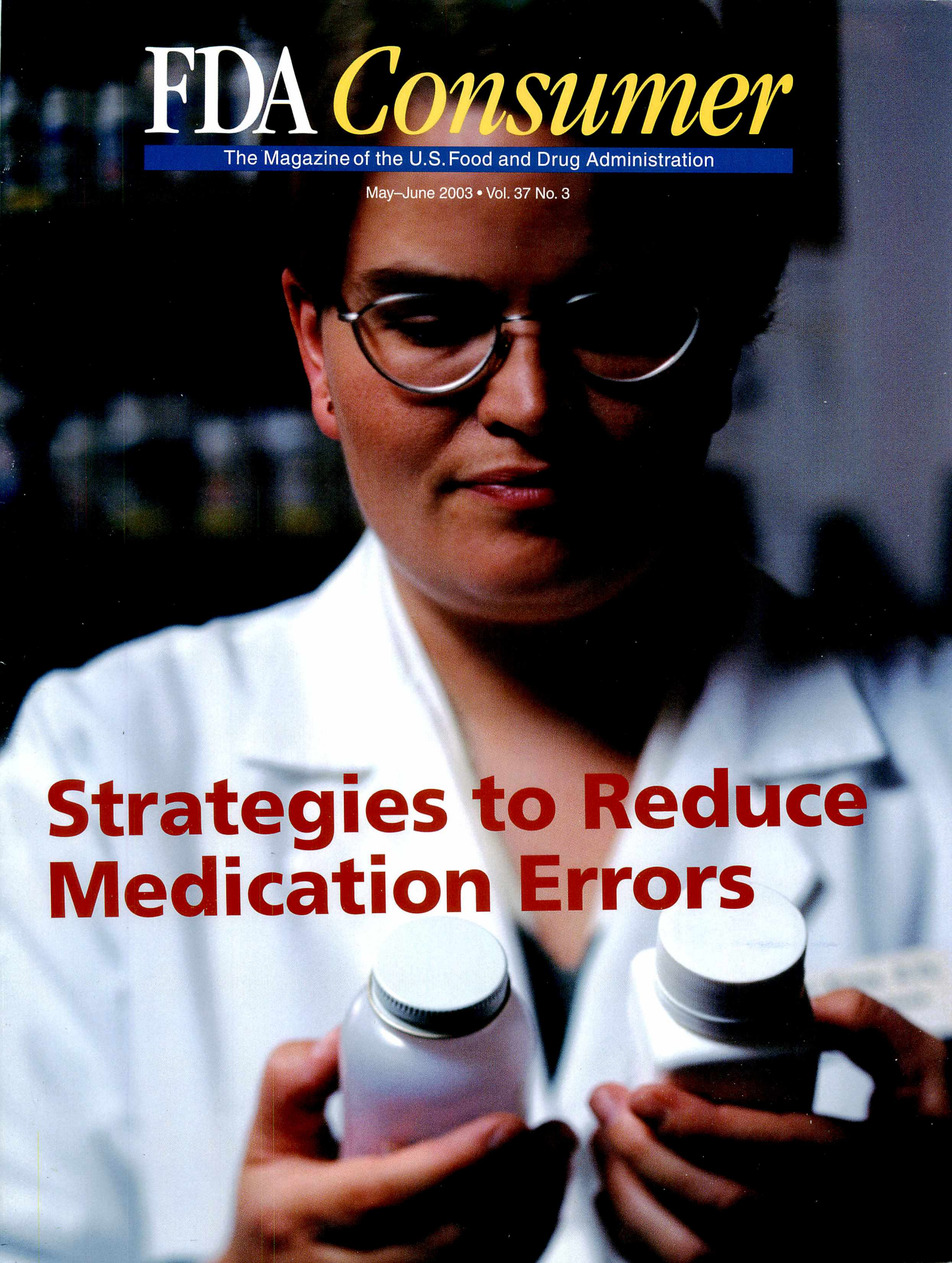


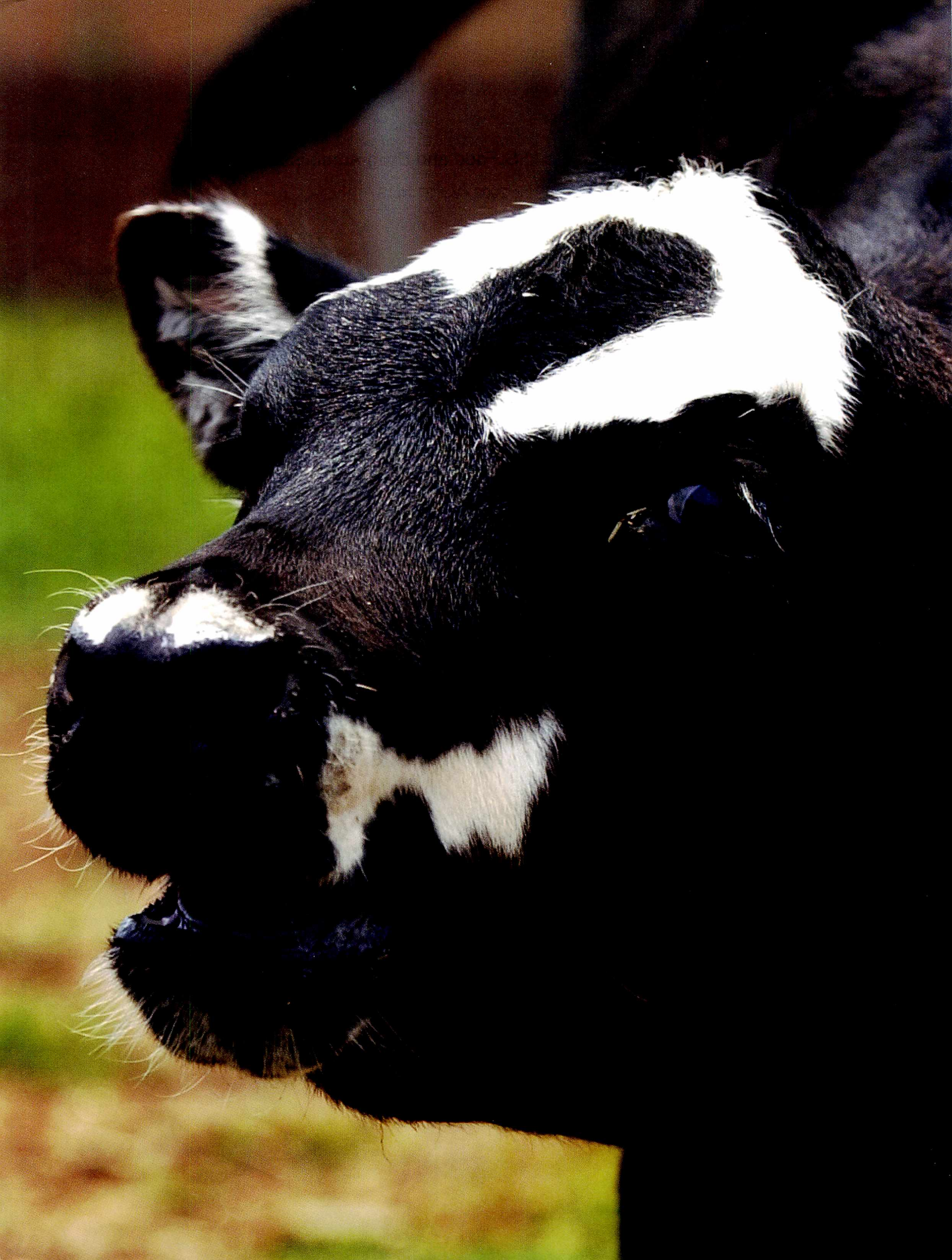
FDA *Consumer*

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

May-June 2003 • Vol. 37 No. 3

Strategies to Reduce Medication Errors





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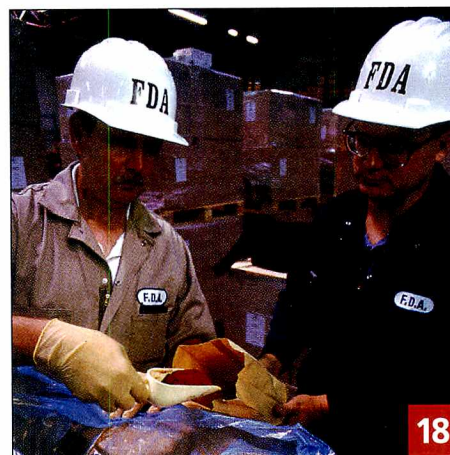
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This cow clone was produced using "nuclear transfer" technology. See page 28 to learn more about the FDA's role in this new technology.

OBSERVATIONS

Bar codes—those tiny arrays of vertical lines and numbers that have become a nearly ubiquitous fixture on everything from newspapers to SUVs—may soon be required on medications regulated by the Food and Drug Administration.

In March, HHS Secretary Tommy G. Thompson proposed placing codes on drugs to help make them easier to identify and to ensure that safe doses are given. In addition, the FDA has proposed a rule that would revamp the way the agency records negative side effects of medications called “adverse events.”

A 1999 Institute of Medicine report estimated that as many as 98,000 Americans may die each year due to preventable medical errors. About 7 percent of these deaths involve errors related to medication.

In addition to the human suffering they cause, medication errors represent significant economic cost to the United States. According to the Institute of Medicine and other experts, thousands of deaths and millions of hospitalizations result from medication errors. Bar codes and other measures aimed at preventing medication adverse events could result in an annual benefit of as much as \$3.9 billion.

“[These] actions are the start of a comprehensive strategy to build a medical patient protection system for the 21st century,” FDA Commissioner Mark B. McClellan, M.D., Ph.D., said in announcing the proposed rules.

For more on these proposed rules and the steps the FDA is taking to reduce medication errors, see our cover story titled “Strategies to Reduce Medication Errors” beginning on page 20.

According to experts, breast-feeding is one of the most important contributors to infant health. Researchers have



found that breast-feeding improves a baby's growth, immunity and development.

Despite these findings, the rates of breast-feeding in the United States are low—only 29 percent of all U.S. mothers were breast-feeding their infants at six months after birth in 1998, the most recent statistics available. Even more alarming, researchers say, is the fact that African-American women breast-feed their infants at rates significantly below the overall U.S. rate.

The Department of Health and Human Services has developed a “Blueprint for Action on Breastfeeding” in an effort to increase the rates of breast-feeding among U.S. women. For more on the plan, see our feature story beginning on page 12.

Interest in the cloning of livestock for commercial reasons has generated numerous inquiries to the FDA in recent years. The agency's Center for Veterinary Medicine is looking into the safety of animals and their progeny produced as a result of somatic cell nuclear transfer—the method used to produce “Dolly the Sheep.” For more on cloning and the FDA's role, see our feature article beginning on page 28.

Baltimore Orioles pitcher Steve Bechler had “significant amounts” of a popular weight-loss supplement containing ephedra in his system when he suffered heat stroke and collapsed in February, the Broward County (Fla.) medical examiner says. Find out more about the steps taken by HHS and the FDA to protect consumers tempted to use products containing ephedra on page 8.

We also offer tips on how to stay well during a cruise, and discuss the latest agency-wide initiatives aimed at helping to bring new medical products to the marketplace in the shortest possible time.

Ray Formanek Jr.
Editor

TO THE EDITOR

West Nile Encephalitis

The article “West Nile Virus: Reducing the Risk” in the January–February 2003 issue of *FDA Consumer* states, “In a small number of people—about 1 in 150—the virus causes life-threatening inflammation of the brain (encephalitis) or inflammation of the membrane surrounding the brain and spinal cord (meningitis).”

I invite you to learn more about encephalitis from the people it has touched. Encephalitis Global

(www.encephalitisglobal.com) is a Web site offering information and support to survivors, caregivers and loved ones of all types of encephalitis, including West Nile.

Wendy Station (Encephalitis survivor)
Encephalitis Global
North Vancouver, British Columbia
Canada

Direct-to-Consumer Advertising

Please accept our comments on the article, “The Impact of Direct-to-Consumer Advertising” (March–April 2003 *FDA Consumer*). We strongly believe that patients would be helped much more if the large amounts of money spent on direct-to-consumer advertising of prescription drugs were used to help lower the high cost of prescription drugs.

Nettie K. and Norman Wofsy
Clinton Township, Mich.

Final Rule on Antibiotic Drug Labeling

Encouraging physicians to prescribe antibiotics only when clinically necessary and to counsel their patients about the proper use of antibiotics is the aim of a final rule published by the FDA in February. The rule outlines new labeling regulations designed to help reduce the development of antibiotic-resistant bacteria.

Antibiotics are often prescribed to children and adults with coughs or colds caused by viruses, not bacteria. Prescribing antibiotics for viral infections can hasten the development of bacterial strains that are resistant to

that antibiotic. Antibiotic-resistant bacteria can be passed on to other people, making treatment of their illnesses even more complicated.

The new rule requires statements in the labels of human antibacterial drugs advising physicians to prescribe these drugs only to treat bacterial infections. The rule also requires a statement in the labeling encouraging physicians to counsel their patients about the proper use of these drugs.

For more information on antibiotic resistance, see: www.fda.gov/oc/opacom/hottopics/anti_resist.html.

Wider Use of Rapid HIV Test

Every year, about 8,000 HIV-infected people who come to public clinics for HIV testing don't return a week later to receive their test results. With a rapid HIV test, results are available on the spot in about 20 minutes.

In January, HHS Secretary Tommy G. Thompson announced that the availability of a rapid HIV test would be extended from 38,000 laboratories to more than 100,000 sites, including physicians' offices and HIV counseling centers. The OraQuick Rapid HIV-1 Antibody Test, manufactured by OraSure Technologies Inc. of Bethlehem, Pa., is performed on a finger-stick sample of blood and provides results in as little as 20 minutes. Studies show the test has an accuracy rate of 99.6 percent. As with all HIV screening tests, if the OraQuick gives a reactive test result, the result must be confirmed with an additional specific test.

The FDA approved OraQuick last November for use in laboratories that perform tests of moderate complexity. Wider availability of the test is likely to increase overall HIV testing and decrease the number of people who are unaware they are infected with HIV.

FDA Proposes Standards for Supplements

A new regulation proposed by the FDA in March 2003 would, for the first time, establish standards to ensure that dietary supplements are not adulterated with contaminants or impurities. The regulation also would require current good manufacturing practices (CGMPs) for dietary supplements and ensure that manufacturers accurately label them to reflect the active ingredients and other ingredients in the products.

In recent years, analysis of dietary supplements by a private lab suggests that a substantial number of supplements may not contain the amounts of ingredients indicated on their product labels. In addition, the FDA has discovered products being marketed that are not accurately labeled or that contain harmful contaminants. For example, one firm recalled dietary supplements contaminated with excessive amounts of lead, which may have posed a health risk to many consumers, especially children and women of childbearing age. Another firm recalled its product after it was found that a dietary supplement containing folic acid, often taken by women to reduce the risk of having a baby with neural tube defects, contained

only 35 percent of the amount of folic acid claimed on the label.

To view the proposed regulation, go to www.fda.gov/OHRMS/DOCKETS/98fr/03-5401.html.

Lab Test Rules Out Heart Attack

A new laboratory blood test that significantly increases a doctor's ability to rule out heart attacks in people who experience severe chest pains has been cleared for marketing by the FDA. The agency's action in February 2003 marks approval of the first new blood test for evaluation of heart attacks since 1994, when a blood test for troponin, a protein present in the blood after a heart attack, was introduced.

The latest product, Albumin Cobalt Binding (ACB) Test, manufactured by Ischemia Technologies Inc. of Arvada, Colo., works by measuring how much cobalt is bound to the blood protein albumin. Changes in the structure of albumin occur in several conditions, including heart attacks.

The ACB is not a stand-alone heart attack test. It is intended to be used along with an electrocardiogram (ECG) and a blood test that measures troponin. A normal ACB test with a normal ECG and normal troponin gives doctors increased confidence that a person did not have a heart attack.

CORRECTION

In the chart that accompanied "The Lowdown on Depression" (January-February 2003 *FDA Consumer*), some drugs were incorrectly identified as "selective serotonin reuptake inhibitors" (SSRIs). Of the 10 drugs listed as "Serotonin transport blockers" only five are SSRIs: Celexa (citalopram), Prozac (fluoxetine), Luvox (fluvoxamine), Paxil (paroxetine), and Zoloft (sertraline). The other drugs listed, though their actions include serotonin transport blockade, are not SSRIs since they have other pharmacological actions as well.

New Drug for Parasitic Infections in Children

The FDA has approved Alinia (nitazoxanide) for Oral Suspension to treat diarrhea caused by two parasitic infections—cryptosporidiosis and giardiasis—in children ages 1 through 11. Alinia is the first drug approved specifically to treat cryptosporidiosis, and it's the only drug in suspension form that is approved to treat giardiasis in this age group.

Cryptosporidiosis, an illness caused by the protozoan *Cryptosporidium parvum*, is characterized by diarrhea, abdominal cramps, loss of appetite, low-grade fever, nausea, and vomiting.

Infected people may experience no symptoms, acute diarrhea, or persistent diarrhea that may continue for several weeks. The disease can be prolonged or life-threatening in severely immunocompromised people, and has been associated with malnutrition, impaired growth, and death in children in developing countries. Giardiasis, caused by the protozoan *Giardia lamblia*, is characterized by diarrhea, abdominal cramps, bloating, weight loss, or malabsorption. Giardiasis has also been associated with impaired growth

in children in developing countries.

To date, the safety and effectiveness of Alinia has not been established in people who are HIV-positive or immunodeficient. In studies of children not infected with HIV, the most frequent problems reported in association with Alinia for Oral Suspension were mild, and included abdominal pain, diarrhea, vomiting, and headache.

Alinia is marketed by Romark Laboratories of Tampa, Fla.

First Biologic Treatment Approved for Psoriasis

Adults with moderate to severe plaque psoriasis now have a new option to relieve their symptoms—the



Biogen Inc.

first FDA-approved biologic treatment for this autoimmune condition.

Amevive (alefacept), an injected medication, treats plaque psoriasis

through a unique immunosuppressive action. It is believed to work by simultaneously blocking and reducing

the number of overactive white blood cells that play a role in psoriasis.

Plaque psoriasis is the most common form of psoriasis, a chronic relapsing disease of the skin that is characterized by scaling and inflammation. Psoriasis affects as many as 5.5 million Americans, according to the National Institutes of Health. Psoriasis is more common in adulthood, but may have its onset in childhood. People with psoriasis may have pain and itching, restricted motion in their joints, and emotional distress.

The approved labeling for Amevive states that it must be administered

under the supervision of a physician and that physicians should inform patients of the need for regular monitoring of white blood cell counts while taking Amevive. Patients should also be informed that Amevive suppresses their immune system, which could increase their chances of developing an infection or malignancy.

Amevive is manufactured by Biogen Inc. of Cambridge, Mass.

