

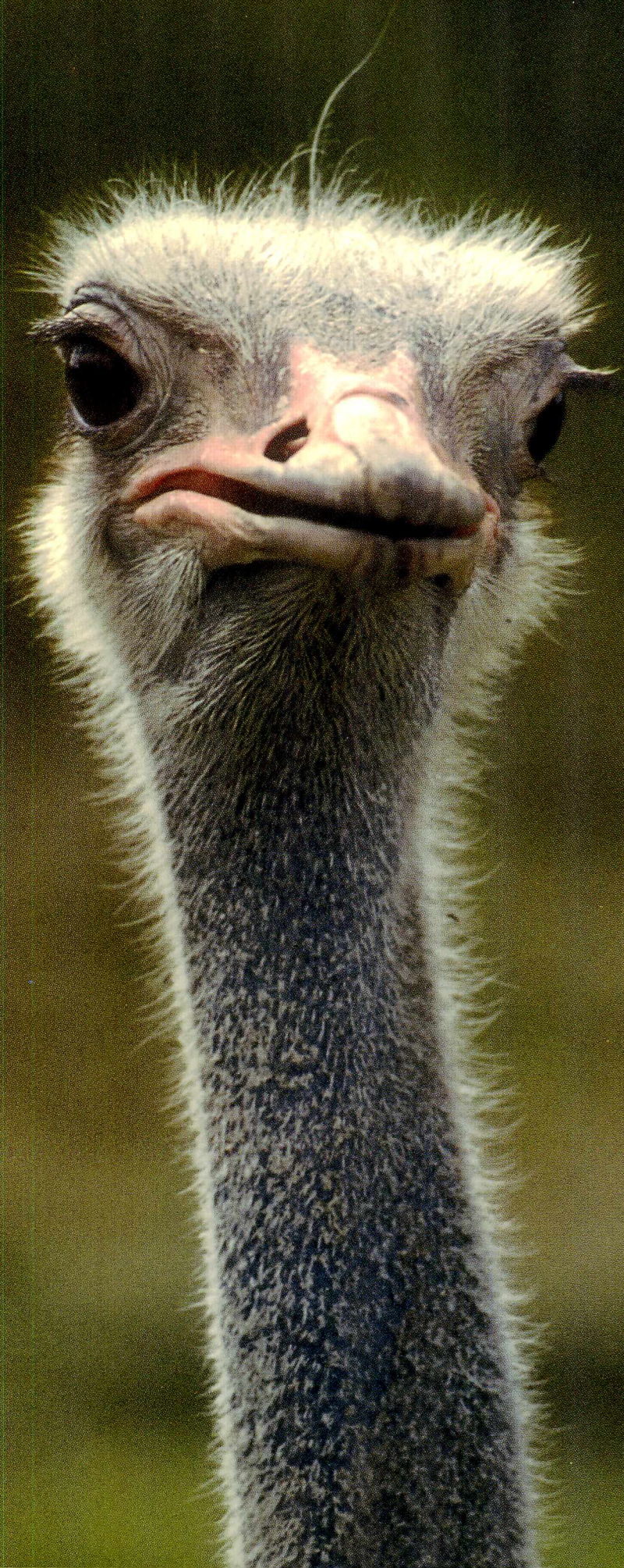


FDA Consumer

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

September–October 2002 • Vol. 36 No. 5

Imported Drugs Raise Safety Concerns



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Currently, there are no FDA-approved drugs to treat this ostrich if it gets sick. See page 30 to learn more about the steps being taken to develop and make available medications for ostriches and other “minor species.”

OBSERVATIONS



Recent ads in newspapers and magazines claim that it's now legal to import drugs into the United States for personal use. In fact, some ads

on the Internet and elsewhere claim that people can legally bring up to a 90-day supply of their prescription medications bought outside the United States home with them.

Neither of these claims is true.

Under the Federal Food, Drug, and Cosmetic Act, unapproved, misbranded, and adulterated drugs are prohibited from importation into the United States. In general, all drugs imported by individuals fall into one of these prohibited categories. This includes drugs that are foreign versions of FDA-approved medications and drugs dispensed without a prescription.

"Opening our borders to re-imported drugs potentially could increase the flow

of counterfeit drugs, cheap foreign copies of FDA-approved drugs, expired and contaminated drugs, and drugs stored under inappropriate and unsafe conditions . . . that's a risk we simply cannot take," Health and Human Services Secretary Tommy G. Thompson recently told a biotechnology summit in Canada.

Our cover story, "Imported Drugs Raise Safety Concerns," (page 18) examines the dangers associated with some imported drugs and the FDA's efforts to warn U.S. citizens about the risks surrounding such medications.

Today's supermarket shelves are stocked with foods as diverse as the people who roam the aisles. And, while advances in food packaging have helped extend shelf life, food quality remains a concern. Our feature article "Food Freshness and 'Smart' Packaging" (page 25) takes a look at how scientists at the FDA's National Center for Toxicological Research are developing "smart packaging" that someday will help consumers determine when good food goes bad.

Ever wonder what an ostrich takes for a sore throat? Ostriches, along with sheep,

goats, game birds, zoo animals, finfish, and species other than cattle, horses, pigs, chickens, turkeys, dogs and cats, are among animals considered to be "minor species" by the FDA. Check out our feature article (page 30) to learn about the challenges facing those who treat minor species.

Do you think that only women need to be concerned about the bone-thinning condition osteoporosis? Think again. Our article will give you the latest research findings on this condition that increases the risk for bone fractures among older people (page 15).

Ray Formanek Jr.
Editor

*The staff of
FDA Consumer joins
with those mourning
the losses of
Sept. 11, 2001.*

UPDATES

New Drug Approved for Colorectal Cancer

Cancers of the colon and rectum (colorectal) are the fourth most commonly diagnosed cancers and rank second among cancer deaths in the United States.

The FDA has approved Eloxatin (oxaliplatin) injection for use with infusional 5-fluorouracil (5-FU) plus leucovorin. The combination treats people with colorectal cancer whose disease has recurred or become worse following initial therapy with a combination of irinotecan with bolus 5-FU plus leucovorin.

The combination with Eloxatin was shown to shrink tumors in some people and delay resumed tumor growth. There are no data yet on the effects of the combination on survival.

The FDA reviewed the marketing application for Eloxatin in seven weeks—the fastest review to date for a cancer drug. The agency was able to review and approve the drug rapidly because of "rolling review" procedures available under new drug applications that are designated as "fast track." Drugs in development that have the potential to be an advance in treatment for serious illness may be identified as "fast track" drugs. Under this designation, rolling applications allow for the submission of some parts of the application before remaining sections are submitted.

Eloxatin is intended for use by physicians experienced in the use of cancer agents. A warning, boxed in black for emphasis, details this use and highlights reactions associated with the drug.

