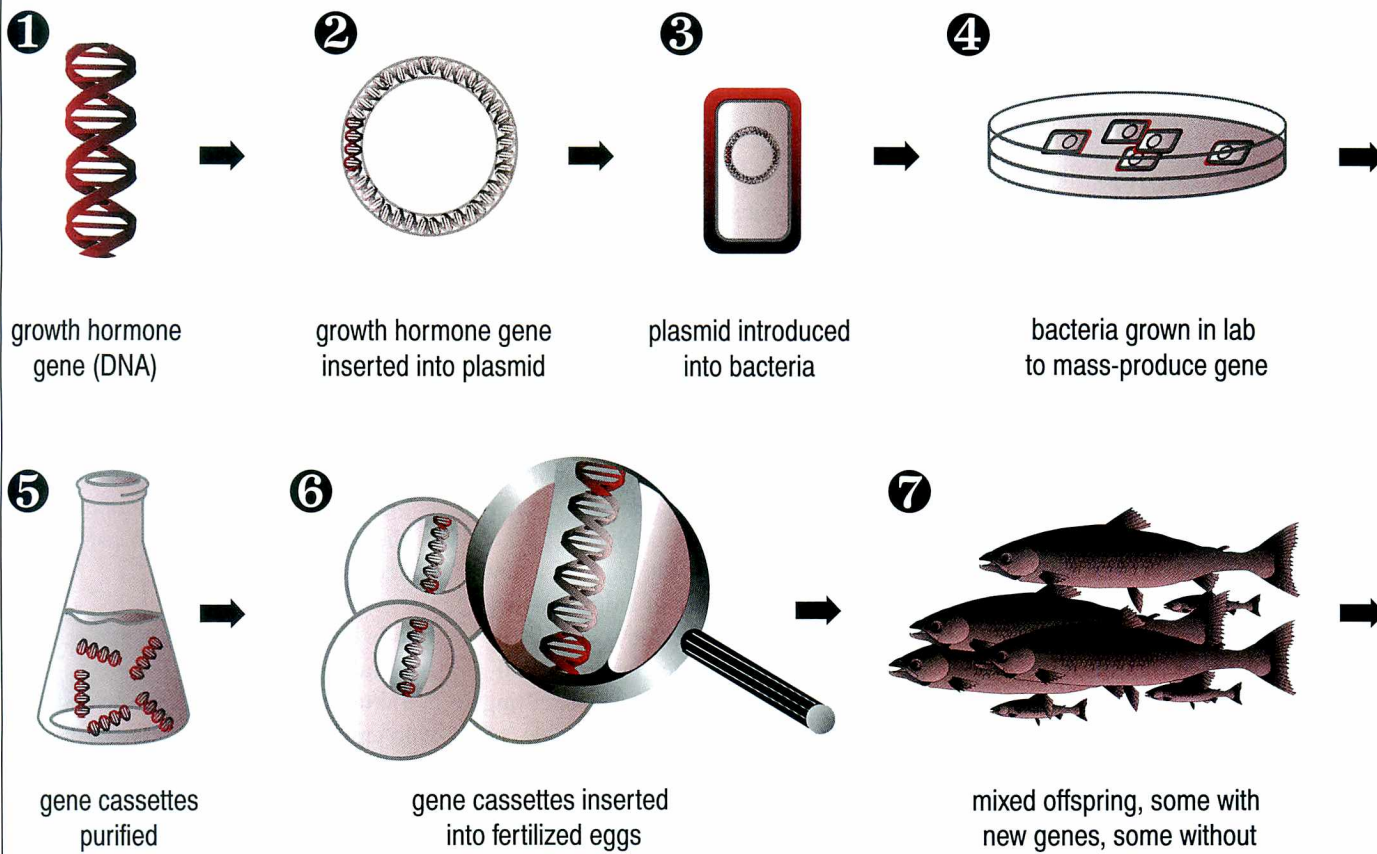
Making a transgenic animal is deceptively simple, especially when compared to traditional breeding approaches. In traditional breeding, when farmers or breeders want to introduce some new characteristic into a type of animal, they must find an individual animal that
(Continued on page 18)

These salmon are the same age, yet the larger one grew faster than its siblings thanks to species transfer of growth-enhancing genes.

(Photo courtesy of AquaBounty Farms, Prince Edward Island, Canada)



Creating A New Variety of Fish: The Technique to Make Transgenic Animals



transgenic fish identified and used to create breeding stock

Breeders can now use the tools of biotechnology to introduce new characteristics into animals. For example, researchers have figured out how to give a type of salmon a gene that directs the production of a growth hormone, causing the fish to grow to full size in substantially less time. Here is an outline of the steps needed to introduce the new growth hormone gene into the salmon.

1. Scientists duplicate the DNA carrying the genetic information for the growth hormone.

2. The gene is inserted into a circular piece of DNA called a plasmid that can be reproduced inside bacteria.

3. Next, the plasmids go inside the bacteria.

4. When the bacteria grow in the laboratory, they produce billions of copies of the plasmid carrying the growth hormone gene.

5. After the copies of the plasmid carrying the growth hormone gene have been produced, they are isolated from the bacteria. The plasmid is then genetically edited, changing its circular structure into a linear bit of DNA. The linear DNA is sometimes called a gene cassette because it contains several sets of genetic material in addition to the growth hormone gene.

6. The gene cassette is either directly injected or mixed with fertilized fish eggs in such a way that the eggs absorb the DNA, making the cassette a permanent part of the fish's genetic makeup. Since scientists insert the growth hormone gene into the fish's egg, the gene will be present in every cell in the fish's body.

7. The eggs are allowed to hatch, producing a school of fish in which some are genetically changed and others are not.

8. Fish that now carry the growth hormone gene are identified. Fish with the properly integrated gene are used to create a breeding stock of the new, faster-growing variety.

The concern about genetically engineered foods “is in marked contrast to the public acceptance of genetically engineered drugs. When faced with serious illness, most people are willing to take risks to combat a disease.”

—Carol Tucker Foreman, Consumer Federation of America

(Continued from page 16)

carries the desired trait. They then mate the individual to try to create a new line of animals sharing the genes that express the desired quality.

With genetic engineering, scientists possess the tools to isolate and manipulate single genes in the laboratory. In recent years, researchers have learned to insert single genes into the fertilized eggs of animals in such a way that the new gene is turned on in the resulting adult. (See “Creating A New Variety Of Fish” on page 17.)

First the scientist isolates the gene that conveys a particular trait of interest—disease resistance or faster growth, for example. Then a molecular vehicle is created that will carry the gene into the nucleus of the cell and permanently integrate it into the chromosome. The entire construct—the transplanted gene, called

a transgene, and its transport vehicle—might be physically injected into a fertilized egg using a glass needle viewed under a microscope. Other approaches use disabled viruses to inject the construct into the cell. If the egg survives and begins to grow and divide, then the potential embryo is implanted into a surrogate mother. Of the offspring that make it to birth, only a very small number will carry the new gene integrated in such a way that it actually functions.

But when it works, the result is a new individual of a variety of animal with a characteristic never before seen. The individual animal can then be multiplied by conventional breeding. The resulting animal may be enormously valuable. Inserting a single gene into an animal, that then manufactures a rare protein in its milk, could produce a drug that is worth many millions of dollars an ounce. The

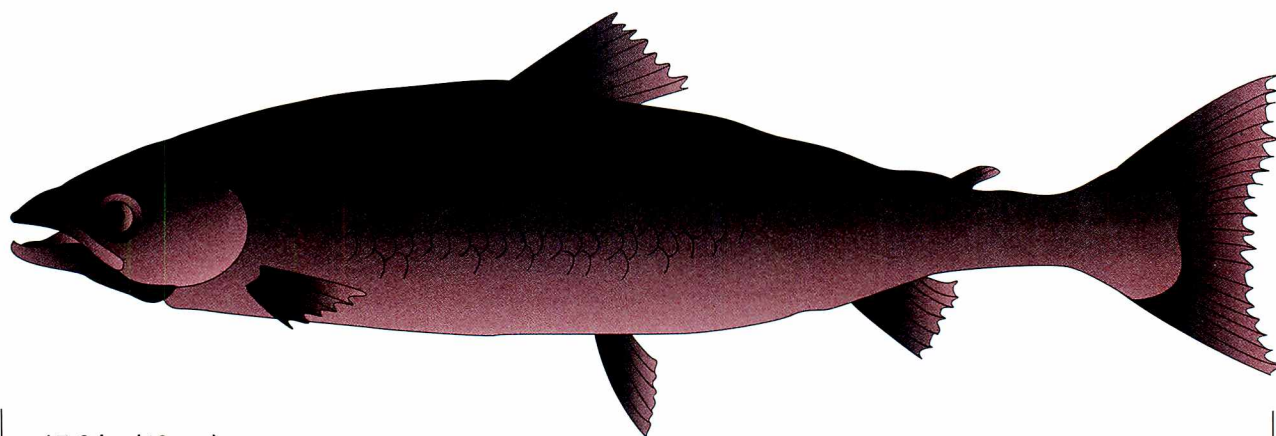
Genzyme Transgenics Corporation of Cambridge, Mass., for example, has created a goat that carries the gene for anti-thrombin III, a blood protein that can prevent blood clotting in people. The company purifies the protein out of the goat’s milk.