Expanded Use of HPV Test

A laboratory test to detect the presence in women of human papillomavirus (HPV), one of the most common sexually transmitted infections, has been approved for an expanded use.

The FDA initially approved the HC2 High-Risk HPV DNA Test in 2000 for testing women who had abnormal Pap test results to determine whether they needed to be referred for further examination. The

expanded use allows the test to be used, in conjunction with the Pap test, for screening of women over age 30 for HPV infection.

Most women who become infected with HPV are able to eradicate the virus and suffer no apparent long-term consequences to their health. But a few women develop a persistent infection that can eventually lead to pre-cancerous changes in the cervix. The HPV DNA test can identify 13 of

the high-risk types of HPV associated with the development of cervical cancer. With proper screening, cervical cancer is avoidable and, if caught early, curable.

The HPV DNA test, manufactured by Digene Corp. of Gaithersburg, Md., is not intended to substitute for regular Pap screening.

Safeguards for Gene Therapy Trials

Some of the gene therapy trials temporarily halted by the FDA in January may be allowed to continue if appropriate safeguards are put in place.

The FDA had placed the studies on hold after it learned that two children treated in a French gene therapy trial had developed a leukemia-like condition. The children had been successfully treated by gene therapy for X-linked severe combined immunodeficiency disease (X-SCID), also known as "bubble baby syndrome."

In February, an FDA advisory committee recommended possible safety measures to minimize the risks in human studies that use retroviral vectors. These modified viruses are used to insert new genes into blood stem cells to treat life-threatening diseases.

These safety measures include revisions to the informed consent document for patients and steps study sponsors should take to monitor for early leukemia-like symptoms.

The FDA's continuing review of adverse event reports from all U.S. studies involving retroviral vectors has so far found no evidence of leukemia caused by the gene therapy. The FDA is reviewing the recommendations of the advisory committee and working closely with study sponsors to help them continue to develop innovative new treatments, while doing everything possible to better understand and prevent any adverse events.

Counterfeit Procrit

The FDA's Office of Criminal Investigations recently uncovered the existence of a counterfeit version of a drug used to treat severe anemia. Investigators say that the illicit vials, labeled Procrit, contain bacteria and represent a significant potential health hazard to consumers.

Procrit (epoetin alpha) is used to treat severe anemia by stimulating the production of red blood cells.

In addition to finding bacteria, FDA laboratory testing demonstrated that

some of the counterfeit product contains no active ingredient. Ortho Biotech Products L.P. of Bridgewater, N.J., issued a warning to health care providers and others in a letter dated March 8, 2003.

The three lots of counterfeit products, labeled as Procrit (epoetin alpha), 40,000 units/mL, are:

- P007645, Expiration 10-2004
- P004677, Expiration 02-2004
- P004839, Expiration 02-2004

The FDA urges health care providers and consumers to check packaging and vials very carefully before using this product. Anyone who finds counterfeit Procrit should not use it, should isolate it, and should immediately contact the FDA's Center for Biologics Evaluation and Research at 1-800-835-4709 and Ortho Biotech at 1-800-325-7504. For more information, visit Ortho's Web site at www.procrit.com/counterfeit/letter.html.

New Class of Medications Approved for Advanced HIV

People infected with the virus that causes AIDS and who no longer respond to other treatments now have another option with approval of a new class of medications. Fuzeon (enfuvirtide) was approved by the FDA in March for use in combination with

other drugs that fight HIV.

Fuzeon is the first "fusion inhibitor" drug. When HIV infects a cell, it first attaches to the outside surface of the cell. Then the virus fuses its membrane with the infected cell's membrane, thereby introducing the virus into the cell. Fuzeon stops this process of fusion.

According to the Centers for Disease Control and Prevention, 850,000 to 950,000 people in the United States are currently infected with HIV. About 40,000 new infections occur each year. The new class of medications is particularly timely since a significant percentage of patients with chronic HIV have developed infection resistant to many existing medications.

A combination of medications is needed for effective HIV treatment, experts say. Fuzeon, manufactured by Roche Pharmaceuticals of Nutley, N.J., can be used as part of a medication regimen in patients for whom there are limited options. Fuzeon is administered as an injection and should be used only in adults and children ages 6 years and older who have previously used other anti-HIV medications and who have ongoing evidence of viral replication.

We're eager to hear what you like and what you don't like. We also want to know the subjects you'd like to see covered.

To contact *FDA Consumer*:

Letters to the Editor should be 300 words or less. If you would like your comments to be considered for publication, please include your name, address, and telephone number during business hours. The editor reserves the right to edit letters for space and appropriateness. E-mail your letters to FDAC-letters@oc.fda.gov or send to the address below.

Inquiries about the magazine: E-mail other questions to FDAC-queries@oc.fda.gov or write to the address below.

General FDA questions: E-mail webmail@oc.fda.gov.

Mailing address: Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857

Skin Decontamination Lotion Cleared for Military Use

The FDA has cleared for use by the U.S. military a liquid decontamination lotion intended to remove or neutralize chemical warfare agents and T-2 fungal toxin from the skin.

The lotion, called Reactive Skin Decontamination Lotion (RSDL), must be applied to exposed skin as soon as possible after exposure to a chemical agent.

The lotion is impregnated in a sponge pad packaged as a single unit in a heat-sealed foil pouch. When exposed to chemical warfare agents, the

user wipes the exposed skin with the lotion. The lotion removes the agents or the T-2 toxin and also reacts with the chemical agents, rapidly neutralizing them to make them non-toxic.

"If used in time, this lotion can help prevent the serious burns and deaths that result from exposure to chemical warfare agents," says FDA Commissioner Mark B. McClellan, M.D., Ph.D. "The FDA worked with the U.S. Army to expedite review of this product to make it available to our men and women in uniform as quickly as possible."

The FDA cleared the lotion for use based on studies conducted by the U.S.

Department of the Army that showed it is safe and effective. The Army tested the product's safety by conducting skin irritation, sensitization, and photoirritation studies in more than 300 people. It tested the lotion's effectiveness by using it to treat animals that had been exposed to chemical agents. The Canadian military and the U.S. military worked together to develop the scientific data on which the FDA based clearance of the product.

RSDL is manufactured by O'Dell Engineering Ltd./E-Z-EM Canada Inc., Canada.

Labeling Changes for Lindane

The FDA has issued a public health advisory concerning Lindane Lotion and Lindane Shampoo, prescription medication treatments for scabies and lice.

The advisory announces significant changes to the labeling of these products, which now includes a boxed warning emphasizing that Lindane products are indicated as a second-line therapy. The FDA believes the benefits of Lindane outweigh the risks when used as directed. But given the potential for neurotoxicity, people should only be treated with these medications if others are not tolerable or have failed.

The boxed warning also states that Lindane Lotion and Lindane Shampoo should be used with caution in people who weigh less



PhotoDisc

than 110 pounds. Lindane is not recommended for use in infants, especially premature infants. These warnings are based on reports to the FDA of problems in children.

It is estimated that up to 1 million prescriptions are written each year in the United States to treat new cases of head lice and scabies, which occur mostly in school-age children. Because Lindane is absorbed through

the skin, and because younger children have more skin surface area per pound of body weight than adults, the amount absorbed may result in higher blood levels of Lindane in children than in adults. Because most of the serious adverse events reported with Lindane products are due to misuse and overuse, especially with the lotion, product package sizes will be limited to 1 and 2 ounces. It is very important that consumers use this medication in a manner consistent with the product labeling. Instructions and warnings for Lindane products will be given to consumers in a Medication Guide.

Health care providers should consider this new safety information when deciding whether to prescribe Lindane Lotion or Lindane Shampoo.

Contaminated Honey Seized

U.S. Marshals have seized contaminated imported honey at the request of the FDA in three enforcement actions since last fall. The latest action occurred in February in Baytown, Texas, where marshals took possession of 266 drums of honey (each containing 639 pounds of bulk honey) and five totes (each containing a net weight of 3,000 pounds) from Hoyts Honey Farm Inc. Earlier seizures

took place in Texas and Louisiana.

The import seizures occurred after the FDA tested and confirmed the presence of chloramphenicol, an antibiotic and an unapproved food additive. Food products that contain chloramphenicol cannot be sold in or imported into this country, in accordance with the Federal Food, Drug and Cosmetic Act.

Chloramphenicol is a broad-spectrum antibiotic drug used to treat life-

threatening infections in humans, usually when other alternatives are not available. Use of this antibiotic is limited because of a potentially life-threatening side effect, idiosyncratic aplastic anemia.

The FDA will continue to detain or seize any honey imports that contain chloramphenicol to ensure that this product is not released for human or animal consumption in the United States. ■

NCI Study: More than 2 Million U.S. Women Could Benefit from Tamoxifen

A new analysis of U.S. cancer data by the National Cancer Institute (NCI) indicates that more than 2 million American women could benefit from taking the drug tamoxifen to prevent breast cancer.

As with all medicines, tamoxifen has side effects that may affect some women and not others. With tamoxifen, the effects are rare, but serious. The study, published in the April 2, 2003, issue of the *Journal of the National Cancer Institute*, weighed these risks, which are especially high for older women, against the benefits of tamoxifen to determine how many women in the United States are likely to have a net benefit from the drug.

Tamoxifen was approved as a chemoprevention drug for breast cancer by the FDA in 1998, after the NCI released the results of the Breast Cancer Prevention Trial (BCPT), a six-year study of the drug. In BCPT, tamoxifen was found to reduce the incidence of breast cancer by 49 percent. Based on that study, the FDA approved the drug for women at high risk of developing invasive breast cancer.

Using data on cancer risk factors from the 2000 National Health Interview Survey, Andrew N. Freedman, Ph.D., and colleagues at the NCI calculated the number of U.S. women eligible to take tamoxifen based on FDA-approved indications. They also projected the number of white and black women who would most likely have a net positive benefit from taking the drug based on a benefit-risk analysis. Because accurate data on the frequency of adverse tamoxifen effects in Hispanic women were not available, estimates of how many Hispanic women would likely benefit from the drug could not be calculated, Freedman says.

The researchers estimated that 15.5 percent of women 35 to 79 years old in this country, or about 10 million,



Getty Images

would be eligible to take tamoxifen based on breast cancer risk alone.

The decision to take tamoxifen will depend on a woman's age, breast cancer risk factors, family history, how she weighs the benefits and risks, and her specific medical situation, lifestyle, personal values, and preferences, says Wortia McCaskill-Stevens, M.D., one of the co-investigators on the NCI study.

"Women with increased risk of breast cancer must carefully consider the benefits and risks in consultation with their physicians," says Freedman.

When analyzed by race, 18.7 percent of white women ages 35 to 79 in the United States, or 9.4 million, would be eligible for tamoxifen, but only 4.9 percent, or 2.4 million, are likely to benefit from the drug. About 6 percent of U.S. black women in the same age range, or 430,000, would have a high enough risk to take the drug, but only 0.6 percent, or 43,000, would likely

derive a net benefit from it. The rates are lower for black women than white women, Freedman says, because the overall risk for breast cancer in black women is lower and because the rates of stroke, deep vein thrombosis, and pulmonary embolism are higher among black women than among white women.

The researchers found that younger women are less likely than older women to experience the drug's adverse effects. This means that if a 40-year-old woman and a 60-year-old woman had the same breast cancer risk, the younger woman would likely derive a better overall benefit from the drug.

For more information, go to the NCI's Web site, <http://cancer.gov/bcrisktool/>, or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). ■

Public Health Officials Caution Against Ephedra Use

Health officials caution consumers against using dietary supplements containing ephedra. The stimulant can have dangerous effects on the nervous system and heart.

By Michelle Meadows

The death of Baltimore Orioles pitcher Steve Bechler in February 2003 brought renewed attention to the dangers of using the herb ephedra. Bechler died from multiple organ failure due to heat stroke, and a dietary supplement containing ephedra was a contributing factor, according to Joshua Perper, M.D., chief medical examiner in Broward County, Fla.

Soon after Bechler's death at age 23, minor league baseball banned ephedra, joining other sports organizations that had already banned its use—the



Getty Images

Ephedra was a factor in the death of Baltimore Orioles pitcher Steve Bechler.

National Football League, the National Collegiate Athletic Association, and the International Olympic Committee.

Health officials recently cautioned American consumers against using ephedra-containing products, especially if strenuous exercise is involved, or in combination with other



FDA/Michael Ermarth

stimulants such as caffeine. Because ephedra is an adrenaline-like stimulant, it can have potentially dangerous effects on the nervous system and heart.

A naturally occurring substance derived from ma huang, a Chinese herbal medicine, ephedra has been promoted to help people lose weight, enhance athletic performance, and increase energy. Its principal active ingredient is a chemical called ephedrine.

Because ephedra is an herb, it is considered a dietary supplement regulated under the Dietary Supplement Health and Education Act of 1994. Under that law, the FDA does not review dietary supplements for safety and effectiveness before they are marketed. Rather, the law allows the FDA to prohibit sale of a dietary supplement only if it "presents a significant or unreasonable risk of injury."

Synthetic ephedrine, however, is regulated as a drug. Ephedrine-containing products taken orally can be sold over-the-counter (OTC) without premarket approval as long as they conform to the final monograph for OTC drug products used for temporary relief of asthma symptoms. Final monographs cover the formulation,

use, and labeling of OTC drug products. Prescription medicines with ephedrine for uses other than those covered by the monograph require premarket review for safety and effectiveness.

Synthetic ephedrine can be found in OTC and prescription drugs taken orally for temporary relief of shortness of breath, chest tightness, and wheezing due to bronchial asthma. Synthetic ephedrine can also be used as a topical nasal decongestant (nose drops, sprays, or jelly) for temporary relief of nasal congestion due to colds, hay fever, sinusitis, or other upper respiratory allergies. As a regulated drug product, synthetic ephedrine has mandatory warnings and labeling for short-term use. It also isn't allowed to be used in combination with caffeine or other stimulants that could interact with it. The controlled availability of synthetic ephedrine drug products under FDA regulation has not been reported to be associated with the same level of severe adverse events that have been reported with dietary supplements containing ephedra.

Still, Barbara Michal, a paralegal in San Bernardino, Calif., says she's extremely concerned about the OTC availability of ma huang, ephedra, and

ephedrine, whether in herbal form in dietary supplements or as synthetic ephedrine in drugs. She founded a nonprofit group called Halt Ephedrine Abuse Today (HEAT) after her son Kristopher died in 1997, at age 24, of sudden cardiac arrest due to an accidental ephedrine overdose.

"I got a frantic call from Kristopher's wife, Nicole, saying that he collapsed," says Michal. "All the paramedics could tell me was that he was down for 10 minutes and that they were working on him," she says. "I drove for three hours to get there—knowing without really knowing that my son was dead."

Michal says Kristopher was using one of two over-the-counter products containing synthetic ephedrine at different times: maximum strength Efedrin and Mini Two Way Action, formerly called Mini Thins. "The products are labeled as asthma aids, but I've known people who bought them from gas stations, truck stops, convenience stores and liquor stores, and used them as stimulants," Michal says. "Kristopher took them for a pick-me-up and, like many people, had no idea of the risks. For one thing, if he wasn't drinking Mountain Dew, he was drinking coffee. I have since learned that caffeine makes ephedrine even more dangerous." Both beverages contain caffeine.

HHS Announces New Actions

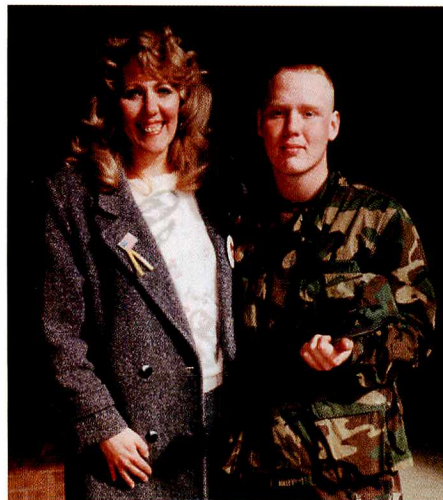
In February 2003, researchers at the RAND Corporation released results of a federally sponsored study that examined available information on products containing the herb ephedra and the drug ephedrine. The study included a review of more than 1,500 adverse event reports related to ephedra that were voluntarily reported to the FDA, and 125 such reports related to products containing synthetic ephedrine.

The researchers concluded that ephedra is associated with risks of side effects such as heart palpitations, psychiatric and upper gastrointestinal effects, and symptoms of hyperactivity such as tremor and insomnia, especially when taken with other stimulants.

RAND's review of some 15,000 additional reports submitted by Metabolife International in the summer of 2002 revealed two deaths,

four heart attacks, nine strokes, one seizure, and five psychiatric cases involving ephedra, in which no other contributing factors were identified. RAND called such cases "sentinel events" because they may indicate a safety problem, but don't prove that ephedra caused the adverse event. The review also found some evidence of ephedra's modest effect on short-term weight loss and scant evidence of its effect on performance enhancement in certain physical activities.

In February 2003, the Department of Health and Human Services and the FDA



Robert Johnson

Barbara Michal with her son Kristopher, who died in 1997.

announced a series of actions designed to protect Americans from potentially serious risks of dietary supplements containing ephedra. These include:

- Seeking rapid public comment on the new information on health risks associated with dietary supplements containing ephedrine alkaloids. This will establish an up-to-date public record to support new restrictions on products containing ephedrine alkaloids.
- Seeking rapid public comment on whether currently available information and medical literature present a "significant or unreasonable risk of illness or injury" from dietary supplements containing ephedra. In seeking comment, the FDA reopened a 1997 proposed rule titled "Dietary Supplements Containing Ephedrine Alkaloids." That rule would have required a warning statement for these products, as well as restrictions on dosage. The FDA withdrew parts of this

1997 proposed rule because of concerns expressed by the General Accounting Office about the information used to establish dose limits.

- Seeking public comment on a mandatory warning label on any ephedra products that continue to be marketed. The proposed warning label warns about the risks of serious adverse events, including heart attack, seizure, stroke, and death, and further cautions that the risk can increase with dose, with strenuous exercise, and when used with other stimulants, such as caffeine. The proposed label specifies those who should never use these products, such as women who are pregnant or breast-feeding. It also lists other conditions, such as diabetes and the use of certain medications, that rule out the use of products containing ephedra.

- Taking actions against ephedra products making unsubstantiated claims about sports performance enhancement. The FDA has sent more than two dozen warning letters to firms marketing dietary supplements that contain ephedrine alkaloids. The letters explain that any claims products make on the structure and function of the human body must be truthful and not misleading. The agency letters also warn companies that they must not make claims about their products' ability to treat or cure a disease or condition, such as obesity. Under the Federal Food, Drug, and Cosmetic Act, dietary supplements with disease claims are considered unapproved new drugs and therefore subject to prompt regulatory actions, including injunctions against firms and seizures of their products.

The FDA continues to work closely with the Federal Trade Commission to ensure that makers of dietary supplements containing ma huang or ephedra don't make false and misleading claims.