Eloxatin can have a toxic effect on

nerve endings that may result in either an acute or cumulative pattern of side effects. This may cause the feeling of numbness or tingling, especially in the hands and feet or around the mouth and throat. For some patients, these symptoms may be worsened by exposure to cold. Another side effect, which generally improves after treatment is complete, is difficulty performing ordinary daily tasks such as buttoning clothes.

Other common side effects of Eloxatin are vomiting, diarrhea, anemia, increased risk of bleeding or infection, or allergic reaction. Women should be advised to avoid becoming pregnant while receiving this treatment because it may harm the fetus.

Eloxatin will be distributed by Sanofi-Synthelabo, Paris.

New Palm Test for Cholesterol

The FDA has cleared a new laboratory test to measure cholesterol levels in the skin of adults with severe coronary artery disease.

Cholesterol 1,2,3, manufactured by International Medical Innovations Inc., of Toronto, can help determine the amount of cholesterol in skin using the palm of the hand. Other tests currently used by



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laboratories measure cholesterol from blood samples.

To do the palm cholesterol test, an applicator pad, much like an adhesive bandage, is placed on the palm of the hand. Drops of solution are added to the pad for three minutes. A hand-held reader attached to a computer reads the amount of blue color in the pad. The results are displayed on the computer screen. The deeper the blue, the more cholesterol is present.

Specifically, the new test is for people suspected of having severe coronary artery disease, defined as 50 percent closure of two or more arteries, and those with a history of heart attack. Cholesterol 1,2,3 is not intended to be used as a substitute for the standard blood tests, nor can it substitute for an evaluation of other risk factors used to identify coronary artery disease.

Skin contains about 11 percent by weight of all body cholesterol. When severe coronary artery disease is present, the numeric values obtained with the skin cholesterol test increases. The test was not shown to be useful in identifying people with less severe coronary artery disease, and should not be used as a screening tool to determine coronary artery disease risk in the general population.

The test cannot be used on people with skin diseases on the hand or on those who recently applied skin lotions or topical medications.

HHS to Study Ephedra, Step Up Enforcement Against Illegal Marketing

Health and Human Services Secretary Tommy G. Thompson has announced new efforts to expand research on the safety of herbal ephedrine alkaloids, commonly referred to as ephedra. Marketed in the United States as weight loss, energy, and sports supplements, ephedrine alkaloids are active chemicals found naturally in a number of plants. They can also be produced synthetically.

Adverse event reports have raised questions about the safety of these products, and the FDA has advised that further scientific research is needed. HHS recently funded the RAND Corporation to conduct a review of the existing science on ephedrine alkaloids, particularly in dietary supplements. The National Institutes of Health will use this information to guide an expanded research effort on the safety of ephedrine alkaloids.

Thompson also announced plans to aggressively pursue the illegal marketing of non-herbal synthetic ephedrine alkaloid products. In June, the FDA sent six warning letters to firms unlawfully selling these products over the Internet. The FDA also warned another company for illegally promoting its ephedrine product as an alternative to street drugs.

The firms that do not correct the violations described in the warning letters face further enforcement actions. This could include seizure of the illegal product and injunction from manufacturing and distributing the product, as well as prosecution of the companies and individuals.

"These products are not for everyone," says FDA Deputy Commissioner Lester M. Crawford, D.V.M., Ph.D. "Consumers should read the labels carefully to ensure their proper use."

Consistent with industry standards and warnings that appear on many products, consumers under the age of

18 and women who are pregnant or nursing should not use these products. Consumers should consult a health-care provider before using such products if they are using a prescription drug or if they have ever had high blood pressure, heart or thyroid disease, a seizure disorder, depression, diabetes, difficulty urinating, prostate enlargement, or glaucoma.

Anyone using a monoamine oxidase (MAO) inhibitor (a drug used in the treatment of selected atypical depression) or any allergy, asthma, or cold medications containing ephedrine, pseudoephedrine, or phenylpropanolamine should consult with a physician before using dietary supplements con-



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taining ephedrine alkaloids. Phenylpropanolamine may also be found in over-the-counter (OTC) weight-loss products. Because of safety concerns, the FDA recommended in November 2000 that consumers stop using products with phenylpropanolamine and has proposed that it be removed from the market. Consumers may still have products containing the ingredient in their medicine cabinets.

Consumers should discontinue use of ephedrine alkaloids if any of the following symptoms are experienced: rapid or irregular heartbeat, chest pain, severe headache, shortness of breath, dizziness, loss of consciousness, sleeplessness, or nausea.

Thompson urged manufacturers to include the FDA's MedWatch telephone number, 1-800-FDA-1088, on product labels to encourage consumer reporting of adverse events.

FDA Steps Up Seafood Sampling

The FDA is increasing its sampling of imported shrimp and crayfish (also known as crawfish) to check for the presence of the antibiotic chloramphenicol. The agency is taking this action because low levels of the drug in imported shrimp and crayfish have been detected by some states and other countries.

Chloramphenicol is a potent, broad-spectrum antibiotic used to treat serious infections in people. Federal regulations prohibit its use in food-producing animals and animal-feed products because it has not been possible to identify a safe level of human exposure to chloramphenicol.

"The FDA is concerned about any detection of chloramphenicol in shrimp and crayfish," says FDA Deputy Commissioner Lester M. Crawford, D.V.M., Ph.D. "The agency will take whatever action is necessary to protect the public health."

FDA actions include issuing an import alert and directing inspectors to test seafood and refuse U.S. entry to any product identified and confirmed as containing more than 1 part per billion (ppb) of chloramphenicol, the lowest level currently detectable by FDA analysis methods. The agency is modifying its methods to detect 0.3 ppb, which will place U.S. methodologies in line with those used by Canada and the European Union.

The FDA is also working cooperatively with the states and other countries to share methods for determining levels of chloramphenicol in shrimp and honey, says Arnold Borsetti, Ph.D., a chemist and associate director for operations in the FDA's Center for Food Safety and Applied Nutrition. In July, the FDA held a conference call with officials in all 50 states. "We want to assure that information available to FDA, to include sampling and testing methodologies, is shared with all the states," says Borsetti. "Since there are many ports of entry for imported food products across the U.S., this informa-



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tion-sharing is very important to aid in the coordination and consistency of effort at both the federal and state level."

Because some states detected chloramphenicol in shrimp and cray-

fish imported from China and other southeast Asian countries, FDA and Chinese officials met in June to discuss these drug residues and exchange information on testing methods. Chinese officials informed the FDA that China has banned the use of chloramphenicol in animals and animal feeds. They are also testing shrimp, crayfish, and other animal-derived foods intended for export to ensure the absence of chloramphenicol and other drug residues.

The FDA will continue to work with other governments and state agencies to ensure the safety of the U.S. food supply.