But even though the medical applications of transgenics remain intriguing, the animal health and food production applications seem to be generating most of the new excitement and considerable concern.

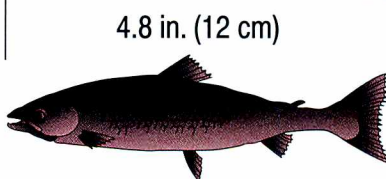
Foods Derived from Transgenic Animals

Taking their lead from the scientists who created new genetically engineered crops that, for example, resist insects without the need for pesticide spraying, researchers involved in the production of food animals began to think about

Growth Hormone-Enhanced Fish



15.8 in. (40 cm)



4.8 in. (12 cm)

Fish endowed with foreign genes that increase production of growth hormones (top) grow to more than twice the size of their siblings of the same age (bottom).

"One of the good things about regulating transgenics as animal drugs, is that we can make sure that the environmental controls and other safety measures are built right into the process."

—CVM director Stephen F. Sundlof, DVM, PhD

how they could use genetic modifications to improve the production or quality of their products.

Typically, says John Matheson, a senior review scientist in FDA's Center for Veterinary Medicine (CVM), "Researchers start with the protein they want to add and work backwards." It's the protein that the transplanted gene encodes that actually gives the animal a new trait.

The best example so far of the transgenic strategy in food animals, and its success, is the faster-growing salmon. The science behind the so-called supersalmon was discovered by accident 20 years ago when Choy Hew, PhD, then a researcher at Memorial University of Newfoundland in Canada, accidentally froze a tank filled with a particular species of flounder. When the tank was thawed out, the flounder were still alive. Initially, no one knew how they survived. This species, it turns out, has a gene that produces a protein that works like the antifreeze in a car's radiator. This antifreeze protein is found in many types of polar fish that must survive extremely cold conditions.

Researchers isolated and copied the part of the flounder DNA that works like a genetic switch to turn on the production of the antifreeze protein. Normally, this genetic switch is only turned on when the fish is exposed to cold.

Hew and his colleagues then attached the flounder's genetic on-switch to a previously isolated gene from Chinook salmon that produces a growth-stimulating hormone. Using transgenic techniques, they inserted the new combination—the flounder on-switch with the salmon growth hormone gene—into fertilized salmon eggs. In the resulting salmon, the flounder's genetic switch appears to stay turned on, producing a continuous supply of salmon growth hormone that then accelerates the fish's development. While the resulting fish do not seem to reach a mature size that is larger than conventional salmon, they

grow much faster.

Breeding transgenic varieties is an effective way to create an animal with a new characteristic, but large mammals—cows, pigs and goats—don't multiply as plentifully or as rapidly as fish. Several research teams have turned to cloning—as in Dolly, the sheep—as a way to expand the herd of transgenic animals. This approach combines two cutting-edge techniques. First, a transgenic animal with the desired characteristics is created. Then, cloning techniques are used to create replicas of the transgenic animal. Using a transgenic approach just makes it easier to get the desired genetic characteristics in the animal, which is then cloned to produce a core breeding herd.

Transgenic Critics

Useful as it may be, animal biotechnology won't go forward without objections. For all the promise that industry sees in the dawning era of genetically engineered animals, others—including animal rights activists, environmentalists, and consumers—see problems.

The concern about genetically engineered foods, says Carol Tucker Foreman, director of the Food Policy Institute at the Consumer Federation of America (CFA) in Washington, D.C., "is in marked contrast to the public acceptance of genetically engineered drugs. When faced with serious illness, most people are willing to take risks to combat a disease." Food is different, she says, since it is so basic, both physically and emotionally. "It's not surprising that consumers are extremely averse to any food-related risk, especially if the risk is perceived as imposed by someone else, beyond individual control and without any countervailing benefit." Consumers, she says, are concerned mostly about such potential health problems as allergic reactions and antibiotic resistance.

But FDA Commissioner Jane E. Henney, MD, points out that foods produced using bioengineering processes

are evaluated to make sure they are not more likely to cause allergies. "Under the law and FDA's biotech food policy," she says, "companies must tell consumers on the food label when a product includes a gene from one of the common allergy-causing foods, unless it can show that the protein produced by the added gene does not make the food cause allergies."

But Art Jaeger believes, "It's not just about dangerous foods—it's also a matter of consumer choice." The assistant director for CFA and advocate for mandatory labeling says consumers need to know when a food is genetically altered because many have religious or cultural convictions that would preclude them from selecting foods produced through transgenic technology. Jaeger says that his organization wants tougher regulations and feels that all information on the safety of biotechnology applications should be made publicly available.

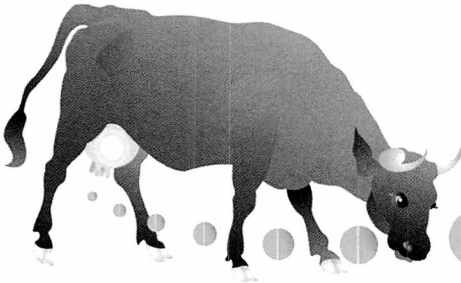
And then there are environmental concerns. Purdue University animal scientist Bill Muir and biologist Rick Howard conducted a study funded by USDA on genetically engineered fish, which led them to warn of possible risks from transgenic fish escaping into nature. They worry that transgenic fish escaping from aquaculture facilities into the wild, for example, could damage native populations, even to the point of extinction. But Elliot Entis, president of A/F Protein, Inc., an international biotechnology firm based in Waltham, Mass., feels that environmental concerns can be addressed by producing transgenic fish in closed aquaculture systems (controlled, artificial environments) or by producing all female, sterile fish.

FDA, in cooperation with other federal agencies, will evaluate these proposed environmental safety measures prior to any approval.

Ethically Speaking

At a time when genetically engineered plant crops have spurred protests in the

Any drug or biologic created through transgenic techniques will need to undergo the same FDA scrutiny as any other treatment, including clinical trials that demonstrate safety and effectiveness.



United States, the use of biotechnology in food-animal production is likely to attract an even larger set of critics because both transgenics and cloning deal with animals.

People for the Ethical Treatment of Animals (PETA), a large animal rights organization headquartered in Norfolk, Va., for example, feels that people shouldn't be tinkering with animals like Frankenstein and is very much opposed to intensive animal agriculture.

In general, CVM's Matheson says that for animal safety, the goal of regulating products of animal biotechnology is to ensure healthful surroundings, proper medical treatment, discovery of any special management measures needed, and freedom from pain and suffering.

Regulating Transgenic Animals

FDA already has the legal authority to regulate most products derived from transgenic animals, whether they are used as drugs, as human food, or as animal feed. Therefore, only guidances or regulations that cover specific aspects of animal biotechnology may need to be added—not whole new statutory frameworks for regulating the products. These guidances will likely address such issues as safety of the target animal and protection of the environment.

Most of the gene-based modifications of animals for food production fall under CVM regulation as new animal drugs. The genetically modified growth hormone for the fish, for example, will be regulated the same way the agency regulates bovine somatotropin, the genetically engineered bovine growth hormone that makes cows produce more milk. Transgenics simply provides another means to add growth hormone to an animal.

"When I speak to folks about the regulation of animal genetic engineer-

ing," says Matheson, "the first reaction is often surprise that genetically engineered animals could possibly be viewed as containing new animal drugs." People are surprised, he says, because their experience with animal drugs is limited to products they buy for their pets.

With transgenic salmon, the inserted growth hormone trait is inherited by subsequent generations. With cows, the drug is periodically injected into each one. Either way, products regulated as new animal drugs in the United States are subject to rigorous premarket requirements to determine effectiveness and ensure food, animal and environmental safety.

"One of the good things about regulating transgenics as animal drugs," says CVM director Stephen F. Sundlof, DVM, PhD, "is that we can make sure that the environmental controls and other safety measures are built right into the process." This process includes target animal safety, safety to the environment, and safety for consumers to eat foods derived from genetically engineered animals.