Commissioner of Food and Drugs Mark B. McClellan, M.D., Ph.D., says the steps announced show the FDA's commitment to taking the most effective actions possible under current law. "The standard for regulating the safety of dietary supplements is largely untested," McClellan says, "but we are committed to finding the right public health solution." ■

FDA Begins Product

By Carol Lewis

In an ideal world, all new medical products proven to be safe and effective would be approved the first time they were considered by the Food and Drug Administration. A company would submit an application with all the required information, and the agency would perform a timely review and then approve the product for marketing.



PhotoDisc

In reality, though, most medical products take more than one agency review cycle to be approved. Poorly designed studies and missing scientific information are just two of the possible reasons that applications often undergo multiple reviews that ultimately lengthen approval times.

If problems and deficiencies in

product applications can be identified earlier, review times likely will fall and people will have access to new products more rapidly, FDA officials say. Nearly 5,000 new drugs, biologics, medical devices and animal drugs were approved in 2002. With fewer repeated reviews, called "cycles" by the FDA, there could have been even more.

Approvals that take more than one review to complete are not in the best interest of the public, the agency, or the company submitting the product application. From a public health standpoint, multiple-cycle reviews—when an application must be corrected and resubmitted a number of times before an FDA review can be

Approval Initiative

completed—mean that safe and effective new products are not available to patients and health care providers in a timely manner. Multiple-cycle reviews prior to approval also can require substantial additional resources both for the FDA and the sponsor.

To help make innovative medical technologies available sooner, and to reduce the costs of developing safe and effective medical products, the FDA launched an initiative in January that offers guidance to companies it regulates so that they will have a better sense of what is expected on product applications. The initiative involves all four of the agency's medical product review centers (drugs, biologics, medical devices, and veterinary medicine) and focuses on:

- Reducing delays and costs in product approvals by avoiding multiple-review cycles
- Improving the review process through a quality systems approach to medical product review
- Expanding guidance documents to reduce uncertainty and increase efficiency for product development.

The agency has begun analyzing the root causes of product approvals that require more than one review cycle. With the reauthorization of the Prescription Drug User Fee Act (PDUFA), and the enactment of the similar Medical Device User Fee and Modernization Act (MDUFMA), the FDA expects to improve the quality and frequency of communications between the agency and drug, biologic, and medical device manufacturers. Both of these laws require fees paid by manufacturers to give the FDA the resources it needs to determine if a new drug, biologic or medical device should

be approved.

In addition, the FDA will form working groups to oversee guidance development for priority areas such as treatments for cancer, diabetes and obesity.

Finding Solutions

Common problems with product applications significant enough to delay approval include unexpected safety issues or failure to demonstrate a drug or device's effectiveness.

"While an application might be administratively complete; that is, all components are present," says senior scientific reviewer Mitchell J. Shein of the FDA's Division of Cardiovascular Devices, "if the information in the application is not adequately detailed, we might not be able to perform a favorable review. We want to make sure that companies provide adequately robust information."

A manufacturer may need to conduct additional studies involving more people or different types of people, or for a longer period of time. Manufacturing issues, such as a facility not being prepared for inspection, are also reasons that product approval may be delayed or denied. Any manufacturing deficiencies found would need to be corrected before approval.

Mary H. Parks, M.D., deputy director of the FDA's Division of Metabolic and Endocrine Drug Products, says that close communication with the agency during critical stages of drug development or when significant problems arise reduces the chances that the application would have to go through more than one review cycle.

"Companies are made aware of the

possibility of FDA meetings to help sponsors better prepare their applications," she says.

Although the FDA generally has been meeting its PDUFA review time goals (six months for priority product applications and 10-12 months for standard applications), actual time to approval can be much longer when an application goes through multiple cycles.

"It also bears repeating that the reviewers don't have just one application to work on," says Enid Galliers, chief of the project management staff in the FDA's metabolic and endocrine drug products division. Galliers says that submission of a complete and well-organized application, as a result of timely communication between sponsors and the agency, allows for a more efficient review cycle.

Commissioner of Food and Drugs Mark B. McClellan, M.D., Ph.D., says that by making the FDA's requirements for approval clearer from the start, reduction in approval times and costs will build excellence and predictability into the product development process.

But, says McClellan, "Improvement in the rate of single-cycle approval must result from better product development, not lower standards." The quality systems approach and the specific guidance McClellan envisions "should help establish an improved regulatory paradigm—one that will improve the development of innovative medical technology and reduce the costs of technology development, while maintaining FDA's traditional high standard of consumer protection." ■

HHS Blueprint to Boost Breast-Feeding

By Carol Lewis

Two decades of scientific research, and years of proactive measures by health experts and others, are beginning to pay off. Attitudes and behaviors toward breast-feeding in the United States are changing.

During the last 15 years, the importance of breast-feeding has been recognized as one of the most valuable medical contributors to infant health. In 1990, the United States signed a formal declaration on the protection, promotion, and support of breast-feeding adopted by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). At the same time, the Department of Health and Human Services (HHS), through a national health promotion and disease prevention initiative called Healthy People 2000, and subsequently Healthy People 2010, established breast-feeding objectives for the first year of an infant's life.



Getty Images

Recognition of the benefits of breast-feeding has already spread to many health and professional organizations, such as the American Academy of Family Physicians, the American Dietetic Association, and the American College of Obstetricians and Gynecologists. Moreover, the American Academy of Pediatrics considers breast-feeding to be "the ideal method of feeding and nurturing infants."

A Blueprint for Breast-Feeding

To further these efforts, the HHS Office on Women's Health (OWH), in cooperation with other federal agencies and health care professional organizations, developed a comprehensive national breast-feeding policy, called the *HHS Blueprint for Action on Breastfeeding*.

The OWH has been given funds to translate the recommendations of the Blueprint into the National Breastfeeding Awareness Campaign to promote breast-feeding among first-time parents. The overall goal of both the Blueprint and the campaign is to increase the number of mothers who breast-feed their babies in the early period following their birth (postpartum) to 75 percent and to raise to 50 percent those who are breast-feeding at 6 months postpartum by the year 2010.

The Blueprint introduces an action plan for breast-feeding that reaffirms its superiority for most newborns. The plan is based on education, training, awareness, support, and science, and includes key recommendations of the HHS Subcommittee on Breastfeeding.

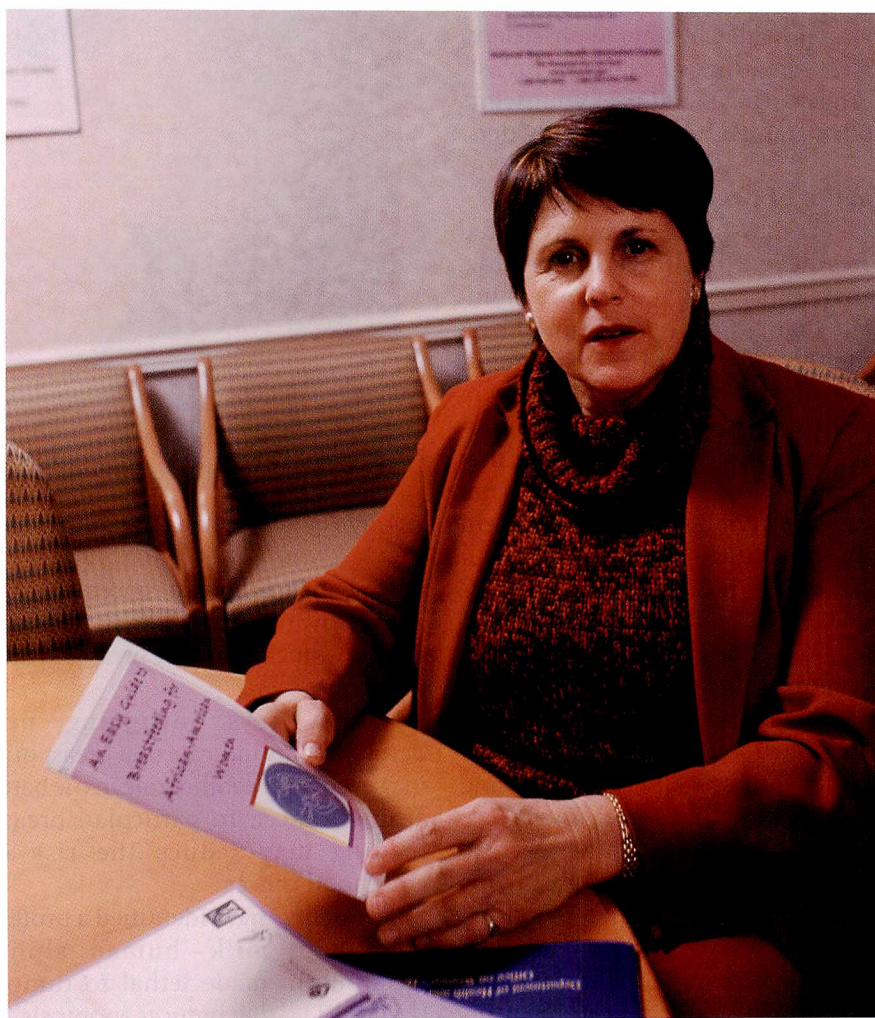
"The Blueprint has been widely circulated and the number of requests for the document has been unprecedented," says Suzanne G. Haynes, Ph.D., chairwoman of the HHS Subcommittee on Breastfeeding and senior science advisor at the OWH. "It is being used in teaching settings, in hospitals, and in communities," she adds, noting that the U.S. Department of Agriculture is using the document to promote breast-feeding in nine state projects.

As part of the National Breastfeeding Campaign, a comprehensive three-year media campaign will be launched in the summer of 2003. The campaign will

be marketed in partnership with selected organizations and will get the message out through public service announcements, bus-stop posters, billboards, articles in community newspapers, parenting and women's magazines, Web sites, and educational pamphlets.

In addition, 18 community-based demonstration projects throughout the

growing. As of 1999, 33 states had enacted laws relating to a wide range of issues involving various aspects of breast-feeding, such as redefining indecent exposure rules, allowing breast-feeding in public places, jury duty postponement due to breast-feeding, and promotion of breast-feeding programs. Hawaii, for example, prohibits employers from discriminating against a mother who



Black Star/Dennis Brack

Suzanne G. Haynes, Ph.D., chairwoman of the Department of Health and Human Services' Subcommittee on Breastfeeding, discusses a national campaign to raise the number of mothers who breast-feed.

United States will work with the OWH and the Advertising Council to implement the National Breastfeeding Awareness Campaign on a local level. The projects will attempt to educate women about the benefits of breast-feeding, encourage them to choose to breast-feed, and create awareness that breast-feeding is normal, desirable, and achievable.

Legislative support of breast-feeding is

breast-feeds or expresses milk with a pump at the workplace.

In addition, several health plans are working to make women aware of the many health benefits breast-feeding holds for their newborns and for themselves. "We have the support of the leading policy groups for health plans," says Haynes. According to the American Association of Health Plans (AAHP), health plans have a vital role to play in

increasing the number of women who successfully breast-feed their babies.

Health plans can influence both families and health care providers through targeted educational interventions promoting breast-feeding, and breast-feeding support services, provided before, during, and after birth. Additionally, health plans can support breast-feeding mothers during the critical first days and weeks postpartum by offering all mothers access to special services provided by trained physicians, nurses, lactation specialists (breast-feeding coaches), and peer counselors or other trained health care providers.

Benefits of Breast-Feeding

Science has proved that breast-fed babies have a healthier start in life. Human milk contains a balance of nutrients that closely matches infant requirements for brain development, growth and a healthy immune system. Human milk also contains immunologic agents and other compounds that act against viruses, bacteria, and parasites. Since an infant's immune system is not fully developed until age 2, human milk provides a distinct advantage over formula.

Because breast milk provides protection against germs that a baby or mother may carry, studies in infant feeding have found lower rates of several chronic childhood diseases, including respiratory infections and ear infections, as well as symptoms such as diarrhea, among children who were breast-fed.

Research also suggests that breast-fed infants gain less weight and tend to be leaner at 1 year of age than formula-fed infants. This early indicator may influence later growth patterns, resulting in fewer overweight and obese children.

But infants aren't the only ones who benefit from breast-feeding. Mothers, too, are the recipients of many positive hormonal and physical effects. Breast-feeding releases a hormone in a woman's body that causes her uterus to return to its normal size and shape more quickly and reduces blood loss after delivery. In addition, according to the Blueprint, studies have shown that breast-feeding for longer periods of time (up to 2 years) and among younger mothers may reduce the risk of premenopausal and possibly



Black Star/Larry Evans

Amy Finnerty nurses her daughter Veronica.

postmenopausal breast cancer. Also, the risk of ovarian cancer may be lower among women who have breast-fed their children.

Haynes says intriguing new developments indicate that breast milk may even have another role in the battle against cancer. In particular, breast-feeding may reduce the risk of childhood cancer.

Researchers have identified a protein in human milk—human alpha-lactalbumin made lethal to tumors (HAMLET)—that induces apoptosis, or programmed cell death, in which cells, responding to environmental signals, self-destruct. Apoptosis, a relatively new study in biology, is the natural mechanism the body uses to recycle material that is not needed for functioning. When apoptosis is initiated, the cell's genetic material becomes shredded so that the cell cannot replicate itself. With cancer cells, apoptosis is inhibited, allowing rapid growth of dysfunctional cells. Haynes says that the isolation of HAMLET as a trigger for apoptosis in cancer cells could give further weight to evidence

linking breast milk to reduced incidences of some cancers.

From a budget standpoint, breast-feeding can save a family hundreds of dollars a year, even with the added cost of breast pumps, devices regulated by the Food and Drug Administration that allow mothers to express milk when they are away from their babies or when they want to save extra milk to be given to the baby at other times. According to the Blueprint, breast-feeding also saves money for insurers and employers by cutting down on doctor visits and sick days.

Overcoming Obstacles

Why, then, with all these benefits, don't more mothers breast-feed?

Breast-feeding requires a substantial commitment from a mother. Some mothers feel tied down by the constant demands of a nursing newborn. Others feel embarrassed or concerned about breast-feeding, especially in public places.

"That's just the type of image we're trying to change," says Haynes. "We're trying to normalize breast-feeding so that people won't blink an eye when they see it." Haynes says removing these

kinds of barriers is a major challenge of the campaign.

But she also emphasizes that breast-feeding is not the end of a woman's independence. Women can use pumps to express milk when they are going to be away from their babies so that others can bottle feed them, allowing mothers to keep up their milk supply. She adds that women can return to full-time work with careful planning and a discussion with employers about a private and sanitary area to express milk.

Carol Huotari manages the Center for Breastfeeding Information at the Schaumburg, Ill., headquarters of La Leche League, an international breast-feeding support and educational organization. She says, "It's not uncommon for mothers to face difficulties." While the ability to breast-feed is not necessarily inherent in a mother, Huotari says with the proper information and support, the experience of breast-feeding is more often than not successful, and when it is successful it can be profoundly fulfilling. "It's more than just the benefits to the baby—it's about the benefits to the mother, too." While obstacles can sometimes hinder success, Huotari says that most can be overcome.

Because diabetes and allergies run prevalent on both sides of Amy Finnerty's family, the 29-year-old Huntley, Ill., resident especially wanted to breast-feed her baby. But obstacles, like her baby's inability to latch on to her breast properly as the result of a stressful birth experience and the temporary pain she experienced early on, nearly convinced Finnerty that, for her, breast-feeding just wasn't meant to be.

"I remember thinking, 'I'm not going to be a good mom,'" she says. "I didn't think I could take the pain anymore." But the support she received both from the local La Leche League group and her husband clinched it for Finnerty. "Meeting with women who shared my common interest of breast-feeding certainly helped bolster my commitment to nursing," she says. "And Bill would encourage me each time to get through one more feeding, even though I was feeding several times a day. Eventually he was right. I stayed with it and it just clicked." Finnerty is

today happily and successfully nursing her daughter, Veronica.

Huotari says that professional and family support can influence a mother's breast-feeding choice and practices. "It's important to begin sharing positive information on breast-feeding to both boys and girls in school," she says. And health care providers can promote breast-feeding during pregnancy check-ups. "We know that decisions made to breast-feed are often made well before the baby arrives, yet some others do decide that they will breast-feed when their newborn is in their arms for the first time."

Even the childbirth experience can make a great impact on the way breast-feeding begins and continues, says Huotari. "Amy did a lot of preparation for birth beforehand," she says, "and despite the fact that Veronica's birth didn't go the way she planned, Amy is

now a well-established breast-feeding mom."

The La Leche League has chapter meetings throughout the country where expectant and new mothers can learn about breast-feeding, nutrition, and other aspects of child care. (See "For More Information," page 17, for the number to call for local chapters.)

Cautions About Breast-Feeding

Despite the benefits, not every mother is able to breast-feed or chooses to do so. In rare cases, a mother's health may prevent her from breast-feeding. Women who test positive for HIV and AIDS or who have human T-cell leukemia virus type 1 (HTLV-1) should not breast-feed or provide their breast milk for the nutrition of their own or other infants because of the risk of transmission to the child.

Under certain conditions, a case-by-

The FDA and Breast-Feeding

Two of the FDA's regulatory centers have a responsible role with regard to breast-feeding.

The FDA's Center for Devices and Radiological Health (CDRH) is responsible for ensuring that devices such as breast pumps are safe and effective for nursing moms. Breast pumps are classified as either powered or non-powered devices. All powered breast pumps are subject to premarket review and clearance prior to marketing in the United States. Non-powered breast pumps do not require any premarket review unless the manufacturer makes a fundamental change in the technology of the device. Both types of breast pumps are, however, subject to other regulatory controls, such as good manufacturing practices and record keeping.

To report an adverse experience by telephone, or to register a complaint about breast pumps, contact the FDA's Office of Emergency Operations at 1-888-463-6332.

The FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for the safety and nutritional adequacy of commercially prepared infant formulas.

In the rare circumstances when breast-feeding is not possible or recommended, or for various reasons a mother may choose not to breast-feed, commercially prepared infant formula can be used as an alternative form of feeding. Infant formulas are liquids or reconstituted powders fed to infants and young children. They have a special role to play, because often they are the only source of nutrients for infants during a very vulnerable period of rapid growth and development.

Current laws require that infant formula manufacturers must provide the FDA assurance of the nutritional quality of each formulation before marketing. The FDA has provisions that include requirements for certain labeling, nutrient content and manufacturers' quality control procedures (to assure the nutrient content), as well as for company records and reports.