First-of-its-Kind Treatment for Women with IBS

The FDA has approved the first treatment for women with irritable bowel syndrome (IBS) whose primary symptom is constipation. Until this approval, medications were only available to treat women with IBS whose primary bowel symptom was diarrhea.

Zelnorm (tegaserod maleate), made by Novartis Pharmaceuticals Corp. of East Hanover, N.J., increases the movement of stools (feces) through the bowels, while drugs such as Lotronex (alosetron hydrochloride) for diarrhea-predominant IBS slow stool movement. Zelnorm also reduces pain and discomfort in the abdomen and reduces bloat-

ing and constipation, but it does not cure IBS, nor does it treat diarrhea-predominant IBS.

The drug has not been shown to be safe and effective in men.

IBS is a disorder of the intestine in which the intestine isn't functioning normally, but there is no sign of disease that can be seen or measured. Abdominal pain, cramps, gas, bloating, diarrhea and constipation are among the symptoms.

The adverse side effect most often associated with Zelnorm was diarrhea, but the majority of people treated with the new drug reported only a single episode. In most cases, diarrhea occurred during the first week of treatment.

CLARIFICATIONS

Despite its name, Botox Cosmetic is a drug and not a cosmetic (see "Botox Cosmetic: A Look at Looking Good," July–August 2002 *FDA Consumer*). The Federal Food, Drug, and Cosmetic Act defines drugs as articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, and articles (other than food) intended to affect the structure or any function of the body. Drugs, including those used for cosmetic purposes, are subject to a strict FDA approval process to assess

their safety and efficacy. Cosmetics (articles intended to be rubbed, poured, sprinkled, or applied to the body such as shampoos, makeup and moisturizers) do not undergo the same rigorous review. Increasingly, the word "cosmetic" is being used as a medical term to describe a number of surgical and non-surgical treatments that are intended to enhance appearance and are performed only by a licensed health-care professional. Botox Cosmetic is one such treatment. ■

HHS: PDUFA Reauthorization Good for Americans

On June 12, President Bush signed into law the reauthorization of the Prescription Drug User Fee Act

(PDUFA) that will allow the agency to collect \$1.2 billion over the next five years.

Health and Human Services Secretary Tommy G. Thompson says the reauthorization will help all Americans by providing more

promptly review applications and get safe, effective new drugs into the hands of the people who need them."

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

The 1992 PDUFA expired in 1997, and the FDA Modernization Act of 1997 amended PDUFA and extended it through Sept. 30, 2002.

Fees collected under the reauthorization will enable the FDA to increase the staff of the drug review program

by 450 full-time employees and to improve working conditions and training. Equally important is the authorization to spend \$70 million of the user fees to increase the agency's surveillance of the safety of drugs during the first two years (or, for potentially dangerous medications, three years) on the market. It is during this initial period, when new medicines enter into wider use, that the agency is best able to identify and counter adverse side effects that did not appear during the clinical trials.

"PDUFA will be stronger and more effective than ever. With the additional resources and an enhanced ability to monitor safety of new drugs as they enter the marketplace, we're taking a step forward in transforming FDA into an even more efficient agency, while maintaining our high standards of safety," says FDA Deputy Commissioner Lester M. Crawford, D.V.M., Ph.D.



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resources for the FDA to review new drug applications in a timelier manner.

"Americans deserve timely access to potentially lifesaving new drugs as soon as possible once they are proven safe and effective," Thompson said. "This law will ensure that the FDA has the expert staff and resources to

'Nicotine Water' is Unapproved Drug

The FDA has determined that a product called "nicotine water" is an unapproved drug under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and cannot be marketed without new drug approval by the agency.

"FDA's decision underscores our commitment that consumers be protected from drug products that have not undergone our rigorous review process," says FDA Deputy Commissioner Lester M. Crawford, D.V.M., Ph.D.

The FDA's decision was issued in response to a citizen's petition regarding the regulation of nicotine water. The petition, which was sub-

mitted to the FDA in December 2001, requested that the agency classify and regulate nicotine water as a drug or as a food containing an unapproved food additive under the FD&C Act. The petition was submitted on behalf of several groups, including the National Center for Tobacco-Free Kids, the American Medical Association, and the American Lung Association.

The FDA concluded that nicotine water is an unapproved drug under the FD&C Act because it is intended to treat or mitigate nicotine addiction as a smoking cessation product. Because nicotine addiction is considered a disease, the FDA requires safety and effectiveness data to support any claims intended to treat this disease.

The FDA also determined that the

product cannot be legally marketed as a dietary supplement, as it was being promoted by the manufacturer. Under the FD&C Act, a "dietary supplement" does not include a product that contains an active ingredient that the FDA has already approved for use in a drug. Because the nicotine and nicotine polacrilex in nicotine water are both active ingredients in FDA-approved smoking cessation drugs such as Nicoderm CQ, Prostep, Habitrol, and Nicorette, nicotine water cannot be marketed as a dietary supplement.

The FDA will continue to monitor the marketplace to ensure that consumers are protected from unapproved drug products.

Labeling Changes for Arthritis Drug

The FDA has approved labeling changes for Celebrex (celecoxib) based on the results of the Celecoxib Long-Term Arthritis Safety Study (CLASS).

CLASS evaluated about 4,000 people with osteoarthritis (OA) and rheumatoid arthritis (RA) treated with Celebrex at doses of 400 mg twice a day (twice the highest approved dose of Celebrex to treat RA), compared to about 4,000 people treated with standard doses of ibuprofen or diclofenac. These are non-steroidal anti-inflammatory drugs (NSAIDs).

The use of low-dose aspirin for prevention of heart attack and stroke (up to 325 milligrams per day) was permitted during the study.

The results of the CLASS study did not support a change in the label related to serious gastrointestinal (GI) events, but important information about the drug was obtained. Inclusion of patients on low-dose aspirin in the study was valuable for the safety assessment of Celebrex. But the use of aspirin, a drug known to cause stomach ulcers and bleeding, may have obscured the ability to accurately compare the GI safety of Celebrex to other NSAIDs.

The agency concluded that the drug labeling for Celebrex should continue to include the standard warning

about risks associated with all NSAIDs, including risks of GI ulceration, bleeding and perforation.

The FDA also determined that safety data from CLASS should be incorporated into the labeling. The overall safety of Celebrex at twice the highest approved dose for rheumatoid arthritis was similar to commonly used doses of ibuprofen and diclofenac. Despite the high dose used, the rates of hypertension, swelling, and serious adverse events, including cardiovascular problems such as heart attacks, were no higher in people treated with Celebrex than in people treated with ibuprofen or diclofenac. People taking low-dose aspirin and Celebrex had a higher rate of upper GI events than those taking Celebrex alone.

The geriatric section of the labeling will include new information about the risk of serious GI and kidney effects in elderly people. Such findings have also been reported with other NSAIDs, and it is known that elderly people are at higher risk of GI ulcers and bleeding. Another observation reported in the labeling is that patients treated with Celebrex experienced less anemia than patients taking ibuprofen or diclofenac.