CVM intends to use various approaches, including a contract with the National Academy of Sciences, to identify further environmental safety issues associated with investigation and commercial use of transgenic animals. To do this, the agency will cooperate closely with other federal and state agencies that

have related authorities, such as the Fish and Wildlife Service and the National Marine Fisheries Service, in the case of transgenic Atlantic salmon.

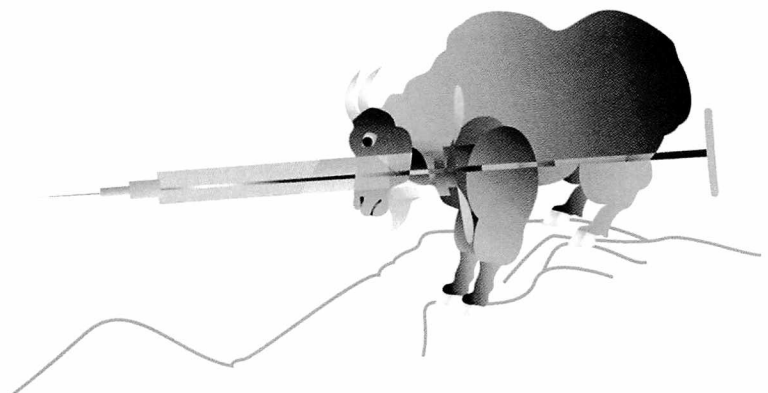
Looking to the Future

The agency already is gearing up for the major debates it expects regarding transgenic animals—debates likely to mirror the discussions now underway for bioengineered crops. At this time, no transgenic animals have been approved to enter the human food supply, but a few individual transgenic animals have been allowed to be rendered and used in animal feed.

While it's true that new compounds to combat specific diseases or to optimize the nutritional value of food products can also be created by conventional means, researchers believe that transgenics technology can help make it possible to produce them more quickly, in larger quantities, and ultimately, at lower cost to consumers.

"After over 10 years of examining products on a case-by-case basis," says Matheson, "I can say that the guidance and regulatory structure for animal biotechnology is starting to evolve. I hope we can learn from our experiences with plant biotechnology to make the road a little smoother." ■

Carol Lewis is a staff writer for FDA Consumer.





Heading Off Hair-Care Disasters

Use Caution With Relaxers And Dyes

By Michelle Meadows

i

t's never a good sign when the hairdresser panics. That's what happened to Barbara Cabrera-Avila, 38, when she returned to the salon about six weeks after having her hair straightened a couple of years ago. The cause for alarm: several bald spots in the back of her head.

The Adelphi, Md., resident began having her curls straightened at the age of six so her hair would be easier to comb and style. She says over-processed hair likely played a role in her hair loss, and stress could have been a factor. What's certain is that three dermatologists advised her to take a break from hair straighteners, also known as relaxers.

Barbara says giving up the straight hair she had grown comfortable with wasn't easy. After all, people's personal preferences

Hair-Care

about how they want to look tie into self-esteem—a fact that makes for good sales in the hair business. In addition to paying for trims and cuts to achieve a certain look, consumers spend millions of dollars each year to get hair that's different from what nature intended—whether it's to tame tight curls, give flat hair a boost, or get rid of the gray.

According to the Food and Drug Administration's Office of Cosmetics and Colors, hair straighteners and hair dyes are among its top consumer complaint areas. Complaints range from hair breakage to symptoms warranting an emergency room visit. Reporting such complaints is voluntary, and the reported problem is often due to incorrect use of a product rather than the product itself. FDA encourages consumers to understand the risks that come with using hair chemicals, and to take a proactive approach in ensuring their proper use. The agency doesn't have authority under the Federal Food, Drug, and Cosmetic Act to require premarket approval for cosmetics, but it can take action when safety issues surface.

When the Product Is the Problem

When consumers notify FDA of problems with cosmetics, the agency evaluates evidence on a case-by-case basis and determines if follow-up is needed, says Allen Halper, an FDA consumer safety officer. FDA looks for patterns of complaints or unusual or severe reactions. The agency may conduct an investigation, and if the evidence supports regulatory action, FDA may request removal of a cosmetic from the market.

Take the example of two popular hair relaxer products by World Rio Corp.—the Rio Naturalizer System (Neutral Formula) and the Rio Naturalizer System with Color Enhancer (Black/Licorice). After receiving complaints about these products in November and December of 1994, FDA warned the public against using them. Consumers complained of hair loss, scalp irritation, and discolored hair.

In December 1994, the World Rio



When straightening or dyeing hair at home, consumers should keep products out of children's reach. There have been reports of small children suffering injuries from ingesting hair chemicals.

Look Out For Your Eyes

Corp., Inc. of Los Angeles, Calif., announced that it stopped sales and shipments of the product. But reports indicated that the company continued to take orders, and the California Department of Health also stepped in to stop sales. In January of 1995, the U.S. Attorney's Office in Los Angeles filed a seizure action against these products on behalf of FDA. By then, the agency had received more than 3,000 complaints about the Rio products.

Although most relaxers are alkaline, this product was formulated to be acidic. In the resulting consent decree of condemnation and permanent injunction, FDA alleged that the products were potentially harmful or injurious when used as intended, that they were more acidic than declared in the labeling, and that the labeling described the products as "chemical free" when "allegedly they contained ingredients commonly understood to be 'chemicals.'"

Safer Straightening

FDA has received complaints about scalp irritation and hair breakage related to both lye and "no lye" relaxers. Some consumers falsely assume that compared to lye relaxers, "no lye" relaxers take all the worry out of straightening.

"People may think because it says 'no lye' that it's not caustic," says FDA biologist Lark Lambert. But both types of relaxers contain ingredients that work by breaking chemical bonds of the hair, and both can burn the scalp if used incorrectly. Lye relaxers contain sodium hydroxide as the active ingredient.

With "no lye" relaxers, calcium hydroxide and guanidine carbonate are mixed to produce guanidine hydroxide.

Research has shown that this combination in "no lye" relaxers results in less scalp irritation than lye relaxers, but the same safety rules apply for both. They should be used properly, left on no longer than the prescribed time, carefully washed out with neutralizing shampoo, and followed up with regular conditioning. For those who opt to straighten their own hair, it's wise to enlist help simply because not being able to see and reach the top and back of the head makes proper application of the chemical and thorough rinsing more of a challenge.

Some stylists recommend applying a layer of petroleum jelly on the scalp before applying a relaxer because it creates a protective barrier between the chemical and the skin. Scratching, brushing, and combing can make the scalp more susceptible to chemical damage and should be avoided right before using a relaxer. Parents should be especially cautious when applying chemicals to children's hair and should keep relaxers out of children's reach. There have been reports of small children ingesting straightening chemicals and suffering injuries that include burns to the face, tongue, and esophagus.

How often to relax hair is a personal decision. According to Pearl Freier, an instructor at the International Academy

of Hair Design in South Daytona, Fla., relaxing at intervals of six to eight weeks is common, and the frequency depends on the rate of a person's hair growth. Leslie F. Safer, MD, a dermatologist in Albany, Ga., who has treated women with scalp irritation from relaxers, says straightening every six weeks is too frequent, in his opinion. Relaxers can cause hair breakage in the long term, he says, and blow drying and curling can do more damage.

Consumers should be aware that applying more than one type of chemical treatment, such as coloring hair one week and then relaxing it the next, can increase the risk of hair damage. "The only color we recommend for relaxed hair is semi-permanent because it has no ammonia and less peroxide," compared with permanent color, Freier says.

Hair Dye Reactions

As with hair relaxers, some consumers have reported hair loss, burning, redness, and irritation from hair dyes. Allergic reactions to dyes include itching, swelling of

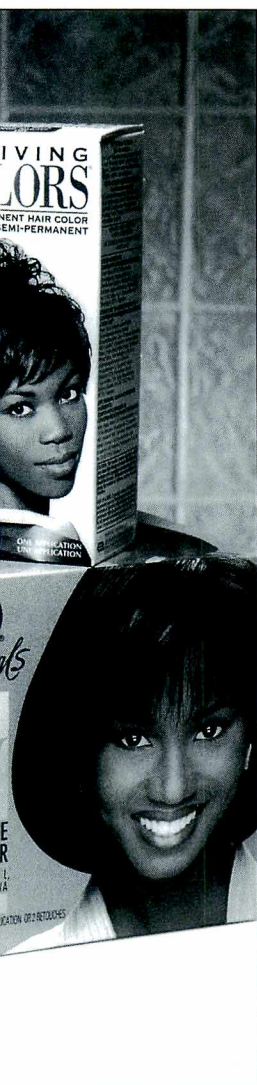
Whether applying hair chemicals at home or in a hair salon, consumers and beauticians should be careful to keep them away from the eyes. FDA has received reports of injuries from hair relaxers and hair dye accidentally getting into eyes. And while it may be tempting to match a new hair color to eyebrows and eyelashes, consumers should resist the urge. The use of permanent eyelash and eyebrow tinting and dyeing has been known to cause serious eye injuries and even blindness. There are no color additives approved by FDA for dyeing or tinting eyelashes and eyebrows.