For more information on commercially prepared infant formulas, visit CFSAN's Web site at www.cfsan.fda.gov/~dms/inf-toc.html. ■

case assessment should be made about whether or not breast-feeding is advisable or should be temporarily stopped. According to the Blueprint, some of these conditions include:

- Exposures to environmental chemicals, such as DDT, dioxin, and methyl mercury
- Hepatitis C
- Illicit drug use, such as amphetamines, cocaine, heroin, and marijuana
- Implants and breast surgery
- Metabolic disorders such as galactosemia, a condition in which the infant cannot metabolize lactose, a sugar found in all mammalian milk
- Tobacco and alcohol use, since alcohol and nicotine are present in breast milk. However, for women who cannot or will not stop smoking, breast-feeding is still advised, since the benefits of breast milk outweigh the risks from nicotine exposure
- Use of drugs such as cyclosporin, doxorubicin, ergotamine, methotrexate, and radioactive isotopes, as well as anti-anxiety, anti-depressant, and anti-psychotic agents. For most prescribed and over-the-counter medications taken by women, the risk to the nursing infant is unknown.

Mothers should always ask their

physicians before continuing or taking new medications while nursing.

The American Academy of Pediatrics (AAP) first issued a statement on the transfer of drugs and chemicals into human milk in 1983, revising its lists in 1989 and 1994. Information continues to become available. The current statement, which can be found on the AAP's Web site (www.aap.org/policy/0063.html), is intended to assist physicians in counseling a nursing mother regarding breast-feeding when the mother has a condition for which a drug is medically indicated.

Susan F. Wood, Ph.D., director of the FDA's Office of Women's Health (OWH) says, "The FDA's Center for Drug Evaluation and Research and the OWH are working to improve the current label on products so that it is more helpful to both mothers and prescribing physicians. However, more research is needed in order for good information to show up in the label, and FDA is also working to encourage such research."

Infant Formulas

For women who are unable to breast-feed, the FDA recommends using only commercially prepared formulas as an

alternative to breast milk. These formulas contain the complex combination of proteins, sugars, fats, minerals, and vitamins needed to support growth in infants. The composition of commercial formulas is carefully controlled, and the FDA requires that these products meet very strict standards.

The safety of commercially prepared formula is ensured by the agency's nutrient requirements and by strict manufacturing quality control procedures. These procedures require manufacturers to analyze each batch of formula for required nutrients, test samples for stability during the shelf life of the product, code containers to identify the batch, and make all records available to FDA investigators.

But, while formulas try to imitate the ingredients in human milk, the exact composition of breast milk cannot be duplicated. Human milk contains living cells, hormones, active enzymes, and immunoglobulins that cannot be replicated in infant formula. It also has carbohydrates, easily digestible proteins, and fat, plus antibodies that can protect the baby from infection. Therefore, performance of infant formulas is measured by the infant's growth, absorption of nutrients, and gastrointestinal tolerance.

Increasing the Rates

As of 2001, the year for which the most recent statistics are available, almost 70 percent of all mothers breast-fed in the early postpartum period, and about 32 percent of all mothers breast-fed at 6 months postpartum. Comparing rates in 2001 to 1996, increases in initiating breast-feeding and continued breast-feeding to 6 months were greater among groups that have been historically less likely to breast-feed: black women, women younger than 20 years old, no more than high school educated, working women, and others.

However, racial and ethnic disparities in breast-feeding rates remain significant and, according to HHS, black women breast-feed at alarmingly low rates.

HHS believes that the nation needs to address these low rates as a public health challenge and put in place national, culturally appropriate



FDA/Michael Ermarth

When breast-feeding is not possible, commercially prepared infant formulas such as these are an alternative.



La Leche League International/Suba Tidball

Jameca Benjamin nurses her baby Jamia. Statistics indicate that fewer black mothers breast-feed their babies compared with either white or Hispanic mothers.

strategies to promote breast-feeding.

There are many reasons for the low breast-feeding rates in the black community, but they are reversible. For one thing, breast-feeding is thought to be painful. Most people do not realize that, although there can be some initial discomfort, if done properly, breast-feeding should not cause pain.

Another reason is that the attitude toward breast-feeding in the black community has not been positive. Experts say the message that breast-feeding is superior to formula-feeding has not been heard. Black women also say it is difficult for them to receive information and education about breast-feeding, to have breast-feeding initiated in the hospital, to continue breast-feeding in the early days in the

home setting, and to continue breast-feeding for an extended period.

The Baltimore-based African-American Breastfeeding Alliance, Inc. (AABA) seeks to make breast-feeding a family affair, since black communities often are based on kinship. The decision to breast-feed is frequently directly related to influence from peers, husbands, boy-friends, and other family members. In other words, a woman is more likely to breast-feed if members of her family—primarily spouses—support it.

"It is often taken for granted that African-American women will not breast-feed so they generally don't receive good breast-feeding education and support," says Katherine Barber, founder and Executive Director of AABA. According to AABA, breast-feeding

education should be an essential component during prenatal care.

Increasing the rates of breast-feeding is a compelling public health goal, particularly among the racial and ethnic groups who are less likely to initiate and sustain breast-feeding throughout the infant's first year. According to the Blueprint, this goal can only be met when breast-feeding is supported in the family, community, workplace, health care sector, and society.

Overall, the Blueprint speaks to federal, state, and local governments, families, and the medical community—especially hospitals, where staff can be re-educated, consultants hired, and peer counselors made available to promote breast-feeding. Recognizing that breast-feeding rates are influenced by various factors, the document suggests an approach in which all interested people and organizations come together to forge a partnership to promote and encourage breast-feeding in the United States. ■

For More Information

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition (HFS-555)
5100 Paint Branch Parkway
College Park, MD 20740-3835
www.cfsan.fda.gov

Office of Women's Health
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
www.fda.gov/womens/

Office on Women's Health
Department of Health and Human Services
8550 Arlington Blvd., Suite 300
Fairfax, VA 22031
1-800-994-WOMAN (1-800-994-9662)
TDD: 1-800-220-5446
www.4woman.gov

La Leche League International
1400 N. Meacham Road
Schaumburg, IL 60173-4808
1-800-525-3243 (for information and local chapter numbers)
www.lalecheleague.org

Operation Liberty Shield:

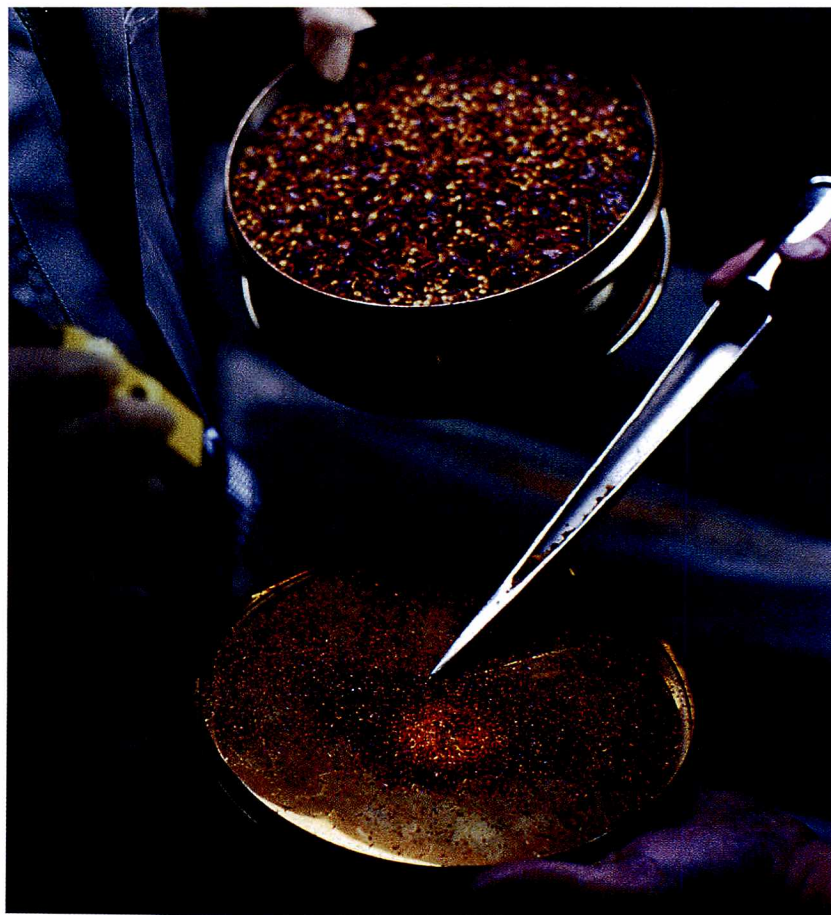
New Food Security Guidance

As part of its continuing efforts to ensure the safety and security of the nation's food supply, the Food and Drug Administration has announced the availability of four guidance documents designed to help manufacturers minimize the risk of tampering or other malicious, criminal or terrorist actions. The FDA also has increased surveillance of domestic and imported foods and enhanced collaboration with other government agencies as part of its Liberty Shield initiatives.

Operation Liberty Shield is a multi-department, multi-agency national plan designed to increase protections for America's citizens and infrastructure. Maintaining the free flow of goods and people across U.S. borders with minimal disruption to the nation's economy and way of life is among the goals of the plan.

The FDA's new Liberty Shield initiatives build on Health and Human Services Secretary Tommy G. Thompson's leadership on food security, including new regulations in process to enhance import security and contain outbreaks of foodborne illness; over 800 new inspectors and field personnel; greater laboratory testing and response capabilities; and new use of intelligence information to help guide food security activities. The agency has initiated the following new activities:

- Working with the food industry to reduce threats—The FDA has issued



To check for contaminants, FDA inspectors take samples from incoming shipments and place them on a filth screen.

new industry guidance on security measures and has encouraged specific additional industry security measures in response to the increased threat level.

- Increased surveillance of the domestic food industry—The FDA has increased facility inspections and product sampling.
- Increased monitoring of imported foods—The FDA has increased examinations and sampling of imported foods.
- Enhanced collaboration with other government agencies—The FDA has increased its joint activities with federal, state, and local partners to help ensure a safe and secure food supply, including work with the Centers for

Disease Control and Prevention to ensure that outbreaks of illness or unusual patterns of illness or injury are quickly investigated.

"Securing our food supply against terrorist threats is one of our most important public health priorities, especially at a time of heightened alert," says Thompson. "FDA is responsible for 80 percent of what we eat. Americans depend on FDA to keep food safe and secure, and we will keep doing all we can to fulfill this critical mission."

"The guidance documents ... as part of the government-wide Liberty Shield initiative cover each segment of food and cosmetic operations, focusing on practical steps that will improve safety

and security," says Mark B. McClellan, M.D., Ph.D., Commissioner of Food and Drugs. "In conjunction with increased surveillance of domestic and imported foods for biological and chemical agents of terrorism, these steps represent a new level of commitment at FDA to keep the food supply secure."

Two of the guidances are revised, final documents, and two are proposed guidances.

The FDA accepts comments on any of these guidance documents at any time and determines whether further revisions are appropriate. However, the FDA is requesting comments on the two draft guidance documents within 60 days of publication. The agency will consider these comments as it develops the final guidance documents, which will be published in the *Federal Register*. The four documents are:

Docket #01D-0583:

- Food Producers, Processors, and Transporters: Food Security Preventive Measures Guidance



FDA inspectors take a sample from a bag of crushed pepper.

- Importers and Filers: Food Security Preventive Measures Guidance

These final documents will help operators of food establishments (for example, firms that produce, process, store, repack, re-label, distribute, or transport food or food ingredients) and

operators of food importing establishments, storage warehouses, and customs brokers identify preventive measures to improve the security of their operations.

Docket #03D-0092:

- Retail Food Stores and Food Service Establishments: Food Security Preventive Measures Guidance
- Cosmetics Processors and Transporters: Cosmetics Security Preventive Measures Guidance

These draft guidances cover food stores and food service establishments such as bakeries, bars, cafeterias, commissaries, convenience stores, fairs, grocery stores, food service for airlines and trains, restaurants, and vending machine operators as well as cosmetic establishments. They also identify preventive measures that operators can take to minimize the security risks to their products.

Written comments on both final and draft guidance documents can be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments can be sent electronically to www.fda.gov/dockets/ecomments. It is important to include the docket numbers when providing comments.

Additional information about provisions of the Bioterrorism Act under the FDA's jurisdiction and the agency's implementation plans is available at www.fda.gov/oc/bioterrorism/bioact.html. Additional information on other agency bioterrorism activities can be found at the bioterrorism home page, www.fda.gov/oc/opacom/hottopics/bioterrorism.html. For more on Operation Liberty Shield, see www.dhs.gov. ■

Proposed Regulations to Safeguard the Food Supply

The FDA is proposing two regulations that would enhance the agency's ability to monitor and protect the nation's food supply against terrorist acts and other threats. These proposals are important milestones in implementing the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.

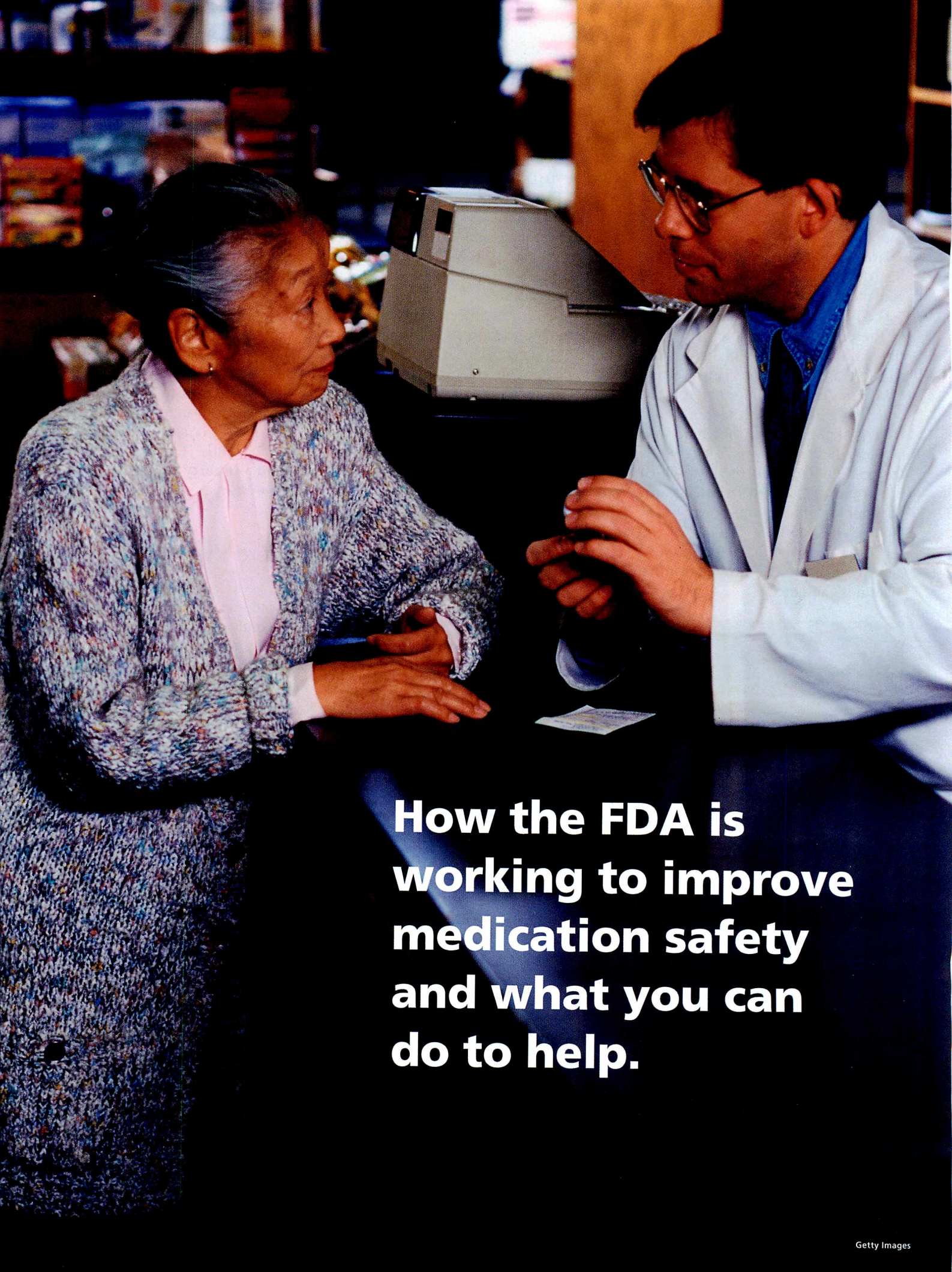
Under one proposal, owners, operators, or agents in charge of a domestic or foreign facility would be required to submit a registration to the FDA that includes basic information about the company, as well as the categories of food the facility handles. Except for specific exemptions, the new regulation would apply to all facilities for all foods and animal feed products regulated by the FDA, including dietary supplements, infant formula, beverages (including alcoholic beverages, which are not regulated by the FDA), and food additives. All facilities that manufacture, process, pack, or hold food for human or animal consumption in the United States will be required to register.

A second proposal would require that prior notice be given to the FDA before food is imported or offered for import in the United States. This would give the FDA advance information of imported food shipments, which would allow the agency to target inspections more effectively and to help ensure the safety of imported food products before they enter domestic commerce.

Under the proposal, the FDA must be notified by noon of the calendar day before the imported food will arrive at the U.S. border crossing or port of entry. This notice would be submitted electronically through an Internet-based system that would be available 24 hours a day, seven days a week. The FDA anticipates it will receive an average of 20,000 of these notices a day.

According to the Bioterrorism Act, both of these requirements will come into effect by Dec. 12, 2003, even if the FDA has not issued final regulations.

"Our ability to efficiently and effectively help protect the nation's food supply is a critical part in our agency's counterterrorism mission ... the Bioterrorism Act gives FDA this important new authority," says FDA Commissioner Mark B. McClellan, M.D., Ph.D. ■



**How the FDA is
working to improve
medication safety
and what you can
do to help.**

Strategies to Reduce Medication ERRORS

By Michelle Meadows

When Jacquelyn Ley shattered her elbow on the soccer field two years ago, her parents set out to find her the best care in Minneapolis. "We drove past five other hospitals to get to the one we wanted," says Carol Ley, M.D., an occupational health physician. Her husband, an orthopedic surgeon, made sure Jacquelyn got the right surgeon. After a successful three-hour surgery to repair the broken bones, Jacquelyn, who was 9 at the time, received the pain medicine morphine through a pump and was hooked up to a heart monitor, breathing monitor, and blood oxygen monitor. Her recovery was going so well that doctors decided to turn off the morphine pump and to forgo regular checks of her vital signs.