Pharmacia of Peapack, N.J., manufactures Celebrex. The drug was approved to treat rheumatoid arthritis and osteoarthritis in 1998.

Advisory for Norplant Contraceptive Kits

In July, Wyeth Pharmaceuticals of Madison, N.J., announced that due to limitations in product component



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supplies, the company will no longer distribute the six-capsule Norplant System (levonorgestrel implants). The Norplant capsules are implanted under the skin of the upper arm and provide contraception for five years.

The FDA advises that women using the system contact their doctors about other contraceptive options to use after the five-year expiration date of their Norplant system. For women who prefer to have the Norplant capsules removed, Wyeth will pay for removal until December 31, 2002.

Wyeth also announced that women with Norplant capsules from certain lots may now safely stop using backup contraception. Previously, these women were advised to use backup contraception because of concerns about lower than expected release of the hormone levonorgestrel from several lots. Testing of the specified lots has not shown the effectiveness of the implants to be different from that seen in clinical trials and described in product labeling.

Norplant users who depend on condoms for protection against sexually transmitted diseases should continue to use them.

For more information, contact the Norplant System Information Line at 1-800-364-9809.

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

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

FDA Warning on Chinese Diet Pills Containing Fenfluramine

The FDA is alerting the public about Chinese weight-loss products, Chaso (Jianfei) Diet Capsules and Chaso Genpi, because they pose a potential public health risk.

The agency is alerting the public to this health risk because several people in Japan have become ill, and some have died, after consuming these diet products.

"FDA is taking this action as a precautionary measure to help assure that people are not exposed to this potentially dangerous product," says FDA Deputy Commissioner Lester M. Crawford, D.V.M., Ph.D.

Products of this type are often sold in small urban markets as alternatives to Western medicine. In 2001, the FDA issued a nationwide alert on the recall of 13 "Treasure of the East" herbal products because of a dangerous ingredient, aristolochic acid, which is toxic to the kidney.

The deaths in Japan linked to these Chinese weight-loss products may have resulted from the presence of such active drug ingredients as fenfluramine in the capsules.

Fenfluramine and another diet drug, phentermine, were used in combination for weight loss until it was determined that the combination of drugs was linked to valvulopathy, a serious and sometimes fatal heart disease. Fenfluramine and a chemically similar drug, dexfenfluramine, were removed from the market in 1997. Phentermine, when used alone, has not been associated with valvulopathy and remains on the market.

The FDA has advised its import operations personnel to be on the alert for Chaso Diet Capsules and Chaso Genpi.

The agency is urging consumers not to take these diet pills and to notify their local FDA office if the products are found in their area.

Xyrem Approved for Muscle Problems in Narcolepsy

The FDA recently approved Xyrem (sodium oxybate or gamma hydroxybutyrate, also known as GHB) for treating a small population of people with narcolepsy who experience episodes of cataplexy—weak or paralyzed muscles. Because of safety concerns associated with the use of the drug, the distribution of Xyrem will be tightly controlled.

In the early 1990s, GHB was marketed purporting to be a dietary supplement for enhancing athletic performance and sexual activity and for inducing sleep. It was also abused as a recreational drug and is well-known for use in date rape. As a result of a number of serious adverse events, including death, the FDA intervened to prohibit the marketing of GHB.

Xyrem has been designated as a Schedule III controlled substance for medical use, meaning it cannot be sold, distributed, or provided to anyone other than for its prescribed use. Illicit use of Xyrem will be subject to penalties under Schedule I, the most restrictive schedule of the Controlled Substances Act.

The FDA approved Xyrem based on the results of two controlled clinical trials that showed that use of the drug reduced the number of cataplectic attacks compared to a placebo. Side effects associated with Xyrem include confusion, depression, nausea, vomiting, dizziness, headache, bedwetting, and sleepwalking. Abuse of Xyrem could also lead to dependence and severe withdrawal symptoms.

Narcolepsy affects about 120,000 people in the United States. This rare condition causes an irresistible tendency to fall asleep even in unlikely circum-

stances, such as in the middle of a conversation. Cataplexy, a symptom of this condition, is a sudden loss of muscular control and weakness usually triggered by emotions such as amusement, anger or excitement, and is estimated to affect about 20,000 to 50,000 individuals. The effects of cataplexy range from dropping of the jaw and slumping of the head, to buckling of the legs and even collapse of the whole body. These effects can last for a few seconds or up to many minutes.

Due to serious concerns and adverse events associated with the use of Xyrem, including some events that resulted in death, the FDA worked with the drug's manufacturer, Orphan Medical Inc., to design a comprehensive risk-management program. The program includes limited distribution, physician education, patient education, the creation of a patient and physician registry, and detailed patient surveillance. Under the program, prescribers and patients will be able to obtain the product only through a single centralized pharmacy. A Medication Guide, a special patient information brochure required by the FDA, further advises patients about proper use, administration and disposal of the drug. People who have further questions are advised to talk to their doctors or to call the central pharmacy at the toll-free number 1-877-67-XYREM (1-877-679-9736).

Xyrem is approved with orphan drug status, which is available for products to treat patient populations of 200,000 or fewer.

Orphan Medical Inc. of Minnetonka, Minn., will distribute the drug. Further information on Xyrem can be found at www.fda.gov/cder/drug/infopage/xyrem/xyrem_qa.htm.

UPDATES

New Sugar Substitute Approved

The FDA has approved Neotame



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for use as a general-purpose sweetener in a variety of food products. Depending on its food application, Neotame is 7,000 to 13,000 times sweeter than sugar. The non-nutritive, high intensity sweetener is made by the NutraSweet Company of Mount Prospect, Ill.

Examples of uses for which Neotame has been approved include baked goods, non-alcoholic beverages, chewing gum, confections and

frostings, frozen desserts, gelatins and puddings, jams and jellies, processed fruits and fruit juices, toppings, and syrups. Neotame has not been approved for use in meat or poultry. Any proposed uses of food additives in meat, poultry or eggs must also be evaluated by the U.S. Department of Agriculture.

The FDA reviewed data from more than 113 animal and human studies to determine the safety of Neotame.

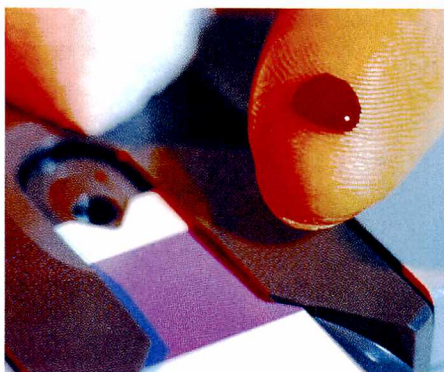
FDA Clears Two Glucose Test Meters

The FDA has cleared two glucose test meters that will allow people with diabetes to more easily track and manage their blood sugar levels through computer technology.