The law does not require that coal tar hair dyes be approved by FDA, as is required for other uses of color additives. In addition, the law does not allow FDA to take action against coal tar hair dyes that are shown to be harmful, if the product is labeled with the following caution statement:

"Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness."

—M.M.

Photograph by PictureQuest



FDA encourages voluntary reporting of adverse reactions to hair products to: FDA, Center for Food Safety and Applied Nutrition, Office of Cosmetics and Colors, 200 C St. S.W., Washington, DC 20204, 202-205-4706.

Hair Color And Cancer

Over the years, some studies have indicated a possible link between hair dye use and cancer, while others have not. In February 1994, FDA and the American Cancer Society released an epidemiologic study involving 573,000 women. Researchers found that women who had ever used permanent hair dyes showed decreased risk of all fatal cancers combined and also of urinary system cancers. The study also revealed that women who had ever used permanent hair dyes showed no increased risk of any type of hematopoietic cancer (cancer of the body's blood-forming systems).

This research, published in the *Journal of the National Cancer Institute*, did suggest that prolonged use (20 years or more of constant use) of black hair dye may slightly increase the occurrence of non-Hodgkin's lymphoma and multiple myeloma, but these cases represented a small fraction of hair dye users. This study followed previous NCI studies that raised concern about the use of hair dyes and higher rates of non-Hodgkin's lymphoma.

In another study, published in the October 5, 1994, issue of the *Journal of the National Cancer Institute*, researchers from Brigham and Women's Hospital in Boston followed 99,000 women and found no greater risk of cancers of the blood or lymph systems among women who had ever used permanent hair dyes.

Then in 1998, scientists at the University of California at San Francisco questioned 2,544 people about their use of hair-color products. After integrating the results of this study with those of animal and other epidemiologic studies, they concluded that there was little convincing evidence linking non-Hodgkin's lymphoma with normal use of hair-color products in humans. The study was published in the December 1998 issue of the *American Journal of Public Health*.

FDA continues to follow research in this field. ■

—M.M.



Photograph by PictureQuest

the face, and even difficulty breathing.

Coal tar hair dye ingredients are known to cause allergic reactions in some people, FDA's Lambert says. Synthetic organic chemicals, including hair dyes and other color additives, were originally manufactured from coal tar, but today manufacturers primarily use materials derived from petroleum. The use of the term "coal tar" continues because historically that language has been incorporated into the law and regulations.

The law does not require that coal tar hair dyes be approved by FDA, as is required for other uses of color additives. In addition, the law does not allow FDA to take action against coal tar hair dyes that are shown to be harmful, if the product is labeled with the prescribed caution statement indicating that the product may cause irritation in certain individuals, that a patch test for skin sensitivity should be done, and that the product must not be used for dyeing the eyelashes or eyebrows. The patch test involves putting a dab of hair dye behind the ear or inside the elbow, leaving it there for two days, and looking for itching, burning, redness, or other reactions.

"The problem is that people can become sensitized—that is, develop an allergy—to these ingredients," Lambert says. "They may do the patch test once, and then use the product for 10 years" before having an allergic reaction. "But you're supposed to do the patch test every time," he says, even in salons.

And what about ending up with something other than the exact shade of strawberry blonde on the shelf? "Don't think the color on the box is the color you'll get," says Freier, the cosmetology instructor. "There are so many variables, like what chemicals are already in your hair and what your natural color is, that go into how your hair will turn out."

When using all hair chemicals, it's critical to keep them away from children to prevent ingestion and other accidents, and to follow product directions carefully. It sounds basic, but some people don't do it, says FDA's Halper. "If it says leave on hair for five minutes, seven minutes doesn't make it better," he says. "In fact, it could do damage." ■

Michelle Meadows is a staff writer for FDA Consumer.



The International Flow Of Food

FDA Takes on Growing Responsibilities for Imported Food Safety

By Jeffrey P. Cohn

Mike Wehr has his bags packed. His tickets are bought, his hotel reservations confirmed, and all other necessary arrangements made. Wehr is about to leave the country, again. Last year alone he was out of the United States a half dozen times. He went to Belgium and Australia twice, and to Japan and Brazil once. In the near future, Wehr expects to go back to each of those countries once and perhaps to Hungary as well. In all, he is on the road at least 60 days a year on official U.S. government business.

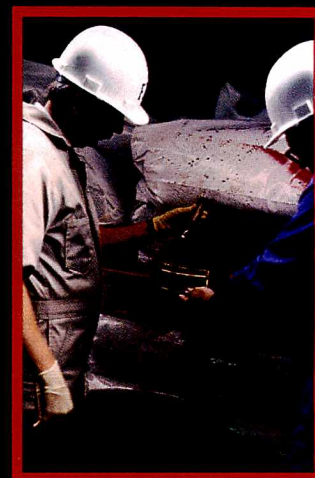
Wehr's mission is simple: to help make the world's food safe to eat here in the United States regardless of where it is planted, produced or packaged. He is one of a small but growing number of **Food and Drug Administration** employees who work with international standards-setting institutions, multinational health and trade organizations, and government and private agencies in other countries around the world.

And it's a changing world. In the past, FDA focused most of its food safety efforts within the U.S. borders, where it has legal authority. But changes in trade, consumer demand for variety, and an increasingly complex regulatory system have created new challenges for the agency. On one hand, the FDA Modernization Act, passed in 1997, requires the agency to cooperate with other countries and international institutions. On the other, FDA often finds that U.S. standards and rules differ from those of other developed countries. Meanwhile, FDA works with



The **International** Flow Of Food



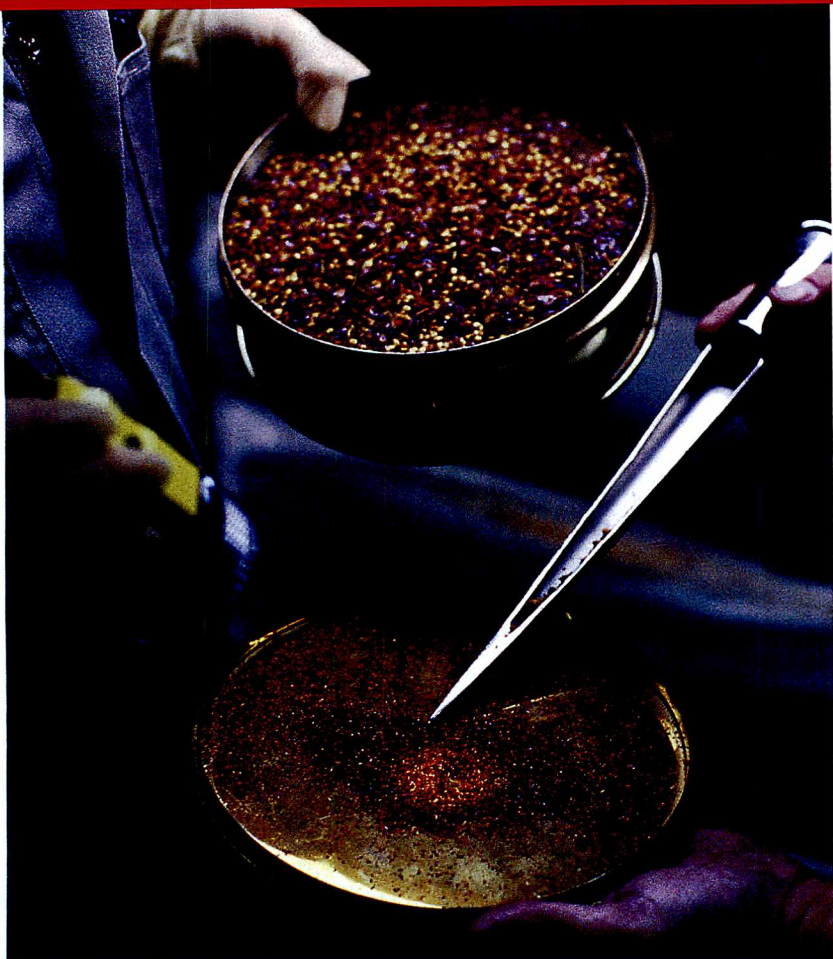


Clockwise from lower left: With 13 berths, 10 container and two gantry cranes, the 570-acre Dundalk Marine Terminal at the Port of Baltimore in Maryland handles every type of import, including automobiles, wood pulp, and food products. Consumer safety officers Matthew M. Henciak (left) and A. Dean Cook, members of FDA's Office of Regulatory Affairs' Baltimore District import operations group, survey the terminal that they regularly inspect. Above, food arrives inside sea containers that Henciak and Cook inspect for filth, insects and vermin. A contaminated container, sometimes swarming with insects, can be slammed shut on the dock and the importer forced to take corrective actions, such as fumigation.

developing countries to help them understand and meet U.S. standards for foods and agricultural products they export to the United States.