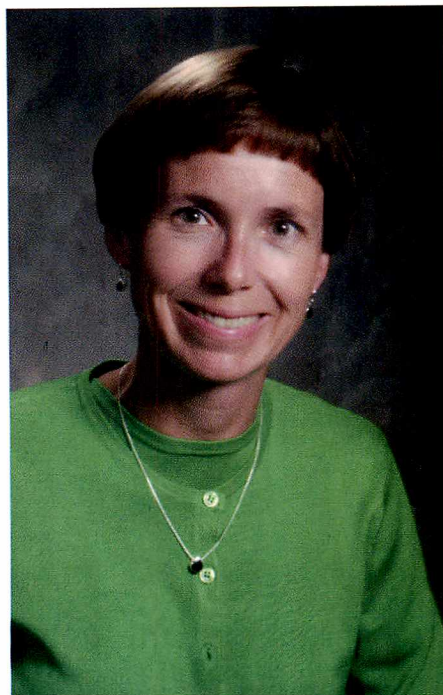
Carol Ley slept in her daughter's hospital room that night. When she woke up in the middle of the night and checked on her, Jacquelyn was barely breathing. "I called her name, but she wouldn't respond," she says. "I shook her and called for help." The morphine pump hadn't been shut down, but had accidentally been turned up high. The narcotic flooded Jacquelyn's body. She survived the overdose, but it was a close call. "If three more hours had gone by, I don't think Jacquelyn would have survived," Ley says. "Fortunately, I woke up."

Ley was pleased with the way the hospital handled the error. "They came right out and said the morphine pump was incorrectly programmed, they told me the steps they were going to take to make sure Jacquelyn was OK, and they also told me what they were going to do to make sure this kind of mistake won't happen again. And that's very important to me." The hospital began using pumps that are easier to use and revamped nurse's training. Ley believes there were many contributors to the error, including the fact that it was Labor Day weekend and there were staff shortages. "It goes to show that this can happen to anyone, anywhere," says Ley, who now chairs the board of the National Patient Safety Foundation.

Multiple Factors

Since 1992, the Food and Drug Administration has received about 20,000 reports of medication errors. These are voluntary reports, so the number of medication errors that actually occur is thought to be much higher. There is no "typical" medication error, and health professionals, patients, and their families are all involved. Some examples:

A physician ordered a 260-milligram preparation of Taxol for a patient, but the pharmacist prepared 260



Howard Berg Photography

Carol Ley, M.D., chairwoman of the board of the National Patient Safety Foundation, says her daughter's medication error strengthened her involvement in patient safety.

drug have been prescribed for other conditions, such as arthritis, asthma, and inflammatory bowel disease.

One patient died because 20 units of insulin was abbreviated as "20 U," but the "U" was mistaken for a "zero." As a

of patient understanding about a drug's directions. "But it's important to recognize that such errors are due to multiple factors in a complex medical system," says Paul Seligman, M.D., director of the FDA's Office of Pharmacoeconomics and Statistical Science. "In most cases, medication errors can't be blamed on a single person."

A medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer," according to the National Coordinating Council for Medication Error Reporting and Prevention. The council, a group of more than 20 national organizations, including the FDA, examines and evaluates medication errors and recommends strategies for error prevention.

A Regulatory Approach

The public took notice in 1999 when the Institute of Medicine (IOM) released a report, "To Err is Human: Building a Safer Health System." According to the report, between 44,000 and 98,000 deaths may result each year from medical errors in hospitals alone. And more than 7,000

The IOM reported that more than 7,000 deaths each year are related to medication errors.

milligrams of Taxotere instead. Both are chemotherapy drugs used for different types of cancer and with different recommended doses. The patient died several days later, though the death couldn't be linked to the error because the patient was already severely ill.

An elderly patient with rheumatoid arthritis died after receiving an overdose of methotrexate—a 10-milligram daily dose of the drug rather than the intended 10-milligram weekly dose. Some dosing mix-ups have occurred because daily dosing of methotrexate is typically used to treat people with cancer, while low weekly doses of the

result, a dose of 200 units of insulin was accidentally injected.

A man died after his wife mistakenly applied six transdermal patches to his skin at one time. The multiple patches delivered an overdose of the narcotic pain medicine fentanyl through his skin.

A patient developed a fatal hemorrhage when given another patient's prescription for the blood thinner warfarin.

These and other medication errors reported to the FDA may stem from poor communication, misinterpreted handwriting, drug name confusion, lack of employee knowledge, and lack

deaths each year are related to medications. In response to the IOM's report, all parts of the U.S. health system put error reduction strategies into high gear by re-evaluating and strengthening checks and balances to prevent errors.

In addition, the U.S. Department of Health and Human Services (HHS) and other federal agencies formed the Quality Interagency Coordination Task Force in 2000 and issued an action plan for reducing medical errors. In 2001, HHS Secretary Tommy G. Thompson announced a Patient Safety Task Force to coordinate a joint effort to improve

data collection on patient safety. The lead agencies are the FDA, the Centers for Disease Control and Prevention, the Centers for Medicare and Medicaid Services, and the Agency for Healthcare Research and Quality.

The FDA enhanced its efforts to reduce medication errors by dedicating more resources to drug safety, which included forming a new division on

transmit information to the hospital's computer, says Lottie Lockett, R.N., a nursing administrator at the Houston VA Medical Center. Nurses have laptop computers and scanners on top of medication carts that they bring to patients' rooms. Nurses use the scanners to scan the patient's wristband and the medications to be given. The bar codes provide unique, identifying

and private label distributors of prescription and OTC drugs would be subject to the bar code requirements. The agency continues to study whether it also should develop a rule requiring bar code labeling on medical devices.

Drug name confusion: To minimize confusion between drug names that look or sound alike, the FDA reviews

Bar coding is a promising way to automate aspects of medication administration.

medication errors at the agency last year. "We work to prevent medication errors before a drug reaches the market and to also monitor any errors that may occur after that," says Jerry Phillips, R.Ph., director of the FDA's new Division of Medication Errors and Technical Support.

Here's a look at key areas in which the FDA is working to reduce medication errors.

Bar code label rule: After a public meeting in July 2002, the FDA decided to propose a new rule requiring bar codes on certain drug and biological product labels. Health care professionals would use bar code scanning equipment, similar to that used in supermarkets, to make sure that the right drug in the right dose and route of administration is given to the right patient at the right time.

"It's a promising way to automate aspects of medication administration," says Robert Krawisz, executive director of the National Patient Safety Foundation. "The technology's impact at VA hospitals so far has been amazing." The Department of Veterans Affairs (VA) already uses bar codes nationwide in its hospitals, and the result has been a drastic reduction in medication errors. For example, the VA medical center in Topeka, Kan., has reported that bar coding reduced its medication error rate by 86 percent over a nine-year period.

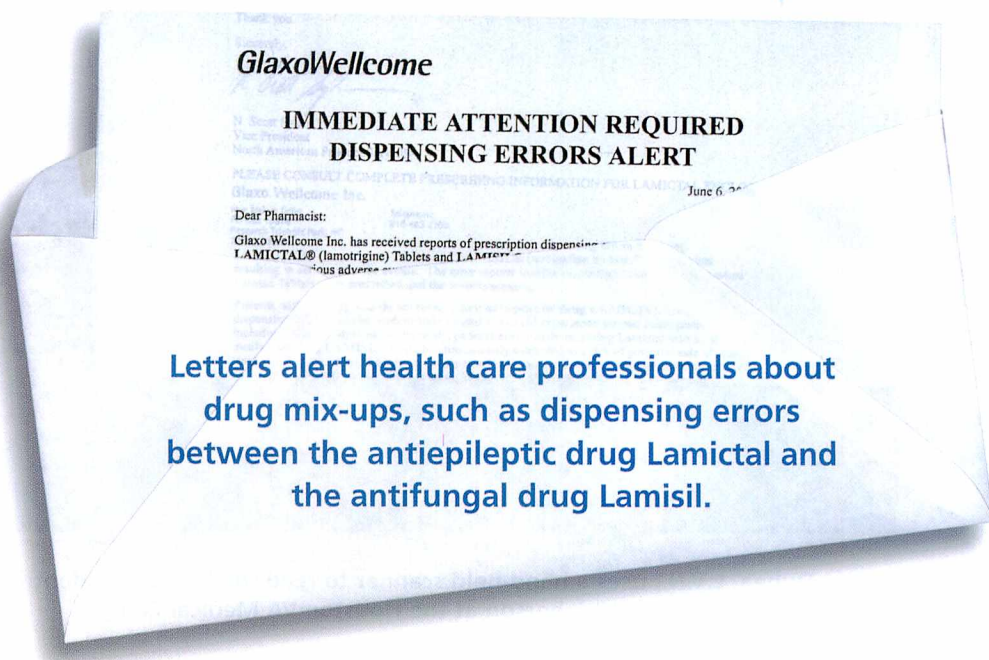
Here's how it works: When patients enter the hospital, they get a bar-coded identification wristband that can

information about drugs given at the patient's bedside. "Before giving medications, nurses use the scanner to pull up a patient's full name and social security number on the laptops, along with the medications," Lockett says. "If there is not a match between the patient and the medication or some other problem, a warning box pops up on the screen."

The FDA's proposed rule on bar code labeling was published on March 14, 2003. The rule, which would take effect in 2006, applies to prescription drugs, biological products such as vaccines, blood and blood components, and over-the-counter (OTC) drugs that are commonly used in hospitals. Manufacturers, repackers, relabelers,

about 300 drug names a year before they are marketed. "We reject about one-third of the names that drug companies propose," says Phillips. The agency tests drug names with the help of about 120 FDA health professionals who volunteer to simulate real-life drug order situations. "We're also creating a computerized program that will assist in detecting similar names and that will help us take a more scientific approach to comparing names," Phillips says.

After drugs are approved, the FDA tracks reports of errors due to drug name confusion and spreads the word to health professionals, along with recommendations for avoiding future problems. For example, the FDA has reported errors involving the inadvertent



administration of methadone, a drug used to treat opiate dependence, rather than the intended Metadate ER (methylphenidate) for the treatment of attention-deficit/hyperactivity disorder (ADHD). One report involved the death of an 8-year-old boy after a possible medication error at the dispensing pharmacy. The child, who was being treated for ADHD, was found dead at home. Methadone substitution was the suspected cause of death. Some FDA recommendations regarding drug name confusion have encouraged pharmacists to separate similar drug products on pharmacy shelves and have encouraged physicians to indicate both brand and generic drug names on prescription orders, as well as what the drug is intended to treat.

The last time the FDA changed a drug name after it was approved was in 1994 when the thyroid medicine Levoxine was being confused with the heart medicine Lanoxin (digoxin), and some people were hospitalized as a result. Now the thyroid medicine is called Levoxyl, and the agency hasn't received reports of errors since the name change. Other examples of drug name confusion reported to the FDA include:

- Serzone (nefazodone) for depression and Seroquel (quetiapine) for

schizophrenia

- Lamictal (lamotrigine) for epilepsy, Lamisil (terbinafine) for nail infections, Ludiomil (maprotiline) for depression, and Lomotil (diphenoxylate) for diarrhea
- Taxotere (docetaxel) and Taxol (paclitaxel), both for chemotherapy
- Zantac (ranitidine) for heartburn, Zyrtec (cetirizine) for allergies, and Zyprexa (olanzapine) for mental conditions
- Celebrex (celecoxib) for arthritis and Celexa (citalopram) for depression.

Drug labeling: Consumers tend to overlook important label information on OTC drugs, according to a Harris Interactive Market Research Poll conducted for the National Council on Patient Information and Education and released in January 2002. In May 2002, an FDA regulation went into effect that aims to help consumers use OTC drugs more wisely.

The regulation requires a standardized "Drug Facts" label on more than 100,000 OTC drug products. Modeled after the Nutrition Facts label on foods, the label helps consumers compare and select OTC medicines and follow instructions. The label clearly lists active ingredients, uses, warnings, dosage, directions, other

Who Tracks Medication Errors?

The Food and Drug Administration

Accepts reports from consumers and health professionals about products regulated by the FDA, including drugs and medical devices, through MedWatch, the FDA's safety information and adverse event reporting program. For information on how to report, call 1-800-332-1088 or go to www.fda.gov/medwatch/how.htm.

Institute for Safe Medication Practices

Accepts reports from consumers and health professionals related to medication.

Publishes *Safe Medicine*, a consumer newsletter on medication errors.

1800 Byberry Rd., Suite 810
Huntingdon Valley, PA 19006-3520

215-947-7797

www.ismp.org/Pages/Consumer.html

U.S. Pharmacopeia

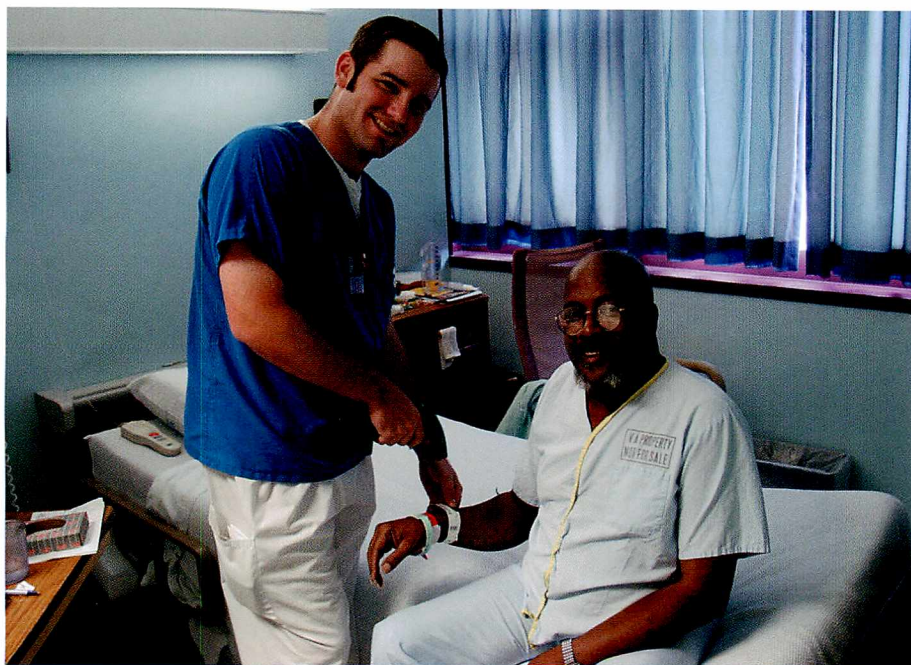
MedMARX is an anonymous medication error reporting program used by hospitals.

www.medmarx.com

12601 Twinbrook Parkway
Rockville, MD 20852

1-800-822-8772

www.usp.org



Houston VA Medical Center/Shawn James

Jeffery Dubea, L.V.N., uses a hand-held scanner to read the bar-coded identification wristband of Willie Hutcherson at the Houston VA Medical Center.

information, such as how to store the medicine, and inactive ingredients.

As for health professionals, the FDA proposed a new format in 2000 to improve prescription drug labeling for physicians, also known as the package insert. One FDA study showed that practitioners found the labeling to be lengthy, complex, and hard to use. The proposed redesign would feature a user-friendly format and would highlight critical information more clearly. The FDA is still reviewing public comments on this proposed rule. The agency has also been working on a project called DailyMed, a computer system that will be available without

cost from the National Library of Medicine next year. DailyMed will have new information added daily, and will allow health professionals to pull up drug warnings and label changes electronically.

Error tracking and public education:

On March 13, 2003, the FDA announced a proposed rule that would revamp safety reporting requirements. For example, the proposal would require that reports on actual and potential medication errors be submitted to the agency within 15 calendar days. FDA's Seligman says, "This rule is part of FDA's overall effort to understand the sources of medication errors and prevent them."

The FDA reviews medication error reports that come from drug manufacturers and through MedWatch, the agency's safety information and adverse event reporting program. The agency also receives reports from the Institute for Safe Medication Practices (ISMP) and the U.S. Pharmacopeia, or USP (see "Who Tracks Medication Errors?" on page 24).

A recent ISMP survey on medication error reporting practices showed that health professionals submit reports more often to internal reporting programs such as hospitals than to external programs such as the FDA. According to ISMP, one reason may be health professionals' limited knowledge about external reporting programs.

The FDA receives and reviews about 250 medication error reports each month, and classifies them to determine the cause and type of error. Depending on the findings, the FDA



Black Star/Dennis Brack

Paul Seligman, M.D., (left) and Jerry Phillips, R.Ph., tap into an FDA database of medication errors. The agency formed a new division on medication errors last year.

homes, and other health care facilities about the hazards of mix-ups between medical gases, which are prescription drugs. In one case, a nursing home in Ohio reported four deaths after an

newsletter for consumers called *Safe Medicine*.

In December 2002, USP released an analysis of medication errors captured in 2001 by its anonymous national

The FDA educates the public on an ongoing basis to prevent repeat errors.

can change the way it labels, names, or packages a drug product. In addition, once a problem is discovered, the FDA educates the public on an ongoing basis to prevent repeat errors.

In 2001, the agency released a public health advisory to hospitals, nursing

employee mistakenly connected nitrogen to the oxygen system.

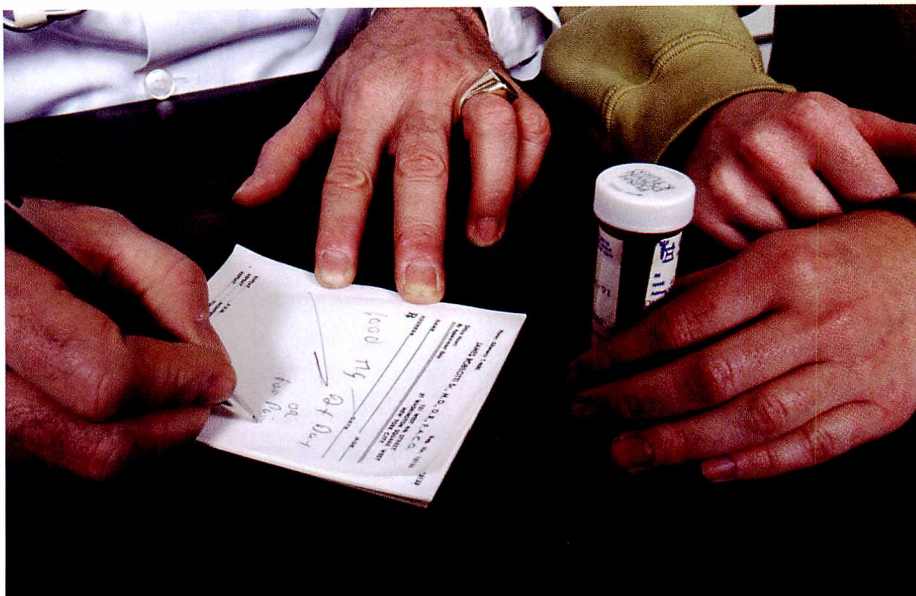
ISMP reports medication errors through various newsletters that target health professionals in acute care, nursing, and community/ambulatory care. Recently, ISMP launched a

reporting database, MedMARX. Of 105,603 errors, 3,361 errors (3.2 percent) involved children. Most of the errors were corrected before causing harm, but 190 caused patient injury and of those, two resulted in death. As a result of this analysis, USP released

recommendations for preventing drug errors in children in January 2003.