The FreeStyle Tracker Diabetes Management System, made by TheraSense Inc. of Alameda, Calif., and the Accu-Check Advantage Module, made by Roche Diagnostics Corp., of Indianapolis, each have two components with associated software. Both integrate parts of each company's currently marketed glucose meters and test strips with a

Handspring Visor Personal Digital Assistant (PDA).

To use the systems, a person first inserts a glucose meter module into



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the handheld computer, then inserts a test strip into the meter. After collecting a blood sample, the user places it onto the test strip. The handheld computer reads the glucose levels from the measurement module, displays the results, and stores the information in an electronic database. The test results also can be uploaded onto a personal computer.

In addition to measuring and tracking glucose level, the new systems allow users to track a variety of other data that may affect their health, such as insulin usage, food intake, exercise, and medicine. ■

RESEARCH NOTEBOOK

Information Source on Rare Diseases

A new Genetic and Rare Diseases Information Center is now available to the general public, health-care professionals and biomedical researchers.

Created by the National Institutes of Health's National Human Genome Research Institute (NHGRI) and Office of Rare Diseases (ORD), the center gives free and immediate access to information specialists who can answer questions on the phone, as well as by e-mail, fax and regular mail.

Information on the more than 6,000 genetic and rare diseases may be hard to

find because they affect relatively few people. The center will help relieve this problem by providing authoritative information about specific illnesses from existing public domain sources, including reliable Web sites, brochures, articles and book chapters. The center does not, however, give medical advice, provide treatment or diagnose illness.

To contact the information center:

Phone: 1-888-205-2311

TTY: 1-888-205-3223

(answered Monday through Friday, 12 p.m. to 6 p.m., Eastern time)

E-mail: gardininfo@nih.gov

Fax: 202-966-5689

(available 24 hours a day)

Write to:

The Genetic and Rare Diseases Information Center
PO Box 8126

Gaithersburg, MD 20898-8126

For more information, visit the ORD Web site at <http://rarediseases.info.nih.gov> and the NHGRI Web site at <http://genome.gov/Health>.

Air Pollution Linked with Risk for Exercise-Induced Heart Damage

Breathing polluted air, especially smoky exhaust that billows from factory smokestacks and the tailpipes of some diesel-powered vehicles, is bad for people with heart disease, a new study indicates.

Many researchers have reported an association between pollution and increased heart attacks and deaths from heart disease. However, the study by Juha Pekkanen, M.D., of the National Public Health Institute in Kuopio, Finland, is the first to look at myocardial strain and to show an association between decreased oxygen supply to the heart muscle (ischemia) and particulate air pollution.

Study participants with heart disease were about three times more likely to have ischemia during exercise testing after exposure to periods of high level air pollution than when they were tested after periods of negligible air pollution, says Pekkanen.



PhotoDisc

The researchers analyzed data from 342 exercise tests that they conducted. They recorded 72 instances of exer-

cise-induced ischemic episodes among the 45 subjects. Twenty-three patients experienced exercise-associated symptoms when air pollution was high two days before a clinic visit. The remaining 22 subjects either had no episodes of ischemia or had episodes at every visit regardless of air quality and were unable to provide information about the relationship between air pollution and myocardial ischemia.

The results were published in the July 29, 2002, rapid access issue of *Circulation: Journal of the American Heart Association*.

Fine particles—those smaller than 2.5 micrometers—represent the type of pollutant mainly associated with emissions from factory smokestacks. Ultra-fine particles have a diameter less than 0.1 micrometers. This is the type of pollutant that spews from exhaust pipes. Both types of particulate air pollution increased the risk of ischemic episodes about three-fold, says Pekkanen.

Cardiovascular Benefits of Long-Term Fruit and Vegetable Consumption

Eating at least three servings of fruits and vegetables each day over an extended period of time may help protect against stroke, heart disease and other cardiovascular problems, a new study indicates.

The study by Lydia A. Bazzano, Ph.D., and colleagues, of the Tulane University School of Public Health and Tropical

Medicine, examined the relationship between fruit and vegetable consumption and the risks of cardiovascular disease (CVD) and stroke in a large group for an average of 19 years. They found that stroke incidence and mortality, as well as mortality from ischemic heart disease and CVD, were all significantly reduced in those who had eaten at least three servings of fruits and vegetables per day.

"Increased fruit and vegetable intakes have been recommended to prevent morbidity and mortality from cardiovascular disease," the researchers conclude in their study, published in the July 2002 issue of the *American Journal of Clinical Nutrition*. "Our findings provide additional evidence to support this recommendation."

The study, part of the first National Health and Nutrition Examination Survey (NHANES I), involved prolonged follow-up of 9,608 adults ages 25 to 74 who were randomly distributed by sex, race and sociological group. All subjects

were free of CVD at the study's inception between 1971-1975. Follow-up data on dietary intake, disease and mortality were collected in 1982-1984, 1986, 1987 and 1992. In determining average daily servings of fruits and vegetables, the researchers used both a three-month food frequency questionnaire and a 24-hour dietary recall record.

People who had eaten at least three servings per day of fruits and vegetables had a 27 percent lower incidence of stroke and a 42 percent lower stroke mortality rate, when all subjects were considered. In addition, the risk of death from ischemic heart disease and CVD was reduced by 24 percent and 27 percent, respectively. Men appeared to benefit more than women and whites more than nonwhites from frequent fruit and vegetable consumption with a few exceptions, such as a 53 percent reduction in stroke mortality for women versus a 23 percent reduction for men. ■