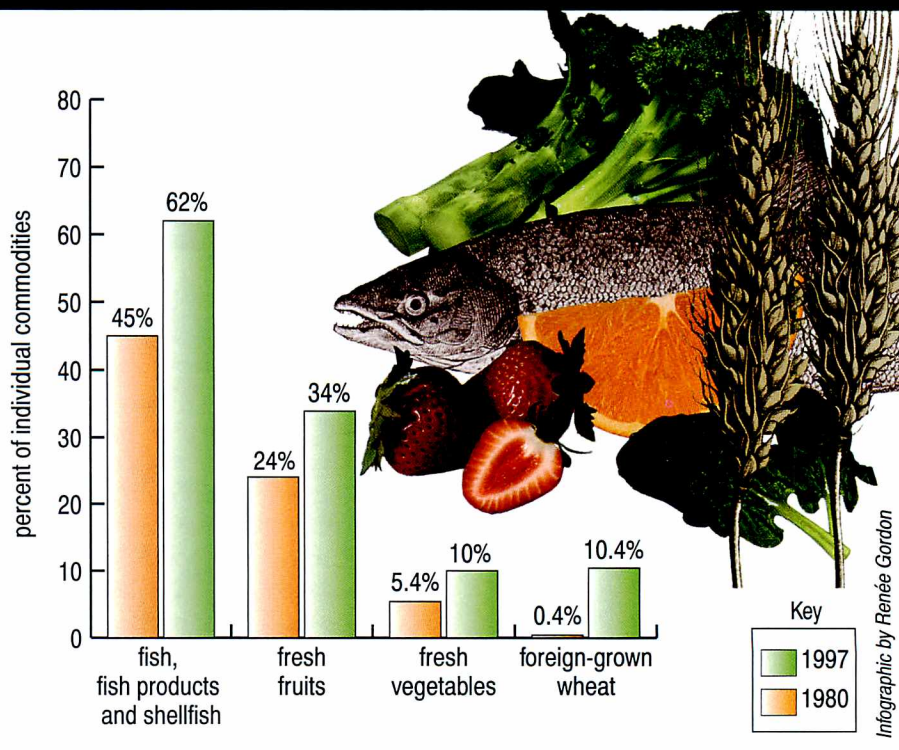
"It's a very different landscape for this agency than it was five or six years ago," says Wehr, one of FDA's representatives on food issues to Codex Alimentarius, an international standards-setting group based in Rome. "There has been a fundamental change in the importance [of international food safety issues to FDA]. We have to be part of the international arena. That is a new role for us. It is a role that continues to evolve every day."

The International Flow Of Food



To check for contaminants, FDA inspectors take samples from incoming shipments and place them on a filth screen (left). Small objects, such as insects, fall through the screen for easier inspection. The tool on the right, called a trier, can be poked through the side of a cloth bag to remove a sample of the contents without opening the entire bag. Above right, A. Dean Cook (left) and Matthew Henciak bag a sample of crushed pepper that will be sent to the FDA laboratory to be examined for insects or other contaminants.

Imported Food Consumption on the Rise



Source: U.S. Department of Agriculture's Economic Research Service

New Ways To Work Together

Even at home, FDA cannot act alone on international food issues since other governmental agencies play major roles, including the U.S. Departments of Agriculture, State and Commerce, the Environmental Protection Agency, and the Office of the U.S. Trade Representative, among others. Further, all federal activities involving Codex are managed within USDA's Food Safety and Inspection Service (FSIS).

As much as anything else, consumer demand drives these changes, especially the shifts in where American companies and consumers get their food. "Food has become a global commodity," says Janice Oliver, deputy director of FDA's Center for Food Safety and Applied Nutrition (CFSAN). "We Americans have changed our eating habits. We used to eat whatever was grown locally and in season, and only one or two varieties of anything. Today, food is international. It is from Central and South America or Europe or the Asian countries or the islands of the world."

More than ever before, Americans can buy more imported foods at local grocery stores and supermarkets, adds Linda Horton, director of FDA's international agreements staff, because of improved ways of packaging and preserving food, and more rapid means of transporting it. That, she says, means American consumers "can get anything from anywhere at almost any time."

According to USDA's Economic Research Service, Americans are eating more imported foods than ever before. So much so that imports of processed foods rose 5.8 percent in 1998, the last full year for which complete records are available. The estimated value of food imports in 1998 hit \$32 billion, a new U.S. record. Moreover, food imports exceeded exports in 1998 by \$2.6 billion, the first U.S. agricultural trade deficit since 1991.

The numbers for individual commodities are even more striking. Sixty-two percent of all fish, fish products and shellfish eaten by Americans, for example, came from abroad in 1997. That's up from 45 percent in 1980.

Similarly, Americans ate almost half

again as much fresh fruits from other countries in 1997 as in 1980, up from 24 to 34 percent. Imported fresh vegetables accounted for more than 10 percent of vegetable consumption in 1997, compared with 5.4 percent in 1980. And foreign-grown wheat totaled 10.4 percent of the American diet in 1997, up from 0.4 percent 20 years ago.

As a result, FDA is more involved in foreign trade issues now than ever, says Catherine Carnevale, director of

spect every food package brought into the United States. "We don't have the resources to examine all imported products or to inspect most overseas production facilities," FDA's Horton says, adding, "We have very porous borders. We need to work with those who export food to the United States [to make sure it's safe leaving those countries]. Cooperating with them is one way of protecting American consumers and promoting public health worldwide."

"Food has become a global commodity. We Americans . . . used to eat whatever was grown locally and in season, and only one or two varieties of anything. Today, food is international. It is from Central and South America or Europe or the Asian countries or the islands of the world."

—Janice Oliver, CFSAN deputy director

CFSAN's office of constituent operations. To ensure that the food Americans eat is safe to consume, the agency inspects imported food and refuses entry to unsafe, adulterated or mislabeled products, using the same standards as for domestic food. Under the evolving international rules, FDA now certifies that American-made seafood and dairy products sold abroad meet the importing country's requirements and are the same products as those sold in this country.

Whatever the specific role, FDA's focus remains on safety. "We are here to protect American consumers," Carnevale says. "Our goal is to improve the safety of all foods consumed in the United States." Similar aims drive U.S. Department of Agriculture policies. "We have legislative mandates to set standards and encourage trade in food products, but safety comes first," says Catherine Woteki, USDA's undersecretary for food safety. "All agencies of the U.S. government are unanimous that a science-based health and safety policy is our paramount guiding principle. Fair trade will follow."

But neither FDA nor USDA can in-

A Codex Consensus

That brings the issue back to Codex, the object of Mike Wehr's many foreign travels. The Codex Alimentarius Commission, as it is formally known, was created in 1962. It is jointly run by two United Nations groups, the World Health Organization (WHO) and the Food and Agricultural Organization (FAO). As its name—Latin for "food code"—suggests, Codex sets international standards of identity for agricultural products and food commodities, and determines safety standards for food additives and contaminants and for veterinary drugs. By the end of 1999, Codex's 165 member-countries had agreed on maximum safe limits for 1,300 food additives, 197 pesticides and 25 contaminants. Codex had also set 204 food standards, completed 54 veterinary drug evaluations, and adopted 43 codes of practice.

Codex exists, Wehr says, because countries have long argued over agricultural trade. Most have traditionally sought to protect their farmers, growers and ranchers by a system of tariffs that imposed duties on and raised the cost of imported food. Since the signing of the General Agreement on Tariffs and Trade

(GATT) in 1948, however, the world's tariffs have generally declined and even have been eliminated for many industrial and agricultural products. The creation of regional trading blocks such as the European Union (EU) and the North American Free Trade Association (NAFTA) has further lowered food duties within these groups' purview.