What Consumers Can Do

In one case reported to ISMP, a doctor called in a prescription for the antibiotic Noroxin (norfloxacin) for a patient with a bladder infection. But the pharmacist thought the order was for Neurontin (gabapentin), a medication used to treat seizures. The good news is that the patient read the medication leaflet stapled to his medication bag, noticed the drug he received is used to treat seizures, and then asked about it. ISMP president Michael Cohen, R.Ph., Sc.D., says, "You should expect to count on the health system to keep you safe, but there are also steps you can take to



PhotoDisc

Michael Cohen, R.Ph., president of the Institute for Safe Medication Practices, advises finding out the name of the drug you are being prescribed and asking your doctor to write the purpose of the prescription on the order.

Patient Safety Proposals

In March 2003, Health and Human Services Secretary Tommy G. Thompson announced two proposed rules from the FDA that will use state-of-the-art technology to improve patient safety. Here is a snapshot of each rule:

- **Bar codes:** Just as the technology is used in retail and other industries, required bar codes would contain unique identifying information about drugs. When used with bar code scanners and computerized patient information systems, bar code technology can prevent many medication errors, including administering the wrong drug or dose, or administering a drug to a patient with a known allergy.

- **Safety Reporting:** The proposed revamping of safety reporting requirements aims to enhance the FDA's ability to monitor and improve the safe use of drugs and biologics. The rule would improve the quality and consistency of safety reports, require the submission of all suspected serious reactions for blood and blood products, and require reports on important potential medication errors. ■

look out for yourself and your family."

- **Know what kind of errors occur.** The FDA evaluated reports of fatal medication errors that it received from 1993 to 1998 and found that the most common types of errors involved administering an improper dose (41 percent), giving the wrong drug (16 percent), and using the wrong route of administration (16 percent). The most common causes of the medication errors were performance and knowledge deficits (44 percent) and

prescription and send you on your way, be sure to ask the name of the drug. Cohen says, "I would also ask the doctor to put the purpose of the prescription on the order." This serves as a check in case there is some confusion about the drug name. If you're in the hospital, ask (or have a friend or family member ask) what drugs you are being given and why.

- **Find out how to take the drug and make sure you understand the**

There are steps you can take to look out for yourself and your family.

communication errors (16 percent). Almost half of the fatal medication errors occurred in people over 60. Older people are especially at risk for errors because they often take multiple medications. Children are also a vulnerable population because drugs are often dosed based on their weight, and accurate calculations are critical.

- **Find out what drug you're taking and what it's for.** Rather than simply letting the doctor write you a

directions. If you are told to take a medicine three times a day, does that mean eight hours apart exactly or at mealtimes? Should the medicine be stored at room temperature or in the refrigerator? Are there any medications, beverages, or foods you should avoid? Also, ask about what medication side effects you might expect and what you should do about them. And read the bottle's label every time you take a drug to avoid mistakes. In the middle of the night, you could mistake ear drops for

If you see different doctors, it's important that they all know what you are taking.

eye drops, or accidentally give your older child's medication to the baby if you're not careful. Use the measuring device that comes with the medicine, not spoons from the kitchen drawer. If you take multiple medications and have trouble keeping them straight, ask your doctor or pharmacist about compliance aids, such as containers with sections for daily doses. Family members can help by reminding you to take your medicine.

- **Keep a list of all medications, including OTC drugs, as well as dietary supplements, medicinal herbs, and other substances you take for health reasons, and report it to your health care providers.** The often-forgotten things that you should tell your doctor about include vitamins, laxatives, sleeping aids, and birth control pills. One National Institutes of Health study showed a significant drug interaction between the herbal product St. John's wort and indinavir, a protease inhibitor used to treat HIV infection. Some antibiotics can lower the effectiveness of birth control pills. If you see different doctors, it's important that they all know what you are taking. If possible, get all your prescriptions filled at the same pharmacy so that all of your records are in one place. Also, make sure your doctors and pharmacy know about your medication allergies or other unpleasant drug reactions you may have experienced.

- **If in doubt, ask, ask, ask.** Be on the lookout for clues of a problem, such as if your pills look different than normal or if you notice a different drug name or different directions than what you thought. Robert Krawisz of the National Patient Safety Foundation says it's best to be cautious and ask questions if you're unsure about anything. "If you forget, don't hesitate to call your doctor or pharmacist when you get home," he says. "It can't hurt to ask." ■

Hospital Strategies

Hospitals and other health care organizations work to reduce medication errors by using technology, improving processes, zeroing in on errors that cause harm, and building a culture of safety. Here are a couple of examples.

Pharmacy intervention: It was a challenge for health care providers, especially surgeons, at Fairview Southdale Hospital in Edina, Minn., to ensure that patients continued taking their regularly prescribed medicines when they entered the hospital, says Steven Meisel, Pharm.D., director of medication safety at Fairview Health Services. "Surgeons are not typically the original prescribers," he says. The solution was to have pharmacy technicians record complete medication histories on a form. In a pilot program, the technicians called most patients on the phone a couple of days before surgery. A pharmacist reviewed the information and then the surgeon decided which medications should be continued. After three months, the number of order errors per patient dropped by 84 percent, and the pilot program became permanent.

Computerized Physician Order Entry (CPOE): Studies have shown that CPOE is effective in reducing medication errors. It involves entering medication orders directly into a computer system rather than on paper or verbally. The Institute for Safe Medication Practices conducted a survey of 1,500 hospitals in 2001 and found that about 3 percent of hospitals were using CPOE, and the number is rising. Eugene Wiener, M.D., medical director at the Children's Hospital of Pittsburgh, says, "There is no misinterpretation of handwriting, decimal points, or abbreviations. This puts everything in a digital world."

The Pittsburgh hospital unveiled its CPOE system in October 2002. Developed by the hospital and the Cerner Corporation in Kansas City, Mo., Children'sNet has replaced most paper forms and prescription pads. Wiener says that, unlike with adults, most drug orders for children are generally based on weight. "The computer won't let you put an order in if the child's weight isn't in the system," he says, "and if the weight changes, the computer notices." The system also provides all kinds of information about potential drug complications that the doctor might not have thought about. "Doctors always have a choice in dealing with the alerts," Wiener says. "They can choose to move past an alert, but the alert makes them stop and think based on the specific patient indications." ■

—M.M.

For More Information

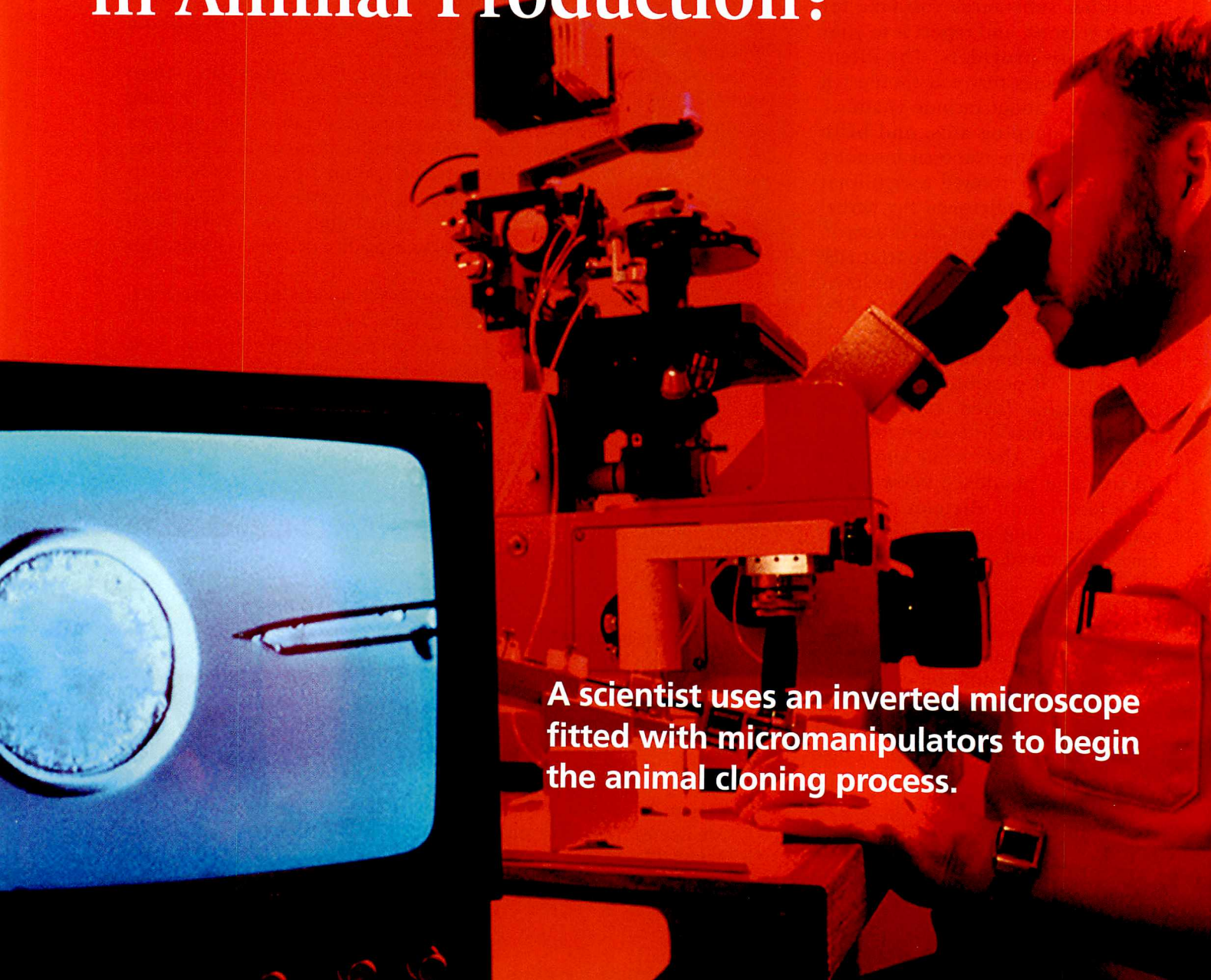
Agency for Healthcare Research and Quality
Brochures: "20 Tips to Help Prevent Medical Errors" and "20 Tips to Help Prevent Medical Errors in Children"
1-800-358-9295

Food and Drug Administration
"Think it Through: A Guide to Managing the Benefits and Risks of Medicines" (www.fda.gov/cder/consumerinfo/think.htm)
1-888-878-3256

Cloning:

Cloning:

Revolution or Evolution in Animal Production?



A scientist uses an inverted microscope fitted with micromanipulators to begin the animal cloning process.

Full Flush is a celebrity. No one asks for his autograph, but they do ask for his progeny. Named for a winning poker hand, the aging grand champion bull can't meet the demand of all the cattle ranchers who want more like him. But the bull's clones may keep his legacy alive.

Full Flush's five clones "were as normal and healthy as any calves I've ever raised," says rancher and veterinarian Donald Coover of Galesburg, Kan., who bottle-fed the young calves and raised them for the first six months of their lives. The calves, born in 2001, will soon be ready to propagate herds of high-quality beef cattle.

To the uninitiated, animal cloning may conjure up visions of strange, robot-like creatures, but real clones are far from this science-fiction fallacy. "This is just an assisted reproductive technology," says Mark Westhusin, Ph.D., director of the Reproductive Sciences Laboratory at Texas A&M University's College of Veterinary Medicine. "We're not trying to resurrect animals or get animals back."

"Clones are biological copies of normal animals," says Larisa Rudenko, Ph.D., a molecular biologist and risk assessor in the Food and Drug Administration's Center for Veterinary Medicine (CVM). "In theory, they're pretty close to identical twins of an adult animal."

Although the technology to clone farm animals was developed more than 20 years ago, today's method of cloning, somatic cell nuclear transfer (SCNT), has been around only since 1996. Coover estimates that only a couple hundred of the 100 million cattle in the United States are SCNT clones. And you won't find meat or milk from SCNT cloned animals in your supermarket yet—the FDA has asked companies that clone animals not to introduce any of them, their offspring, or their food products into human or animal food until the agency has evaluated the safety of these products. The companies are cooperating, says Stephen Sundlof,

D.V.M., Ph.D., director of the FDA's CVM. "And we're being very diligent to make sure if this new technology makes it to the marketplace, that it's safe for people to eat."

potential sources for food and clothing, if the FDA gives the OK.

Mandated with protecting the nation's food supply and animal health, the FDA is working to set a

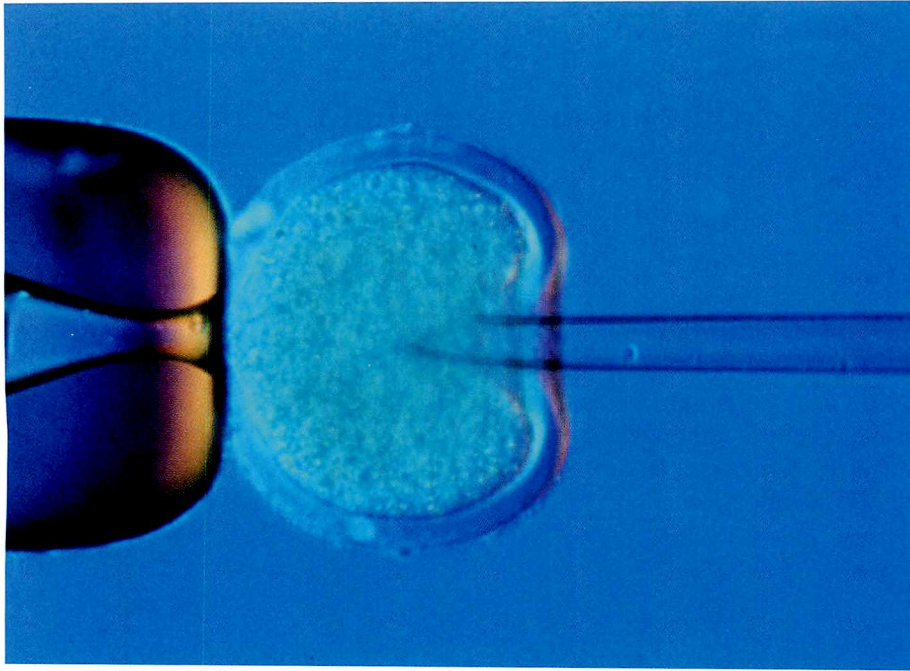


Christy Collins/Collins Cattle Services

Full Flush, a grand champion bull, was cloned to help meet the high demand for his offspring.

It's unlikely that you will eat a cloned animal anytime soon. At a cost of about \$20,000 each to produce, clones are used for breeding—not for food. But some scientists and farmers are looking at the descendants of cloned cattle, pigs, goats and sheep as

policy on cloned animals, based on the best available science. "We do not want these products on the market until there has been a thoughtful, thorough and deliberate evaluation of the issues," says Sundlof. "We want to make sure that the public is clearly informed and



Roslin Institute

Glass pipette holding an egg, with a sharpened pipette ready to remove the DNA.

that they have had a chance to participate in the process."

The Cloning Process

Early methods of cloning in the 1970s involved a technology called embryo splitting, or blastomere separation. Embryos were split into several cells and then implanted into a

surrogate mother for growth and development. But there were a limited number of splits that could be made, and only a few clones could be produced from one egg. The characteristics of the clone were also unpredictable because scientists were cloning from an embryo whose traits could not be predicted.

Even a cat. Unlike the embryo splitting method, in theory, SCNT can be used to make an unlimited number of copies of one animal. The SCNT process starts with an unfertilized egg, or oocyte. Scientists remove the oocyte's nucleus, which contains the egg's genes, or hereditary "instructions." What remains after

removal of the nucleus is a cell that contains nutrients essential for embryo development and other cellular machinery waiting for a new set of instructions.

A somatic cell from the animal to be cloned—or in some cases, just the cell's nucleus—is cultured in an incubator and then injected under the coating of the unfertilized oocyte. (Somatic cells are any cells of the body except sperm and eggs.) Stimulated by a mild electrical pulse, the oocyte cytoplasm (everything in the cell but the nucleus) and the genetic material from the donated somatic cell combine. If fusion is successful, the resulting fused cell divides just as if it were a fertilized egg and produces an embryo. The embryo is placed in the uterus of a surrogate mother and, if development proceeds normally, an animal clone is born. But there's a tricky part to this process, says Rudenko. The nucleus of the adult cell is specialized, or differentiated, for a particular function. "The nucleus has matured to a point where its instructions are 'locked away' in a configuration specific to the job that the cell is intended to perform," says Rudenko. "For example, a muscle cell has a different job from a liver cell, and it has a different set of instructions available to it. The complicated part of cloning that we don't fully understand is how those instructions get reset."

The unlocking and resetting of instructions without making changes to the genetic code is called epigenetic reprogramming. This process allows the cell to develop into a new organism instead of continuing to do its old specified cellular functions. And it's the epigenetic reprogramming that scientists haven't yet mastered and that accounts for frequent cloning failures.

Steven Stice, Ph.D., explains epigenetics as the propensity for different outcomes from identical DNA sequences. An example of an epigenetic effect in normal human birth is the different fingerprint patterns of identical twins, says Stice, a professor in the Animal and Dairy Science Department at the University of Georgia and chief scientific officer for ProLinia Inc., a livestock cloning company in Athens, Ga. Epigenetic changes are not unique to cloning but are more noticeable in clones, Stice adds. "Everything from in vitro fertilization to artificial insemination can have epigenetic effects."

Proponents of livestock cloning see it benefiting consumers, producers, animals and the environment.

Why Clone?

Proponents of livestock cloning see it benefiting consumers, producers, animals and the environment.

"The consumer is looking for a nutritious and wholesome product provided to them in a repeatable and reliable manner and produced in a humane and ethical way," says Coover, who also owns and manages SEK Genetics Inc., a beef cattle semen

distribution company. "If a consumer spends \$30 on a steak dinner at a restaurant, they expect a great steak, but don't always get it."

For farmers whose livelihoods depend on selling high-quality meat and dairy products, cloning can offer a tremendous advantage, says Coover. It gives them the ability to preserve and extend proven, superior genetics. They can select and propagate the best animals—beef cattle that are fast-growing, have lean but tender meat, and are disease-resistant; dairy cows and goats that give lots of milk; and sheep that produce high-quality wool. Through cloning, it would be possible to predict the characteristics of each animal, rather than taking the chance that sexual reproduction and its gene reshuffling provide.

Coover compares the process of identifying a superior animal to spinning a giant roulette wheel.

"Sometimes you win, sometimes you lose, and sometimes you hit the jackpot." But a producer cannot tell if he's hit the jackpot with a young animal. "It's like trying to identify the school kid in the second grade who is going to grow up to solve the riddle of cancer," says Coover. "A rancher may think he has a good bull, but that bull has to sire calves, the calves have to mature and produce calves of their own, and this has to occur for several generations to know that it's not a fluke. By that time, the bull is dead and gone, and its genetics are lost to the industry." Through SCNT cloning, even deceased animals can be cloned if a tissue sample is preserved in life or within a short time after death.