PhotoDisc

Checking Up on Blood Pressure Monitors

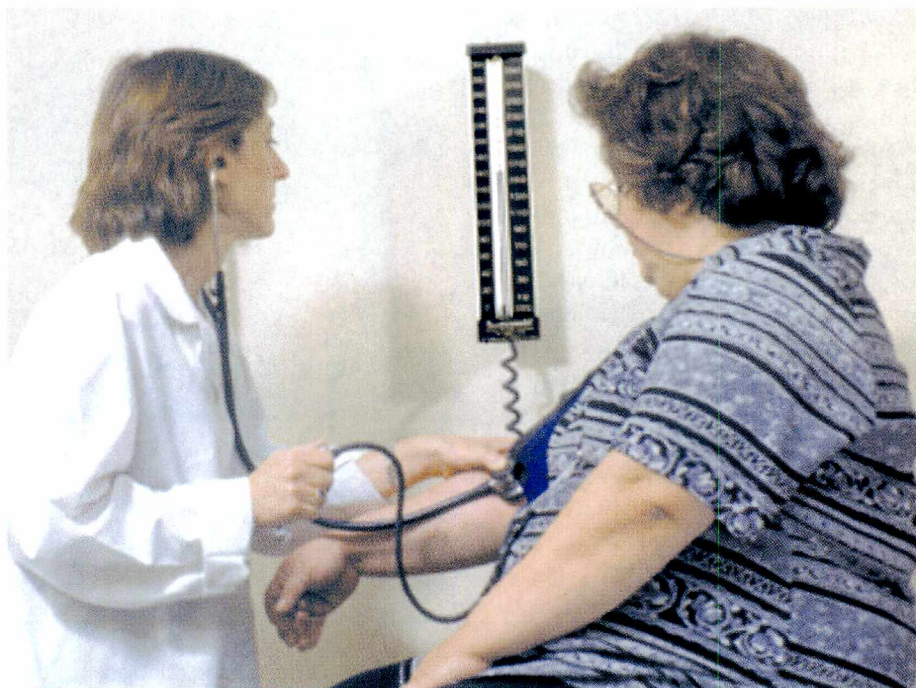
By Carol Lewis

Measuring a person's blood pressure is a routine part of every physical exam. The results can predict long-term health risks, assess suitability for certain physical activities, help manage many types of medical problems, and determine eligibility for insurance. The procedure is done to screen for high blood pressure (hypertension), a major risk factor for serious conditions, such as stroke, kidney failure, and the leading killer in the United States—cardiovascular disease.

The safety of the current “gold standard” instrument used to measure blood pressure—the mercury-filled sphygmomanometer—however, is being called into question due to the environmental health risks associated with mercury. At the same time, medical experts fear that the mercury gauges may be replaced by less accurate devices without consideration for the health risks that could follow.

Although the environmental concerns are serious, the Food and Drug Administration believes that mercury sphygmomanometers are still useful medical devices.

The most accurate means for measuring blood pressure is directly within an artery (intra-arterial) using a catheter. But because this method is invasive, it is neither practical nor appropriate for repeated measurements in non-hospital settings, or for large-scale public health screenings. In addition, different methods for measuring blood pressure can produce different readings. The guidelines for diagnosing and treating hypertension are based upon measurements made using the mercury-filled sphygmomanometer, not upon intra-arterial measurement of blood pressure.



Black Star/Dennis Brack

Shari L. Targum, M.D., a medical officer in the FDA's Division of Cardio-Renal Drug Products, checks Saideh Nadjmabadi's blood pressure with a mercury-filled sphygmomanometer.

The usual method of measurement, therefore, is a noninvasive means that uses a sphygmomanometer, which includes either a column of mercury or pressure-registering gauge. With this technique, the flow of blood is temporarily stopped by an inflated cuff that is wrapped around the upper arm and that puts pressure on the main artery in the arm. Blood flow is then gradually restarted as the user slowly deflates the cuff.

An examiner uses a stethoscope to listen for sounds, called Korotkoff sounds, that can be heard when the blood begins flowing again through the artery and that change in tone and volume while the cuff is deflated. Blood pressure is typically measured in units of millimeters of mercury, and

represents the force of blood against the blood vessel wall. The first number, called the systolic pressure, represents the highest blood pressure that occurs each time the heart beats. The second number, called the diastolic pressure, is the lowest pressure that occurs when the heart relaxes between two beats. The Korotkoff sounds are used to identify a person's systolic and diastolic blood pressure readings.

Both numbers are important because when either is elevated, so is the risk of developing heart and blood problems. According to the National Heart, Lung, and Blood Institute, a blood pressure reading consistently higher than 140/90 is a sign that the blood pressure needs to be brought under control. The typical adult blood pressure is

120/80 or lower, but readings vary depending on age and other factors.

The mercury sphygmomanometer is simple, easy to read, and requires no readjustment. It has been validated in many clinical circumstances against the direct method of measurement through the artery.

The push to replace mercury sphygmomanometers began in June 1998, when the Environmental Protection Agency and the American Hospital Association agreed to limit the amount of mercury waste from hospitals as much as possible by 2005. Other organizations, over time, have joined the effort.

Mercury is a silver-colored metallic element that is liquid at room temperature and tends to break into tiny, highly mobile droplets when spilled. These droplets vaporize and can contaminate the atmosphere. Precautions must be taken to limit the inhalation, ingestion or absorption of mercury in case of a spill or breakage. Exposure to mercury from sphygmomanometers used in health-care settings is extremely rare. Modern mercury sphygmomanometers are available in models that prevent accidental spillage of mercury. And, there have been only a few isolated cases of illness in children from mercury toxicity related to broken glass thermometers.

The FDA, which regulates blood pressure devices, requires companies to show that new monitors are substantially equivalent to models already on the market. They also must demonstrate accuracy through a clinical validation study.

There are two alternative types of blood pressure measuring instruments being marketed. Aneroid devices, which have no liquid, use metal that acts like a spring to measure blood pressure. These have a round compass-like face that is attached to a cuff and accompanied by a stethoscope, and are commonly used in physicians' offices.

Electronic devices measure pressure by converting the readings into measurable electronic waves. Electronic instruments include in-home blood pressure monitoring devices as well as the small stations often seen at drug stores where people place their arms through a mechanical cuff. These use physical

measurements and mathematical formulas to calculate pressure. Electronic monitors were originally designed for use during surgery and in emergency room settings. They are not commonly used by U.S. physicians to diagnose or to monitor hypertension.

The two crucial considerations for substituting aneroid and electronic units for mercury instruments are calibration and validation. Calibration is a way to make sure that measurements begin from zero—much like when a scale is balanced before it is stepped on to measure body weight. If the starting mark is above or below zero, the final measurement will be inaccurate. Validation ensures that the instrument can take accurate measurements over a wide range of blood pressures, ages and clinical conditions.

The FDA also is concerned that aneroid and electronic devices may not be regularly calibrated, potentially making these devices prone to erroneous readings.

Regardless of the type of device used to measure blood pressure, selecting appropriately sized cuffs is critical. The appropriate cuff width is based on the diameter of the upper arm. Taking blood pressure measurement with a cuff that's too narrow could overestimate blood pressure, while too wide a cuff can underestimate the pressure. Inappropriately low blood pressure, or clinical shock, is a medical emergency. Inappropriately high blood pressure can indicate hypertension.