But, as tariffs have come down, other technical or safety issues have sometimes replaced them as barriers to free trade in agricultural and food products. The EU, for example, banned exports of beef products from Great Britain to the rest of Europe in 1996 for fear of spreading bovine spongiform encephalopathy (BSE), or "mad cow" disease. More recent concerns have included the potentially carcinogenic chemical dioxin that was found in egg products from Belgium, the use of growth-promoting hormones in animals raised for their meat in the United States, and EU rules requiring the labeling of food grown using the new techniques of genetic engineering.

Because of increasingly complicated trade negotiations arising from the creation of the World Trade Organization in 1993, Codex's role in international food safety issues "has been consciously elevated," FDA's Wehr says. From a little-known group focused on what were often seen as narrow commodity issues, he adds, overnight Codex "became the standard ... [and] its standards will be difficult to get around."

While Codex's standards are voluntary, Wehr says, "It is to our country's advantage to work with Codex and to follow its standards." Individual countries do not have to adopt them, and countries can also implement stricter standards than Codex if they can scientifically justify a higher level of protection. But countries that do not follow Codex or that lack justification for stricter food standards could lose any trade dispute over food brought before the World Trade Organization, Wehr says.

The Biotech Dilemma

Most issues that come before Codex

are highly arcane and of little interest to the general public. Some, however, may directly affect not only the safety of the food that reaches the American dinner table, but also the practices of U.S. processors and growers. Food produced using modern biotechnology is a good example. American companies have pioneered methods using genetic engineering to alter a plant's genes to improve yields or provide greater resistance to insects, fungus or disease. But, since many people in Europe fear the unknown consequences of genetic engineering, the European Union has enacted rules to require labeling that identifies imported foods produced by biotechnology. Some U.S. officials fear that such rules could be used to keep American food out of European markets.

"We do not regulate food manufacturing processes unless the process matters," says Eric Flamm, an FDA senior policy advisor. "Biotechnology alone does not make a food safe or unsafe." Genetic engineering would have to introduce into plants a potentially dangerous allergen, change the nutritional content of a food, or require different handling, storage, cooking or preservation to warrant additional labeling.

On this issue, USDA policy parallels FDA's. "Biotechnology-produced foods are regulated as foods," food safety official Woteki says. "If the process introduces a significant change in the food, that change must be stated on the label." That position may be correct under U.S. law, says James Maryanski, CFSAN's biotechnology coordinator, but it leaves the United States increasingly isolated in a world apparently poised to adopt stricter regulation of biotech foods. While the number of countries that have given serious consideration to the question of labeling is still small, only a few other countries support the U.S. position.

Resolving the biotechnology debate within Codex will continue to be a complex, cumbersome, and long, drawn-out process. The issue has been before Codex since the mid-1990s. A drafting group met in India in October to prepare

a document that would give countries several approaches to labeling from which to choose. The next full committee meeting is not scheduled until April 2001. "The deadlock is very frustrating," says USDA's Woteki. "We may have to change our negotiating strategy."

Toward that end, last spring FDA announced plans to strengthen premarket reviews of biotechnology-produced foods. FDA is developing a proposed new rule that will require manufacturers to notify the agency at least 120 days before they put on the market foods and animal feeds derived from genetically engineered plants. Under the new rule, once it has reviewed a company's submission, FDA will issue a letter regarding the regulatory status of the product involved. The agency will also help guide manufacturers who want to, or are required to, label their biotechnology products for foreign markets.

Learning to be Cautious

Meanwhile, biotechnology is not the only international food issue to involve FDA or to create a split between the United States and the European Union. The "precautionary principle" has similarly sparked debate among policy makers here and abroad. The precautionary principle, as defined in February 2000 by the EU Commission, would ban, require additional labeling, or otherwise restrict the use of any food if the science to determine its safety or level of risk is judged to be uncertain.

"Scientific uncertainties cannot serve as an excuse for decision-makers to do nothing," says Bernard Chevassus-au-Louis, president of the French Agency for Food Safety. "Science is not always predictive," Chevassus adds. "It is too often too late. It often underestimates the evidence for risk. The use of the precautionary principle is not a denial of science, but a call for more science."

FDA and USDA officials disagree. The precautionary principle "would require another level of risk management based on 'what ifs,'" says FDA's Carnevale. "There may not be any evi-

As tariffs have come down, other technical or safety issues have sometimes replaced them as barriers to free trade in agricultural and food products.



dence that [a food] poses any hazard, despite the scientific uncertainty. Precaution is a part of our food safety process. It is embedded throughout our decision-making, not an add-on for politicians.”

The United States is not opposed to European countries adopting the precautionary principle, Carnevale adds, so long as it is not directed solely against foods they import from the United States. Many Americans are concerned that the French could use it, she says, to restrict imported meat from cattle in the United States that were fed growth hormones, when, for example, French health agencies have so far been unwilling to apply the same principle to *Listeria monocytogenes* in French cheeses. The use of raw milk—which is a known source of the bacterium *Listeria*—to manufacture fresh and soft cheese is of particular concern to FDA. Listeriosis in pregnant women can result in miscarriage, fetal death, and severe illness or death of a newborn infant. Others at risk for severe illness or death are the elderly and those with weakened immune systems.

FDA and USDA are also concerned

because the European Union has asked Codex and the Organization for Economic Cooperation and Development (OECD) to endorse the precautionary principle. OECD is an organization of the United States and other developed countries. “The European Union is doing the right thing in discussing the precautionary principle,” Woteki says, “but it is premature to recommend that it be adopted for all countries. Countries with strong laws and regulations with a strong element of caution in them have no need for a precautionary principle.”

Developing Safety

Unfortunately, not all countries have strong food safety rules or the resources to adopt and enforce them. Yet, for many developing countries, exporting food and agricultural products is key to their economies. Unless they can meet standards set by FDA, FSIS and EPA, however, they may have trouble exporting food to the United States. To help resolve that problem, FDA has designed programs to help developing countries understand and meet U.S. requirements.

“We may not be able to get developing countries to our level [of safety],” Carnevale says, “but we can get them to a higher level.” All food imports, however, must meet FDA safety standards before they can come into the United States.

FDA sponsored multi-agency seminars in Mexico City and Santiago, Chile, in September 1999 and in New Zealand for Pacific Rim and island countries in August 2000. The effort is part of the Food Safety Initiative, a multi-agency program launched by the White House aimed at reducing the incidence of foodborne diseases. The seminars involve experts from FDA, USDA, EPA, the Centers for Disease Control and Prevention, and the State Department. Their job, CFSAN’s deputy director Oliver explains, is to help government officials, food exporters, and academics in other countries understand U.S. requirements. “We tell them what we expect so they can meet our standards and keep the food we import safe,” she says.

Additionally, FDA sponsored a “train-the-trainers” session, also held in Santiago, Chile, last year. That week-long session targeted mid-level government officials, representatives of growers’ associations, and others in a position to train farmers in good agricultural and food handling practices. “We hope to take elements of our safety program and adapt it to their local conditions,” says Camille Brewer, CFSAN’s international coordinator for the Food Safety Initiative. Additional sessions are planned for Brazil and Trinidad and Tobago.

“We are operating more and more in a complex global environment,” Wehr says of FDA’s continuing involvement in international food issues. “It’s not clear yet how these issues will play out. But the decisions that Codex and other international institutions make will drive U.S. and FDA policies. These are big issues for FDA and for agriculture, industry and consumers.” ■

Jeffrey P. Cohn is a writer in Takoma Park, Md.



Hot spots and cool links on FDA's Web site and beyond.

By John Henkel

It's Okay to Be a Loser in This Game

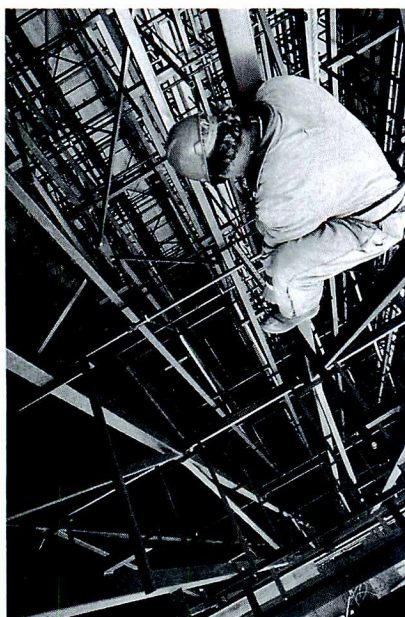
Many of us may fantasize about winning a million bucks on a TV quiz show. But what about a game that has a goal of *losing* a million? FDA's Center for Food Safety and Applied Nutrition has teamed with the National Science Teachers Association to create a fun online game that can boost your knowledge of food safety. Here's how it works: You *start* with a million—a million bacteria, that is. Answer a question correctly and you lose bacteria. To win the game, you need to get all the answers right and wind up with "0" bacteria. If you still have bacteria left at the end of the game, you can take another shot at lowering the bacterial count. That way, everyone has a chance to win, er, *lose* the game. To play "Lose a Million (Bacteria)," go to www.cfsan.fda.gov/~cjm/millintr.html.