Cloning has the potential to improve the welfare of farm animals by eliminating pain and suffering from disease. "From time to time, in nature, you find a naturally disease-resistant

animal," says Rudenko. "You can expand that genome through cloning, and then breed that resistance into the overall population and help eliminate major diseases in livestock."

Cloning can reduce the number of unwanted animals, such as veal calves, says Ray Page, chief scientific officer and biomedical engineer at Cyagra, a livestock cloning company. Veal calves are commonly surplus male offspring from dairy cows. Since the males don't produce milk, they are not as useful to the dairy industry and are turned into veal calves. Cloning can ensure the creation of more female offspring for dairy production.

An environmental benefit could result from cloning grass-fed instead of grain-fed animals. Grain-fed animals are known to be better tasting and more tender, but once in a while, a high-quality grass-fed animal comes along. "If we can move our cattle-raising from



Christy Collins/Collins Cattle Services

These five calf clones are biological "copies" of the champion bull, Full Flush.

a grain economy to a grass-fed economy, we can make food more efficiently and there are benefits to us as a society," says John Matheson, a toxicologist and environmentalist who serves as a senior regulatory review scientist for biotechnology in CVM. Grass is a soil-building crop. In addition to reducing erosion, grass does not need the quantities of fertilizers and pesticides required by grain. And because forage is cheaper than grain, production savings can be passed on to consumers.

curve to be gained in cloning cows."

Matheson explains that the FDA's role is to look at the safety aspects of cloning based on the best available science. The FDA needs to answer an important question to help it develop its regulatory approach to animal cloning, he says. "Is this risky new technology that endangers animals and our food supply, or is this just another small step in the evolution of food production technology?" To answer this question, the FDA is gathering more data.

The FDA commissioned the National

a steak, they're each a little bit different from one another in chemical composition," adds Matheson.

The NAS report cited environmental concerns regarding genetically engineered fish and other animals that could escape into the environment, reproduce, or compete successfully for food and mates with wild animals. But this concern does not extend to cloned domesticated animals, since cattle and other livestock generally do not run wild and have no wild counterparts in the United States with which to

There's always been a fear of new technology.

"Cloning can help spread the best genetics over larger populations of animals," says Stice. When farm animals are cloned, genetic diversity may be reduced, but cloning can also be a tool to preserve rare genetics in livestock and, potentially, wild animals. Stice encourages zoos and wildlife refuges to preserve the tissue of endangered species in the hopes that technology in the theoretical stage today can be developed to regenerate these species in the future.

Cloning Concerns and the FDA's Role

While cloning proponents see enormous capabilities for the technology, cloning critics have concerns on a number of levels. Social, ethical and religious convictions all weigh in to make people wary of cloning. Some find it hard to separate animal cloning from human cloning. But cloning scientists view animal cloning on a continuum of reproductive technology. Improving breeding practices in the hopes that offspring will be improved has been going on for thousands of years. Arab chieftains were using artificial insemination in horse breeding as early as the 14th century, according to historians.

"There's always been a fear of new technology," says Matheson, who notes that cloning animals is not a precursor to cloning humans. "We already know more about reproduction in humans than in any other species, so there's no learning

Academy of Sciences (NAS) to identify and prioritize any safety concerns that bioengineered and cloned animals might present to food, animals and the environment.

After consulting with pioneers in the field of cloning and holding a public workshop, the NAS published its report, *Animal Biotechnology: Science-Based Concerns*, in August 2002. According to the report, "There is no current evidence that food products derived from adult somatic cell clones or their progeny present a food safety concern." The report recommends collecting additional information about food composition to confirm that these food products are, in fact, safe. Food should be analyzed for such essential ingredients as amino acids, vitamins and minerals and to make sure cloned animal products don't differ from those of normal animals in ways that might affect human health.

But this analysis is not as easy as you might think, says Matheson. "We don't know what the composition of 'normal milk' is. It may all taste the same from the market, but it can vary a lot in each individual animal depending on its age, what it eats, and the time of lactation. Qualitatively, most of the same ingredients are always present, but quantitatively, their actual concentration varies from animal to animal." This may be true for meat as well since each animal is different just like each human is different. "Even though we think of a pork chop as a pork chop and a steak as

interbreed.

Cloning may someday reduce the number of animals needed for food and fiber production, according to the report, but could also have adverse effects on animal welfare. Calves and lambs produced through cloning tend to have higher birth weights and longer gestation periods, which may lead to difficult births. Repeated exposure of individual animals to invasive procedures to harvest oocytes for SCNT is likely to cause pain and distress. In addition, the survival rate of cloned fetuses is low, and some survivors have health problems such as heart and lung disease.

Speculation surrounds the death of Dolly the sheep. Dolly had been diagnosed with arthritis in her hind limbs when she was about 4 years old. In February 2003, she was euthanized at the age of 8 because of a degenerative lung condition most probably caused by a virus. Critics blame cloning for Dolly's lung disease and her arthritis. But others attribute her health problems to being overweight and to becoming infected with a virus present in the barn in which she was kept.

Low rates of success are inherent in any new technology, says Page. "But the people doing this are becoming better technicians. We're making improvements in the way we handle cells and embryos. Efficiency rates continue to improve year after year, and more of the embryos are surviving

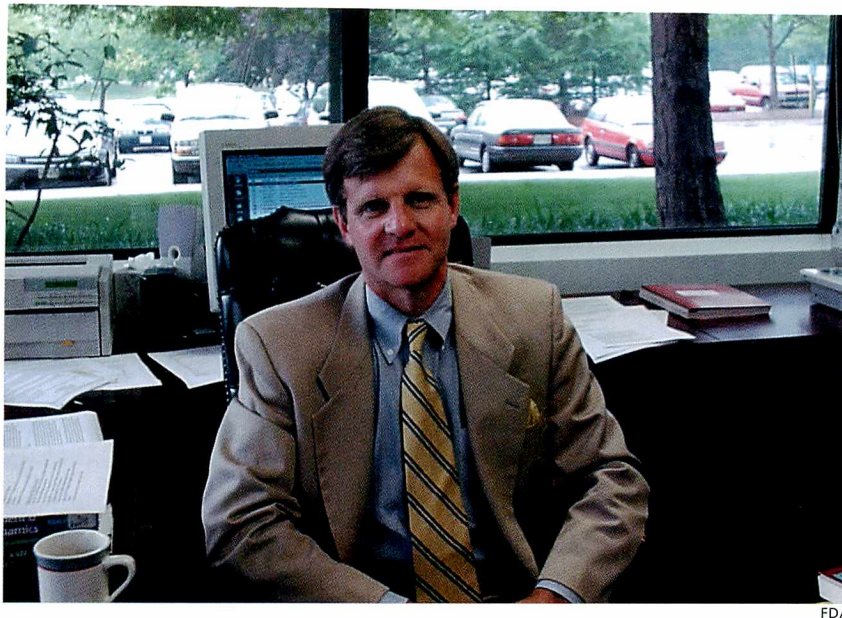
to term and more of the calves are healthy."

The Humane Society of the United States (HSUS) has asked the FDA to ban sales of products from cloned farm animals and their offspring because of "serious concerns about the health and welfare of cloned animals."

"We condemn cloning as yet another move away from regarding animals as animals, and yet another development that will favor large corporations over small ones," says Michael Appleby, Ph.D., HSUS vice president for farm animals and sustainable agriculture. The HSUS commends the FDA for commissioning the NAS report and requesting that food from cloned animals not enter the marketplace.

"These measures show an appropriate, precautionary approach," says Appleby, "and we trust the FDA will further this by putting more weight on the animal safety issues outlined in the report."

The NAS's job was to identify the potential risks of cloning; now the FDA is studying those risks to determine how to manage them. The FDA is developing two risk assessments: one describing the potential risks, if any, of consuming food products from animal clones and their offspring, and the other describing health risks to animal clones and their offspring. The FDA will use these assessments to develop an appropriate science-based regulatory approach, in the form of policy or guidance for industry, to manage any food and animal health risks. The public will have the opportunity to comment on this guidance, planned for release by the end of 2003.



The FDA's role is to look at the safety of animal cloning based on the best available science, says Stephen Sundlof, D.V.M., Ph.D., director of the agency's Center for Veterinary Medicine.

In its commitment to a transparent process, CVM gathered together food producers and food consumers to share their perspectives on bioengineered and cloned animals at a three-day public workshop. Held in Dallas in September 2002, the workshop was co-sponsored by the Pew Initiative on Food and Biotechnology, an independent source of information on agricultural biotechnology.

CVM will continue to inform the public as it moves toward a decision on the type of regulatory structure that will be needed for cloned animals. "The public will be well informed and nothing is going to happen that they won't know about," says Sundlof. ■

For More Information

The FDA Center for Veterinary Medicine's Web site on biotechnology in animals and feeds
www.fda.gov/cvm/biotechnology/bioengineered.html

The National Academy of Sciences' 2002 report, *Animal Biotechnology: Science Based Concerns*
www.nap.edu/catalog/10418.html

Presentations from the September 2002 FDA and Pew Initiative on Food and Biotechnology workshop, "Animal Cloning and the Production of Food Products: Perspectives from the Food Chain"
<http://pewagbiotech.org/events/0924/>

Cloning versus Transgenics

Cloned animals and transgenic animals are sometimes mistaken to be the same, but they are different, says Larisa Rudenko, Ph.D., a molecular biologist in the Food and Drug Administration's Center for Veterinary Medicine (CVM).

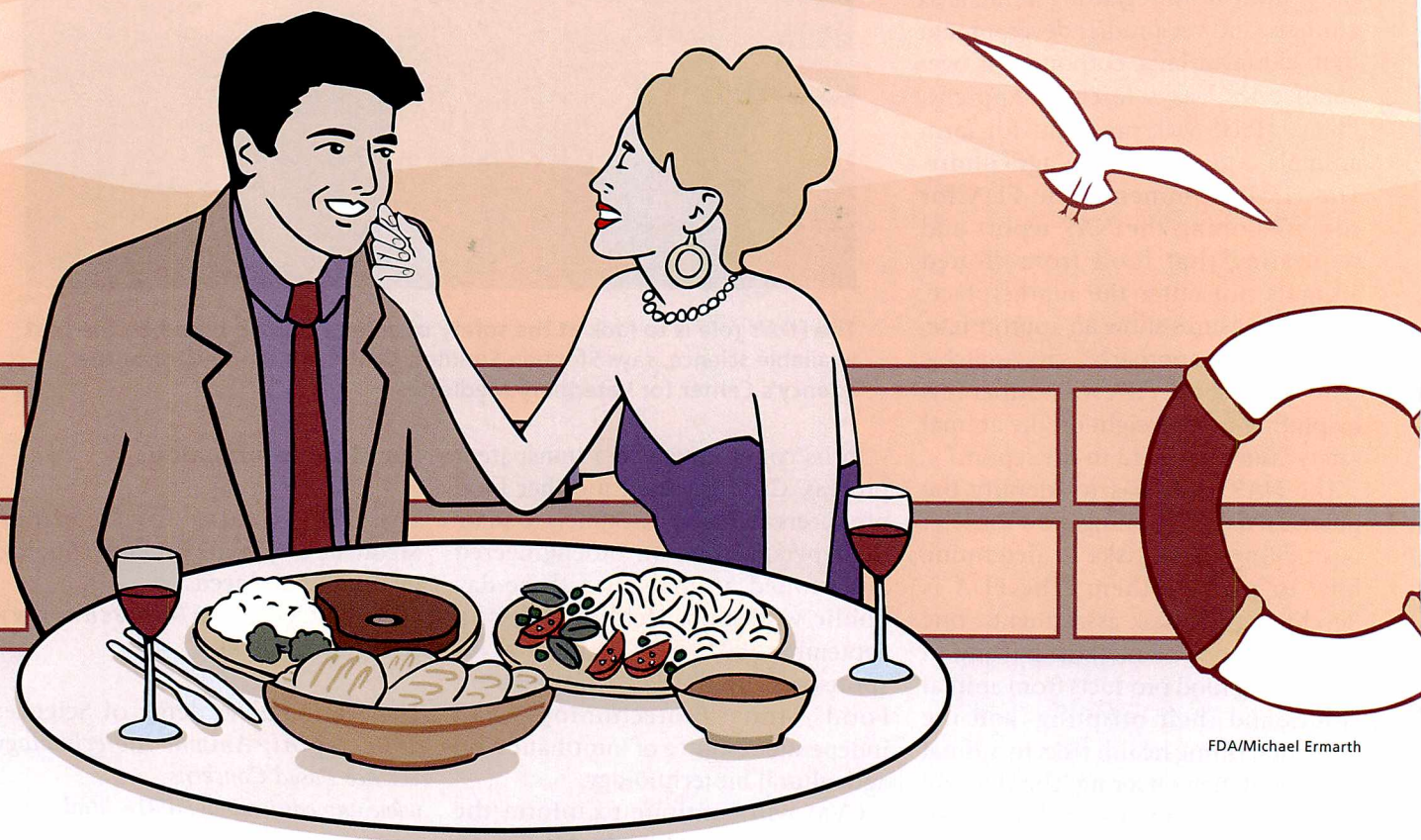
Transgenic animals or plants are produced by adding or removing genes, or by altering the expression of their existing genes. This process can involve genetic information taken from different species or created in DNA synthesizing machines. When a gene for insulin, for example, is inserted into a goat, the animal could produce insulin in its milk, which would then be purified

into an injectable form to treat human diabetes. And genes for growth hormone from one fish species transferred into the genome of salmon can cause them to grow rapidly. (See "A New Kind of Fish Story: The Coming of Biotech Animals," January–February 2001 *FDA Consumer*.)

Cloned animals are produced using bioengineering techniques but are intended to be biological copies of existing animals.

CVM is developing guidance for cloning food production animals. Future guidance for developing transgenic food animals will build on the cloning guidance and further study. ■

Cruising with Confidence



FDA/Michael Ermarth

By Linda Bren

Shaking hands may be the conventional greeting for landlubbers, but on the high seas, the “forearm tap” has become popular. This greeting of knocking elbows together instead of shaking hands was encouraged by a number of cruise lines to raise awareness of the importance of personal hygiene on board ship, according to a representative for Carnival Cruise Lines.

Poor personal hygiene is the likely cause of gastrointestinal illness (gastroenteritis) on cruise ships, according to the Centers for Disease Control and Prevention (CDC). The CDC investigated 22 reports of gastroenteritis outbreaks aboard 18

cruise ships from Jan. 1, 2002, through Dec. 31, 2002. Of the 22 outbreaks, three were blamed on bacteria and seven could not be traced with certainty, but the remaining 12 were confirmed to be associated with noroviruses—a group of viruses that cause gastroenteritis, also known as Norwalk-like viruses.

Symptoms of norovirus infection include nausea, vomiting, diarrhea and stomach cramping that can last from 12 to 60 hours. The symptoms usually begin 24 to 48 hours after a virus is ingested. Although people may feel very ill and vomit frequently, norovirus infections are not considered serious in most individuals. But they may become

serious in the very young, older people, and in those with weakened immune systems.

Noroviruses are found in the stool or vomit of infected people, and infection can spread in several ways:

- Eating food or drinking liquids that are contaminated with the virus
- Touching contaminated surfaces or objects and then placing your hands in or near your mouth
- Having direct contact with another person who is infected and showing symptoms (for example, sharing foods or eating utensils).

Viruses aren’t the vacationer’s only cause of gastrointestinal illness. “Travelers can also get diarrhea from

bacterial infections," says Renata Albrecht, M.D., the director of the Food and Drug Administration's Division of Special Pathogen and Immunologic Drug Products. Bacterial infections usually go away over time without treatment, but doctors may prescribe antibiotics to treat some and shorten the duration of the diarrhea, says Albrecht. No medications are approved for preventing bacterial infection, nor are there medications that prevent or treat noroviruses.

Advice for Travelers

Frequent and thorough hand washing with warm, soapy water is the best prevention against gastroenteritis, says LeeAnne Jackson, Ph.D., a health science policy adviser in the FDA's Center for Food Safety and Applied Nutrition. Travelers who don't have ready access to soap and water may want to carry along a hand gel sanitizer, found in most supermarkets and drugstores.

Jackson also advises travelers to choose foods and beverages carefully. Foods should be thoroughly cooked and served hot. Poor sanitation in some countries may lead to contaminated food and drink, which are the major sources of stomach or intestinal illness while traveling, according to the CDC. Just about any food can become contaminated if handled improperly, but items of particular concern include raw meat, raw seafood, green salads, and raw sprouts. "In some countries, it's wise to steer clear of street food vendors, especially if they serve fresh-cut fruits," says Jackson, who advocates purchasing fruits whole, peeling them and cutting them up yourself.

Travelers should avoid unpasteurized milk or products made with unpasteurized milk, unpasteurized juices and ciders, says Jackson. Beverages that may be safer than tap water in some countries are hot beverages, such as coffee or tea made with boiled water, canned or bottled carbonated beverages, and beer and wine. Avoid ice made with tap water. Water on the surface of a beverage can or bottle may be contaminated, so wipe clean and dry the area of the container that will touch your mouth.

The Cruise Ship Connection

CDC investigators believe that most of the recent norovirus infections on cruise ships were spread person-to-person through hand-to-mouth activity. "We suspect that people are probably coming on board with the virus," says Dave Forney, chief of the CDC's Vessel Sanitation Program. "On a cruise ship, people are out and about in very public areas, and so we have this depositing of the virus on various surfaces that then would be easily picked up by others."

Forney advises cruisers who are ill to avoid contact with other individuals and to report to the ship's medical facility. Unfortunately, many of them don't want to be told to stay in their cabins, adds Forney, so passengers spreading the virus around the ship are contributing to the ongoing problem.

Outbreaks on cruise ships have gained media attention, but an estimated 60 percent to 80 percent of all outbreaks of severe gastroenteritis occur on land, says the CDC. Norovirus infection is the most common cause of non-bacterial gastrointestinal illness in the United States; about 23 million cases of severe gastroenteritis a year are due to noroviruses. Noroviruses may be found in areas where people congregate together for days at a time, such as in schools, hotels, camps, nursing homes, and hospitals. Gastroenteritis is not a reportable illness in the United States except on cruise ships, so the public may be more aware of the shipboard incidences, says Forney.

By law, cruise ships that enter a U.S. port from a foreign port are required to report to the CDC, 24 hours prior to arrival, the number of passengers and crew on board who go to the ship's medical facility with gastrointestinal illness, even if the number is zero, says Forney. Having 3 percent or more of either passengers or crew reported with a gastrointestinal illness is considered an outbreak and cause for investigation.