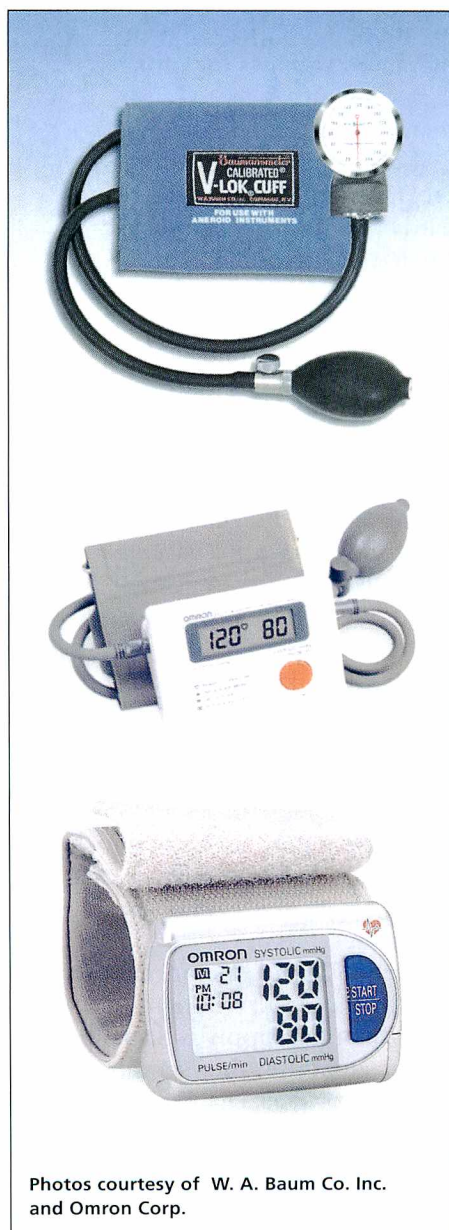
The American Heart Association (AHA) says that physicians who are involved in the management of patients with blood pressure problems must accept responsibility for ensuring that adequate instruments are available. They need to educate themselves on the instruments available for use in their clinics, and encourage the general use of mercury sphygmomanometers as the instrument of choice until others have been better validated.

Where aneroid or electronic devices are used, the AHA recommends validation through the Association for the Advancement of Medical Instrumentation or a similar organization and a program of regular maintenance.

The FDA recommends the following guidelines for in-home monitors:

- Read the labeling to familiarize yourself with its operation.
- Have the device calibrated/validated according to the manufacturer's instructions.
- Look for a statement that says the unit was validated against the direct method of measurement.
- Make no changes in medications based on at-home findings.

FDA experts say it's important to remember that home monitors are not an appropriate substitute for the regular measurement of blood pressure during physician visits. ■



Photos courtesy of W. A. Baum Co. Inc. and Omron Corp.

Vaccine Shortages: An Update

By Michelle Meadows

Judi Chase says she's not winning any popularity contests these days. As a program manager for vaccines at the Texas State Department of Health, she's used to fielding questions from health-care providers who want to know why their vaccines are late and what she's going to do about it. Her department coordinates the vaccine supply for about 3,000 providers in the state's Vaccines for Children program. "I try to tell them it's not us," Chase says.

She also understands the providers' frustration. "It's hard enough to get people vaccinated the first time," she says. "So if they're told the supply is out, it's especially difficult to get them back." The biggest supply challenges for Texas over the past year have been with the chickenpox vaccine and with the pneumococcal vaccine, Prevnar. And while the chickenpox vaccine supply is returning to normal, Prevnar remains a problem.

"We need about 80,000 doses of Prevnar a month, and we get about 15,000 doses a month from the manufacturer," Chase says. One strategy has been to take the available doses and divide them up so that various providers each can have a small percentage. "But then when it's gone, it's gone," she says.

When it's gone, doctors have to track patients and tell them to come back when the supply is back up. In critical situations, they send patients to other providers. Dianna Heyer, R.N., nursing service coordinator at the Macon County Department of Health in Decatur, Ill., says doctors in her area who don't have tetanus and diphthe-

ria (Td) vaccine have referred patients with wounds to the county clinic. The vaccine prevents a neurological disease known as lockjaw and a life-threatening respiratory illness.

"We've been able to give the shot to people with wounds," Heyer says,



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"but we couldn't give routine Td boosters for the last year." For example, Heyer's clinic couldn't give boosters to children in ninth grade last year. As a result of recent vaccine shortages, which have mostly affected childhood vaccines, several states temporarily suspended school entrance requirements for immunizations.

Td boosters are normally given at age 11 or 12 with a subsequent booster given every 10 years, according to the vaccine schedule recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Prac-

tices (ACIP). Now that the Td supply is back to normal everywhere, Heyer says they will probably hold special clinics this year so the children who missed shots last year can catch up.

There are many reasons for the shortages. A major reason is the fact that there are relatively few manufacturers in the vaccine business. It's also difficult to make vaccines; from start to finish, a particular batch of a given vaccine requires roughly a year of production time. Unlike most drugs, vaccines are produced from living cells and organisms. Most require growing the immunizing agent, whether it's bacteria or viruses, in a production facility where growth conditions are complex.

William Egan, Ph.D., deputy director of the FDA's Office of Vaccine Research and Review, says, "No disease outbreaks have resulted from the shortages, but children not being fully immunized is always a concern." Fortunately, projections by manufacturers indicate that serious shortages of several vaccines are easing. Here's an update on vaccines that have been in short supply:

Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP): Calling it a business decision, Wyeth Lederle of Pearl River, N.Y., stopped making DTaP in 2001. This left only two manufacturers of the vaccine, Aventis Pasteur of Swiftwater, Pa., maker of Tripedia, and GlaxoSmithKline of Philadelphia, Pa., maker of Infanrix.

In addition, Aventis Pasteur made changes to remove a mercury-containing preservative called thimerosal

from DTaP and had to go through FDA clearance. The company made the change by switching from multi-dose to single-dose packaging. And this uses a greater amount of vaccine per dose to make sure the full dose can be drawn from a vial. Glaxo's DTaP product was already thimerosal-free.

During the shortage, ACIP recommended that if providers didn't have enough DTaP to vaccinate all children with the standard five doses, they should make it a priority to vaccinate infants with the first three doses. Normally, children receive one dose each at ages 2 months, 4 months, and 6 months, followed by another dose at age 15-18 months and the final dose at age 4 to 6.

The DTaP supply has returned to normal, in part, because the FDA licensed a new DTaP vaccine (DAPTACEL) by Aventis Pasteur in May 2002. DAPTACEL is indicated for immunizing children ages 6 weeks to 6 years.

Measles, Mumps, Rubella (MMR): According to Merck & Company, West Point, Pa., temporary shortages of some vaccines they produce, including the MMR vaccine (M-M-R II), are due to two voluntary interruptions in their manufacturing operations. Merck voluntarily closed one facility after the FDA raised issues during a routine inspection. Another facility closing was already scheduled and took longer than expected.

During the shortage, ACIP recommended administration of the first dose in the 2-dose MMR regimen at age 12-15 months and deferral of the second dose that's recommended at 4-6 years. The supply is now back to normal.

Chickenpox (Varicella): Merck's manufacturing shutdowns also affected production of the chickenpox vaccine, VARIVAX. ACIP recommended that during the shortage, vaccine providers should delay vaccination of children until the age of 18 months or 2 years. Normally, the recommendation is one dose of varicella vaccine between 12 months and 18

months or at any age after 18 months if a child has not had chickenpox or the vaccine.