'Dot Con' Artists Cast a Wide Net

It wasn't long ago when con artists mainly used telephones and the U.S. mail to push their shady schemes. But now these scammers have taken to the Internet, and the Federal Trade Commission says, "Beware!" To help consumers identify and report bogus online ploys, the FTC has created a Web site called "Top Ten Dot Cons" that gives helpful advice on how to know when you are being flimflammed. For example, the site lists medical conditions that often attract health fraud schemes—cancer, AIDS and arthritis, to name a few—and explains some of the ploys con artists use to hook unsuspecting consumers. The site then suggests legitimate, reliable sources of information. Among other scams featured on the site are travel, pyramid schemes, investments and business opportunities. To get a heads-up on con jobs, go to www.ftc.gov/bcp/conline/edcams/dotcon.

Having a Bad Air Day?

Finding out the degree of air pollution in your neighborhood is as easy as going into the Environmental Protection Agency's AIRNOW Web site (www.epa.gov/airnow) and zooming in on your region. The site provides real-time information about air quality in an easy-to-read format. It also has background about the environmental and public health effects of air pollution, along with tips for consumers on how to protect their health, and actions they can take to reduce pollution. The site includes links to Web cameras situated in cities such as Chicago, Denver and St. Louis, so users can visually check out the visibility and air quality in those areas at different times of the day. Currently, AIRNOW focuses on ground-level ozone (smog), but EPA plans to include surveys of other pollutants on the Web site in the future.



Keeping the Workplace Safe

Nearly 50 American workers are injured every minute of the 40-hour work week, and about 17 die on the job each day, according to the Occupational Safety and Health Administration (OSHA). Reducing these tragic numbers is difficult because there are only about 2,500 inspectors to oversee 100 million workers at six million worksites. So OSHA and its state counterparts depend on workers themselves to spot occupational hazards and report them. On "The Workers' Page" (www.osha.gov/as/opa/worker/index.html), OSHA explains workers' rights and responsibilities under the law and describes the procedure for filing a workplace complaint. The site also explains how to handle situations such as refusal to perform dangerous work and what to do if one experiences discrimination after filing a complaint. The site links to many helpful OSHA publications on topics such as chemical hazards, hearing protection, and personal protective equipment.

John Henkel is a member of FDA's Web management staff.

SUMMARIES OF COURT ACTIONS



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

SEIZURE ACTIONS

Food/Contamination, Spoilage, Insanitary Handling

PRODUCT: **Calrose Rice**, at Columbia, Maryland, (D.MD.); Civil Action No. 99-CV-3366.

CHARGED 12-9-99: While held for sale after shipment in interstate commerce, at Hanmi Inc., within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 342(a)(4), the articles of food were adulterated in that they were held under unsanitary conditions whereby they may have become contaminated with filth.

DISPOSITION: The articles were destroyed. (F.D.C. No. 67293; S. No. 72119, 72120; S.J. No. 1)

Drugs/Human Use

PRODUCT: **Oxygen, Compressed USP**, at Aberdeen, South Dakota, (D.S.D.); Civil Action No. CIV98-1025.

CHARGED 6-16-98: While held for sale after shipment of one or more of their components in interstate commerce, at Evergreen Supply, Inc., Aberdeen South Dakota, within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 351(a)(2)(B), 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 or administered in conformity with, current good manufacturing practice to assure that such drugs meet the safety requirements of the Act and have the identity and strength, and meet the quality and purity characteristics which they purport and are represented to possess.

DISPOSITION: The articles were reconditioned. (F.D.C. No. 67233; S. No. 98-717-099; S.J. No. 2)

PRODUCT: **Oxygen, Compressed USP**, at Crofton, Maryland, (D.Md.); Civil Action No. S-99-2142.

CHARGED 7-16-99: While held for sale after shipment of one or more components in interstate commerce, at American Home Medical, Inc., Crofton, Md., 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 or administered in conformity with, current good manufacturing practice to assure that such article of drug meets the safety requirements of the Federal Food, Drug, and Cosmetic Act, and has the identity and strength and meets the quality and purity characteristics which it purports and is represented to possess.

DISPOSITION: The articles were reconditioned. (F.D.C. No. 67276; S. No. DOC 42008; S.J. No. 3)

PRODUCT: **Smokeless Artificial Cigarette (E-Z Quit)**, at Riverdale, New York; Civil Action No. 00 Civ. 4069.

CHARGED 5-31-00: While held for sale after shipment in in-

terstate commerce, at E-Z Quit Inc., Riverdale, New York, within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352(f)(1), the article of drug was misbranded because its labeling failed to bear adequate directions for use, and it is not exempt from such requirement under 21 C.F.R. Part 201.115, because it is an unapproved "new drug," and that as a result of the foregoing, the article of drug, including its components, labeling and packaging is subject to seizure, forfeiture and condemnation pursuant to 21 U.S.C. § 334.

DISPOSITION: The articles were destroyed. (F.D.C. No. 67413; S. No. 69909 et al.; S.J. No. 4)

PRODUCT: **T3 Metabolite**, at Mobridge, South Dakota, (D.S.D.); Civil Action No. CIV00-1015.

CHARGED 6-5-00: While held for sale after shipment of one or more of their components in interstate commerce, at Mass Quantities, Inc., Mobridge, South Dakota, within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352 (f)(1), the articles of drug were misbranded because they did not bear adequate directions for use and are not exempt from such requirement under 21 C.F.R § 201.115.

DISPOSITION: The articles were destroyed. (F.D.C. No. 67405; S. No. 730; S.J. No. 5)

PRODUCT: **Trimethobenzamide**, 5,212 boxes, at Elk Grove Village, Ill., (N.D. Ill.); Civil Action No. 98-C1376.

CHARGED 3-6-98: While held for sale after shipment of one or more of their components in interstate commerce at Solopak Laboratories, Inc., within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 351(a)(2)(B), 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 to assure that such drugs meet the safety requirements of the Act and have the identity and strength, and meet the quality and purity characteristics, which they purport and are represented to possess.

DISPOSITION: The articles were destroyed. (F.D.C. No. 67228; S. No. 98-761-363/366; S.J. No. 6)

PRODUCT: **Various Articles of Drug for Human and Veterinary Use, etc.** at Amarillo, Texas, (N.D. Tex.); Civil Action No. 2-00-CV-067-J.

CHARGED 12-29-99: While held for sale after shipment of one or more of their components in interstate commerce, at Oribi, Inc., dba Meridian Chemical & Equipment, Amarillo, Texas, within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 351(a)(2)(9), the articles 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 to assure that such drugs meet the safety requirements of the Act and have the identity and strength, and meet the quality and purity characteristics, which they purport and are represented to possess.

DISPOSITION: The articles were destroyed. (F.D.C. No. 67401; S. No. 38291 et al.; S.J. No. 7)



Dietary Supplement Maker Fined Twice What Company Profited

By Carol Lewis

Stealing drug-manufacturing chemicals from their employer had been easy. The company didn't keep an inventory of two of its ingredients. No one would notice a gradual disappearance, so it seemed like the perfect crime.

But when the thieves tried to deliver the last 1,200 pounds of stolen chemicals on New Year's Eve 1994 to their partners at an underground lab making methamphetamine—usually called speed on the street—their truck crashed on an icy road outside Colorado Springs, Colo.

Labels on containers in the wrecked truck told police that the chemicals came from the Chemins Company, Inc., a dietary supplement manufacturer in Colorado Springs. When authorities informed James R. Cameron about the truck accident involving his company, he didn't react to the apparent theft. Instead, the owner continued the conspiracy in which he had been lying to the Food and Drug Administration for years about production of an "all-natural" dietary supplement.

Among the products Cameron's company produced was "Nature's Nutrition Formula One," a dietary supplement that was supposed to be made from plant ingredients. But Cameron made his with two pharmaceutical-grade chemicals, ephedrine hydrochloride and caffeine anhydrous.

The coincidental truck crash in 1994 launched a three-year investigation by FDA's Office of Criminal Investigations that landed Cameron in jail for 21 months and cost him and his company more than \$4.7 million in fines and other fees.