Travelers shouldn't shun cruises, says Forney. "It is perfectly safe to go on cruise ships. The standard by which they are held for sanitation is the highest in the world." Extensive cleaning and disinfecting were carried

out on ships immediately following reports of illness, Forney adds. And cruise lines continue to scrub and sanitize public areas of their ships, especially frequently touched surfaces such as handrails, elevator buttons, and even poker chips. ■

For More Information

The Food and Drug Administration's Web site on foodborne illness
www.cfsan.fda.gov/~mow/foodborn.html

The Centers for Disease Control and Prevention's (CDC) Web site on Travelers' Health
www.cdc.gov/travel/

The CDC's Vessel Sanitation Program Web site, including sanitation inspection scores for cruise ships
www.cdc.gov/nceh/vsp/

The Importance of Hand Washing

Health care specialists generally cite hand washing as the single most effective way to prevent the spread of disease, according to the Centers for Disease Control and Prevention. If you do not wash your hands frequently, you can pick up germs and then infect yourself when you touch your eyes, nose, or mouth. Wash your hands before eating, after using the bathroom, and after changing diapers or playing with a pet.

For best results, use warm water to moisten your hands and then apply soap. Rub your hands together vigorously for at least 20 seconds. It is the soap combined with the scrubbing action that helps loosen and remove the germs on your hands. ■

—L.B.



FDA Issues Guidance on Race and Ethnicity Data

By Michelle Meadows

The Food and Drug Administration already requires drug companies to submit race and ethnicity data in drug applications when appropriate. But for the first time, the agency is recommending specific methods for collecting and characterizing racial and ethnic information about clinical trial participants.

In January 2003, the FDA published a draft guidance that recommends collecting racial and ethnic data with methods and categories designated by the federal Office of Management and Budget's (OMB) Directive 15, which was published in 1997. In this directive, OMB told all federal agencies to report statistics using these guidelines starting in January.

The recommended race and ethnicity categories include American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Hispanic or Latino. The FDA's draft guidance recommends that drug companies use the OMB categories when collecting data from study participants within the United States. For studies conducted either inside or outside the United States, more detailed race and ethnic identities may be used, provided that they can be traced back to the major classifications. For example, an Asian person may report having origins in Japan.

Based on the OMB's directive, the FDA recommends that people who participate in clinical trials self-report their racial and ethnic group whenever possible, and that people be permitted to designate a multiracial identity. When self-reporting is not possible, the information should be obtained from an immediate relative or other knowledgeable source.

In a 1998 regulation known as the Demographic Rule, the FDA addressed

the importance of collecting data on clinical trial volunteers by gender, race, and age. "The FDA suggested using the OMB categories in the preamble to the Demographic Rule, and the new guidance recognizes these categories as reflecting the FDA's current thinking on how to characterize the data," says Katherine Hollinger, a senior health promotions officer for the FDA's Office of Women's Health.

Using standard categories will make it easy to compare FDA data with health statistics collected by other federal agencies. "Another goal of the guidance," Hollinger says, "is to enhance consistency in sub-population characterization. This improves our ability to assess potential differences in the ways various racial and ethnic groups respond to drugs."

Some studies have shown racial differences in drug response. In the United States, whites are more likely than people of African or Asian heritage to have abnormally low levels of an enzyme that metabolizes drugs belonging to a variety of therapeutic areas, such as antidepressants, antipsychotics, and beta blockers. Other studies have shown that blacks respond less to several classes of antihypertensive agents, including beta blockers and angiotensin converting enzyme (ACE) inhibitors. Additionally, slower metabolism of some drugs in the psychotherapeutic class has been seen in people of Asian descent compared to whites and blacks. The differences are complex and may be due to genetic factors, diet, environmental exposure, sociocultural issues, or a combination of these factors.

Clyde Yancy, M.D., medical director of heart failure and transplantation at the University of Texas Southwestern

Medical Center at Dallas, says when you look at heart disease, which disproportionately affects racial and ethnic minorities, you then have to ask: Are we confident that the treatment strategies we're using are effective?

"The fact that traditional therapies may have been less effective among blacks than whites points to a possible need for unique heart failure management strategies," Yancy says. Yancy and other investigators began a clinical trial in 2001, which was the first heart failure trial exclusively for black patients. Results are expected in the next two years.

In another study published in the May 3, 2001, issue of *The New England Journal of Medicine*, Yancy found that the beta-blocking drug Coreg (carvedilol) was as effective in blacks as non-blacks. "It's reassuring and pertinent for medicine to be able to say that this regimen works in African American patients," he says.

Despite reported differences in drug response, beta blockers and ACE inhibitors are still the most appropriate therapy to treat heart failure in blacks for now, according to Yancy. "What we don't want is for doctors to make treatment decisions just by looking at people when they walk in the door," he says. "Blacks represent a heterogeneous group, and given the substantial benefit of beta blockers and ACE inhibitors, it would be a disservice to limit treatment in this population."

The FDA's draft guidance on the collection of race and ethnicity data in clinical trials is at www.fda.gov/cder/guidance/5054dft.pdf. ■

By John Henkel

A Closer Look at Invisible Hazards

At first glance, the image could be depicting a scene from Anytown, U.S.A. There are stores, homes, a school, cars, and a factory, all buzzing with apparently harmonious activity. There's even a farm out on the horizon. But this town, Tox Town, has a message: There are hidden toxic substances almost everywhere you go.

Actually, Tox Town is not a real town. It's an interactive Web site created by the National Library of Medicine to show the relationship between chemicals, the environment, and the public health. For example, click on a car or school bus in the town scene and you'll get a list of helpful links that include pages devoted to understanding vehicle emissions, car chemicals, and motor vehicle safety. Another click on the town's schoolhouse explains potential dangers that may lurk within, including lead, asbestos, carbon monoxide, and radon.

Right now, Tox Town is a pilot project, so it includes a limited number of locations and chemicals. Still, it offers a good overview of many everyday potential hazards and something to think about next time you stroll into town. You'll need a free downloadable plug-in to view the site's graphics.

Ready to visit Tox Town? Go to www.toxtown.nlm.nih.gov/main.html.

FREE Information at Your Fingertips

The human genome. Photosynthesis. The Constitution. Cells. Epidemiology. Probability. The topics may seem diverse, but you can learn more about them all in one spot: a Web site called *FREE*, or *Federal Resources for Educational Excellence*.

Managed by the Department of Education, *FREE* brings together teaching and learning materials from 50 federal organizations. Teachers will want to check out the Gateway to Educational Materials, a useful database of more than 17,000 education resources across more than 100 Web sites. Elsewhere, students will find fun learning sites, such as the Agriculture Department's *Science 4 Kids* and the U.S. Mint's *H.I.P. Pocket Change*.

But you don't have to be taking or teaching a class to enjoy the site's huge catalog of interesting information on arts, languages, math, physical education, science, and social studies.

For a *FREE* look, go to www.ed.gov/free.

When Patients Talk, the FDA Listens

Are you a patient or family member who is knowledgeable about cancer, HIV/AIDS, or other serious diseases? You may be eligible to serve as a patient representative, acting as an adviser to the FDA as it conducts regular meetings of its many advisory committees.

As part of the myriad steps that shape how the FDA does business, the agency solicits advice from patients and others. Typically, advisory committees meet when a product or therapy—drug, biologic, or medical device—related to a serious or life-threatening disease is under review for possible approval. There are roles for voting and non-voting patient representatives, and the agency provides reimbursement for expenses related to serving on an advisory committee.

To learn more, go to www.fda.gov/oashi/patrep/patientrep.html and "Bringing Real Life to the Table: Patient Reps Help FDA Review Products," January–February 2002 *FDA Consumer* (www.fda.gov/fdac/features/2002/102_real.html).

A Great Way to 'Access' Government Publications

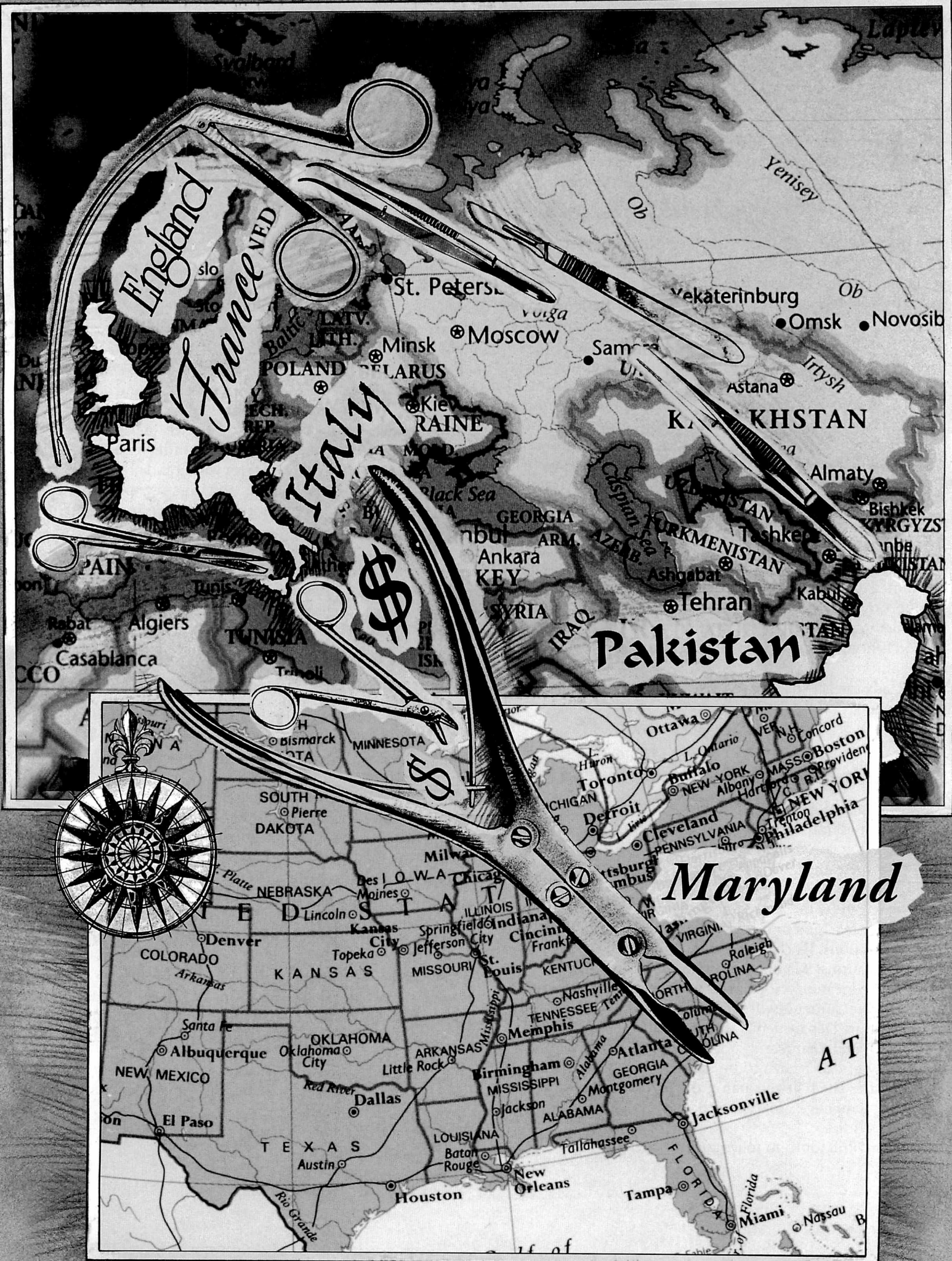
Need to find the text of a bill that's before Congress? Perhaps you need to locate a *Federal Register* item. The U.S. budget? The *Commerce Business Daily*? A listing of Supreme Court decisions?

Time was, you had to hunt these documents down in a library or other source of hard copies. But now, you can find them all on a handy Web site called *GPO Access*, operated by the U.S. Government Printing Office.

The site, at www.gpo.gov/gpoaccess, links to many major publications from all three branches of government, as well as other materials such as a pictorial directory of Congress and the excellent *Ben's Guide to U.S. Government for Kids*.

GPO Access provides online use of more than 2,200 databases of federal information, along with federal agency files available for download and collections of government information available through Federal Depository Libraries. ■

John Henkel is a member of the FDA's Website Management Staff.



Maryland Company Guilty of Smuggling Medical Devices

By Carol Lewis

The president of a U.S. medical supply company and his Pakistani partner each were sentenced to prison terms after pleading guilty to smuggling surgical instruments into the United States and mislabeling them with a false country of origin.

In addition, two executives of the company, Sales and Marketing Services Inc. (SMS) of Columbia, Md., were sentenced to home confinement, probation and community service for their role in the scheme to alter the label of lower-priced tools made in Pakistan so that they resembled high-priced European instruments.

The trio, SMS president Winslow Richard Smith, vice president Laura Johnson, and operations manager Gregory Johnson, all conspired with Qaiser Shabbir, president of QSA Surgical in Pakistan, to defraud the government, according to documents filed with the U.S. District Court in Baltimore. The case is the first U.S. felony criminal prosecution of a foreign surgical instrument supplier.

To bolster company profits, the four conspired to smuggle the surgical instruments into the United States from sham companies set up in England, Pakistan, France, and Italy. In the fall of 1989, Smith and Laura Johnson met with Shabbir and others in Italy to arrange the fraudulent scheme. Investigators charged that Shabbir manufactured a "general practice" line of surgical steel instruments (for non-operating use only) in Pakistan and sent them through England to "front" companies in Italy and France to avoid detection by the Food and Drug Administration and the U.S. Customs Service. The European contacts repackaged the "potpourri of medical instruments" that the FDA case agent identified as scalpels, scissors, tweezers

and a host of obstetrical and gynecological devices, and shipped them to SMS. The company then removed the "Pakistan" markings and etched "Italy" or "France" on the instruments, to fetch a higher price.

The mislabeling of the instruments resulted in customers paying a significantly higher-than-market price for the inferior instruments. According to court records, the overall loss to consumers was between \$70,000 and \$120,000. On occasion, SMS renamed entire shipments of instruments. In these cases, the company received unmarked instruments directly from QSA.

The first order of the mislabeled instruments occurred in October 1989 and was valued at more than \$10,000. At least 20 additional shipments followed between December 1991 and October 1994, investigators say. The total import value of the shipments was \$605,226, according to court documents.

During that period, most of SMS's customers were private medical facilities. However, in 1993, SMS was awarded a federal government contract by the Department of Veterans Affairs to provide surgical steel instruments to veterans' hospitals and other government health care facilities. Under the contract, the government specified that products from Pakistan were prohibited.

SMS representatives, meanwhile, continued to falsely assure government representatives that the instruments originated in Europe.

The FDA's Office of Criminal Investigations first received information from its Baltimore district office in 1995 that SMS was suspected of altering markings on Pakistani surgical instruments to indicate European manufacture. Authorities were alerted that a surgical company in San Jose,

Calif., reported buying surgical instruments from SMS with both "France" and "Pakistan" stamped on the items as the country of origin.

A search warrant issued in June 1996 revealed that no imports of surgical tools had been made from Italy since 1994. And, only two imports from France were found. A review of SMS's importation documents indicated that the majority of surgical instruments were imported by SMS from QSA in Pakistan. The U.S. Customs Service and the Veterans Affairs Office of Inspector General then joined the investigation.

The manner of payment among SMS, QSA and the front companies was by letter of credit. Once the product arrived in Maryland, each of the two front companies received payment directly to their banks. The front companies received between 20 percent and 25 percent more than the cost of the merchandise for shipping the repackaged product.

Shabbir pleaded guilty to conspiracy to defraud the United States in August 1999. He also admitted introducing a misbranded device into interstate commerce and smuggling. In February 2000, U.S. District Judge Andre M. Davis sentenced Shabbir to one year and one day in jail and two years supervised release.

Smith, Laura Johnson and Gregory Johnson pleaded guilty to all but the conspiracy to defraud the government charge. Smith received eight months in jail and two years supervised release. Laura and Gregory Johnson each were ordered to serve two years probation with home confinement and electronic monitoring. They also were fined \$10,000 and \$5,000 respectively and sentenced to community service. ■

Be a Partner in Your Health Care

By Roxanne J. Goeltz



Our health is as much our responsibility as it is our doctors'. It is time to share that responsibility and for the medical profession to encourage and help us in our efforts. We will not be perfect, nor should we expect to be, but we must begin to make our health care journey as safe as it can be.

We need to be a partner in our care, and those of us who have tried are labeled as difficult patients or aggravating family members. Do not accept this label. My friend's mother suffered brain damage because no one wanted to listen to her "overreacting" daughter. No one listened when my friend said, "I cannot wake my mother." She was told that her mother was tired and needed her rest. And in the 36 hours that my friend decided to take a break and leave the hospital, her mother sustained three falls.

This is not a failure of the nurses on duty or the doctors on call. It is a failure in a system that does not provide enough support for those working in it or being cared for by it. A system that has allowed errors to be buried and therefore repeated, instead of learning from them. A system that has not considered how valuable input from the patient and family can be in making it safer.

My brother Mike died three years ago of medical errors after being admitted to a hospital with severe stomach pains. The official cause of death was "blood around the heart," but no one can answer the question of how it got there. Mike's lack of knowledge of specific health problems in our family history and the unwillingness of the medical profession to listen to our requests contributed to his death.

I took one lesson from Mike's death and that is: You don't stay in a hospital alone. I encourage what I call 24/7 care, which is someone in the hospital with you 24 hours a day, 7 days a week. I do not encourage 24/7 to catch a doctor or nurse making an error. I encourage it to help prevent errors by being a partner in your care.

Nine months after Mike died, I had the opportunity to walk the talk.

A tumor was discovered in my chest cavity and I needed surgery to remove it. I set up a network of family and friends and asked them to be partners in my care. They worked with the health care professionals, making my stay

as comfortable and safe as possible. They knew the medications I was on and would verify the information when the nurses gave medicines to me. The nurses were happy to answer their questions because we acted as part of the team, not the family police unit checking on them.

In the hospital I suffered from a blood clot traveling through my heart and into my lungs and was put on Coumadin, a blood thinner. I was scheduled for a second surgery three months later and needed to come off the Coumadin for the surgery. In my appointment with a doctor specializing in blood thinner therapy, we discussed the process of getting me off the drug. I needed to give myself shots and I carefully noted the doctor's instructions.

I went to see a nurse just before the surgery to go over the schedule for my shots, but it was different than what I had written down from my doctor's visit. Did I misunderstand the doctor? I mean, she was the professional and I must have gotten it wrong. The "old" me would have let it go, but after my brother's death, I struggled to become a partner in my care, and this was one of those times to speak up.

She was not happy that I questioned her and began reading the doctor's notes. It was then that I realized how she could have misinterpreted his written instruction. I pointed this out and she offered to check with the doctor to make sure. She called me later and said my understanding was correct.

Remember, this is not about catching someone in an error. It is about being a partner in your care and sharing the responsibility. I wasn't telling her how to do her job, but participating in making sure the care I received was the best and safest possible. ■

Roxanne J. Goeltz is president of Consumers Advancing Patient Safety and one of the founders of the Patient and Family Advisory Council sponsored by the National Patient Safety Foundation.



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