But the story really began in 1992. While FDA was investigating Chemins for violations of an unrelated product, company employees were busy in the back spiking Formula One and other products with the two chemical ingredients. And Cameron told them specifically to hide their actions from FDA.

Formula One's label stated it was an "all-natural nutritional supplement" containing ma huang and kola nut, two naturally occurring sources of ephedrine and caffeine. But Chemins' target potency of 12 milligrams of ephedrine and 40 milligrams of caffeine per capsule could not be obtained using only the natural ingredients, because the capsule would have been too large to swallow. To achieve higher levels of ephedrine and caffeine that would provide added stimulation, keep customers coming back for more, and save on raw material costs, Cameron directed his production manager to substitute phar-

maceutical-grade ephedrine and caffeine for the ma huang and kola nut extracts.

Under the Federal Food, Drug, and Cosmetic Act, before the requirements for dietary supplements changed in 1994, a dietary supplement was adulterated and misbranded if it failed to bear the common and usual name of each ingredient on its label. But including chemically prepared ephedrine and caffeine in the product would subject the manufacturer to more stringent regulatory requirements. So Cameron chose not to list the ingredients on the product's label, rather than stop using them. According to OCI special agent Laura Stewart, who handled the case, the investigation also revealed that "the synthetic ephedrine was sometimes substituted at more than double the usual quantity."

To keep FDA from becoming suspicious about the ephedrine and caffeine additions, Cameron created false records for Formula One that omitted the offending chemicals. He knew that FDA inspectors normally collected manufacturing and inventory records during inspections. Cameron also directed company officials to not record incoming shipments of the drug chemicals in the warehouse logs, nor in the company's computerized inventory, and to not assign lot numbers to those materials.

In 1993, when FDA reinspected Chemins for the earlier, unrelated violation, the company's sales manager told the investigator he could not find a key to the storage shed where raw materials were housed. The criminal investigation later disclosed that at 2 a.m. that same night, three company employees moved ephedrine hydrochloride and caffeine anhydrous from the shed to an employee's residence. The next day the FDA inspector was shown an empty shed. Employees periodically returned to the company with only the quantities of ephedrine and caffeine needed for manufacturing.

Even the death of a Texas woman in May 1994, which authorities believe was linked to Formula One, did not dampen Cameron's wrongdoing. FDA inspected Chemins in June 1994 to determine whether Formula One was, in fact, connected to the death. Inspectors requested Formula One's manufacturing records and warehouse receiving logs and received false records. FDA also took product samples for laboratory analysis. And Cameron went so far as to sign an affidavit prepared by FDA stating that Chemins used only naturally occurring raw materials and that at no time did the company ever add



chemically prepared ingredients to its herbal products.

But analysis of the Formula One samples detected synthetic crystals in the product that could not be accounted for in the manufacturing documents. According to Stewart, FDA's forensic chemistry center later confirmed that the crystals were in fact pharmaceutical-grade ephedrine and caffeine.

FDA immediately recommended seizure of Formula One, based on adulteration and misbranding violations. But impending passage of the Dietary Supplement Health and Education Act (DSHEA) held up the process. DSHEA would require ten-day notification prior to taking legal actions against firms or their products. And all the while, Chemins continued to deny adding chemically prepared ingredients.

But by November 1994, FDA had received enough complaints of serious injuries and deaths associated with Formula One to indicate that the product presented a significant risk of illness or injury. On November 21, the agency issued a warning letter advising the firm that Formula One contained ephedrine and other alkaloids, and that the product was found to be adulterated and unsafe.

"It's interesting that this was a food case and not a drug

case," says compliance officer Shelly Maifarth of FDA's Denver district office. "There was not one drug charge stemming from this entire investigation," she says, because the product was labeled a dietary supplement.

But in a meeting between FDA and Chemins officials to discuss the warning letter, Chemins' attorneys, acting on information given them by Cameron, again denied that the company ever added synthetic chemicals to Formula One or that the formula had in any way been changed.

The New Year's Eve truck crash was instrumental in opening the door for FDA's criminal investigation. Despite extensive documentation, witness interviews, and laboratory analyses, Cameron never admitted to the years-long conspiracy. Of the 14-count indictment on October 21, 1999, charging Cameron and Chemins with conspiracy, violating federal food and drug laws, making false statements, and obstructing an FDA investigation, Cameron pleaded guilty in July 2000 to one count of defrauding the United States government.

Cameron, whose company continues to make dietary supplements, began serving his sentence in September 2000. ■

Hearing The Cry For Help And Information

By Theresa Toigo



The phone rings.

"My mother has cancer," says the woman on the other end of the line. "Her oncologist says that available cancer treatments probably won't help much. The doctor suggested that she consider enrolling in a clinical trial. I don't know how to do that. Where can I get information about clinical trials?"

We get this kind of call just about every day in the FDA Office

of Special Health Issues (OSHI). The patients have serious and life-threatening diseases, particularly HIV/AIDS and cancer. They're afraid. Their families are afraid. They want some options, but they're not sure where to go.

So we take their calls. OSHI tries to provide the information that patients and their families need to make important decisions in such difficult situations. The law limits our discussions about new treatments in the pipeline. We can't share trade secrets or say when new drugs might be approved.

But we can take the time to listen. And we do take the time to answer questions. We can educate consumers about FDA's role in approving drugs, and about what the agency can and cannot do. And we can give them the information that sometimes gives them hope.

The questions have a common thread: clinical trials. The reason is simple. When the known therapies fail, only the unknown remains. There's plenty that's unknown on the frontier of medical research. But there's also hope. Sometimes the new therapies work, miraculously, like the protease inhibitors that helped transform the treatment of AIDS. And the patients who try them first are the ones in the clinical trials.

The common thread means that many of the questions repeat from call to call. Here's a sampling:

What are clinical trials? Clinical trials are research studies designed to test new treatments. No one knows whether the new treatment will work, but there's usually evidence that it may be effective in people. As part of a clinical trial, patients get expert medical care, often in universities. But it's important to remember that the purpose of a clinical trial is to study what a drug's risks and benefits might be. More information can be found in an *FDA Consumer* article, "Testing Drugs in People," available at www.fda.gov/fdac/special/newdrug/testing.html.

How can I find out about new treatments in development and clinical studies currently underway? It is often difficult for patients to learn about opportunities to participate in clinical trials, but the government has created a new database filled with information about clinical trials. It's on the Internet at <http://clinicaltrials.gov/>. Developed by the National Institutes

of Health's National Library of Medicine and the FDA, it contains information on approximately 5,000 federally funded clinical trials. And it will soon include more drug company-sponsored clinical trials. Information about clinical trials is also available from patient organizations, which can be located through a variety of Internet sources, including MedlinePlus on <http://medlineplus.gov>.

Patient advocacy organizations can be enormously helpful because they provide advice and support, often from patients who share the same diagnosis. Other information sources include the AIDS Clinical Trials Information Service (1-800-TRIALSA, www.actis.org) for HIV/AIDS trials, and the Cancer Information Service (1-800-4CANCER, <http://cancernet.nci.nih.gov/>). Non-government-sponsored Web sites include organizations like the Pharmaceutical Research and Manufacturers of America (www.phrma.org/searchcures/newmeds/).

How can I get an investigational drug if I can't participate in a clinical trial? FDA regulations allow your doctor to obtain investigational treatments outside of a controlled clinical trial, in some circumstances, through a variety of expanded-access programs such as single-patient INDs (or Investigational New Drugs) and treatment IND protocols. More information can be found in an *FDA Consumer* article, "FDA Finds New Ways to Speed Treatments to Patients," available at www.fda.gov/fdac/special/newdrug/speeding.html.

How does FDA protect patients in a clinical trial? FDA carefully oversees the clinical research process to protect patients from unreasonable risks. In addition, study procedures are reviewed by an Institutional Review Board (IRB), usually a local administrative review group, made up of scientific and non-scientific members. The IRB helps protect the rights and welfare of research participants. The informed consent process provides an opportunity for the investigator and patient to exchange information and ask questions. Patients invited to enter a trial are not obligated to join, but can consent to participate if they find the potential risks and benefits acceptable.

Clinical trials offer no guarantees when standard treatments fail. But they offer an alternative to giving up. The FDA Office of Special Health Issues staff is knowledgeable about clinical trials and ways to find treatment information. We're here to listen to patients and their families and to help them find the information they need to make better-informed decisions with their doctor.

Contact OSHI by calling toll free, 1-888-INFO-FDA (make the voice mail selections 2-3-3), or 301-827-4460; or by e-mail at OSHI@oc.fda.gov.

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Address: www.fda.gov

Consumers,
Health Professionals,
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to the information
you need.