Vaccination was recommended for susceptible children ages 5 to 12, especially those entering school, and adolescents age 11 or 12. People not vaccinated until age 13 or older should get two doses, four to eight weeks apart. This shortage is likely to improve soon, but it will still take time to build up the inventory of chickenpox vaccine.

Pneumococcal Conjugate: Wyeth Vaccines markets Prevnar, approved by the FDA in 2000 to prevent invasive pneumococcal diseases in infants and toddlers. A shortage has occurred because demand was unexpectedly high,

exceeding supply. Infants normally receive a series of four shots, the first three given at two-month intervals beginning at 2 months and ending at 6 months, with the final shot in the series given at 12-15 months of age. During the shortage, ACIP temporarily changed recommendations so that infants receive the first three doses and will get the fourth dose when the supplies are sufficient. According to manufacturer projections, pneumococcal conjugate vaccine will remain in short supply through 2003.

Tetanus and Diphtheria Toxoids for adults (Td): Along with DTaP, the Td supply was affected when Wyeth Lederle decided to stop producing tetanus and diphtheria toxoids in 2001. In

What's New with the Flu?

Because of distribution delays with the flu vaccine over the last couple of years, the CDC's Advisory Committee on Immunization Practices (ACIP) is recommending that certain groups get their flu shots in October and earlier this year in anticipation of the 2002-2003 flu season.

The groups include people at high risk for complications from the flu (such as those age 65 and up and people of any age with certain chronic health conditions) and health-care workers. Children younger than 9 receiving the vaccine for the first time need a booster dose one month after the initial dose.

Everyone else should begin flu vaccination in November. The optimal months for vaccination are October and November, but ACIP encourages the use of vaccines even later than November because it's still likely to be beneficial. The number of influenza cases in the United States typically has not peaked until late December through early March.

ACIP also is encouraging flu vaccination for healthy children ages 6 months to 23 months and for those who come into close contact with children up to 23 months because of

the increased risk for influenza-related hospitalizations in this age group. A full recommendation for this age group is expected in the next few years.

Making sufficient supplies of flu vaccine is always a challenge because the predominant flu strains change every year. A drop in the number of flu vaccine manufacturers and the slow growth rate of certain strains of the influenza virus have created temporary shortages in the past.

The FDA works closely with companies to determine whether the supply will be adequate. Early last year, the FDA contacted the three influenza vaccine manufacturers—Aventis Pasteur, Evans Vaccines Ltd., and Wyeth—to discuss projections. Production problems limited the number of doses available early in the flu season, but as a result of the meetings, manufacturers produced the largest number of doses ever in a given year during 2001-2002 (about 87 million doses).

The latest manufacturer projections indicate that ample flu vaccine is expected for 2002-2003.

For a complete list of who should get a flu shot, visit www.cdc.gov/ncidod/diseases/flu/who.htm. ■

—M.M.

this case, only one major producer—Aventis Pasteur—remained. Production of the vaccine, from start to finish, takes about a year.

ACIP had recommended that routine Td boosters for adolescents and adults temporarily be deferred and that people return for shots once the supply was sufficient. Compared with distribution levels before the shortage, the amount of Td distributed nationally dropped 40 percent during 2001-2002. Now, the supply of adult Td in the United States has reached levels high enough that the routine Td schedule as recommended by ACIP can be resumed.

Possible Solutions

Prioritizing patients and adjusting the routine schedule of immunizations is clearly a short-term solution. Federal agencies, meantime, have been meeting to address long-term strategies to head off future shortages.

The FDA's Egan says some of the possible solutions being discussed include requiring manufacturers to give sufficient notice before interrupting or ending vaccine production so that other manufacturers can increase production. "We're also looking at what we can do at FDA to speed up lot release to get vaccines on the market sooner," he says.

Experts also are talking about ways to boost the vaccine stockpile. This isn't a big warehouse of extra vaccine, but rather refers to the CDC's Storage and Rotation Contracts with manufacturers. The contracts allow the CDC to buy vaccine beyond the national need so there is a supply to draw from in an emergency.

The CDC has the authority to stockpile six-month supplies of vaccines. It has been drawn on several times. Manufacturers borrow from the stockpile and usually replace it within a year. The CDC sets priorities for vaccine stockpiles, which typically contain vaccines that are routinely recommended and that have a single manufacturer. The MMR vaccine, for example, has been stockpiled since 1983. ■

Adult Immunizations

Check with your health-care provider about whether you need the following vaccines:

• Tetanus and Diphtheria Toxoids Combined (Td):

Boosters should be given at 10-year intervals throughout life. The vaccine protects against tetanus, also known as lockjaw. The disease is caused by a germ that enters the body through a cut or wound. Tetanus causes serious, painful spasms of all muscles. It can lead to a locking of the jaw that prevents opening of the mouth or swallowing.

Diphtheria spreads when germs pass from an infected person to the nose and throat of others. Diphtheria causes a thick coating in the nose, throat or airway and can lead to breathing problems, heart failure, paralysis and death.

• Flu (Influenza) Vaccine:

Given annually in the fall or early winter, the vaccine protects against the flu, a disease caused by a virus that spreads from infected people to the nose or throat of others. The flu can cause fever, sore throat, chills, cough, headache and muscle aches. The virus causes thousands of deaths each year, mostly among older people.

• Pneumococcal Polysaccharide Vaccine:

The vaccine protects against blood-borne pneumococcal disease, which can lead to serious infections of the lungs, the blood and the covering of the brain. Adults age 65 or older are among those who should get the vaccine.

• Measles, Mumps, Rubella (MMR) Vaccine:

Adults who need it include those born after 1956 without written documentation of having the vaccine on or after the first birthday. The vaccine protects against three viruses that spread from person to person through the air.

Measles virus causes a rash, cough,

runny nose, and eye irritation, and can lead to ear infection, pneumonia, seizures, brain damage and death.

The mumps virus causes fever, headache and swollen glands, and can lead to deafness, meningitis (infection of the brain and spinal cord covering), painful swelling of the testicles or ovaries and, rarely, death.

The rubella virus, commonly called German measles, causes a rash, mild fever and arthritis. If a woman gets rubella while pregnant, she could have a miscarriage or her baby could be born with serious birth defects.

• Chickenpox (Varicella) Vaccine:

People of any age without a reliable history of having chickenpox or vaccination are among those who should be vaccinated. The vaccine protects against chickenpox, a common childhood disease that can lead to serious illness and death in adults. The virus can be spread from person to person through saliva droplets in the air or by contact with fluid from chickenpox blisters. The disease causes a rash, itching and fever, and can lead to skin infection, scars, pneumonia and brain damage.

• Hepatitis B Vaccine (HBV):

The vaccine protects against hepatitis B virus, which is spread through contact with the blood and body fluids of an infected person. Adults at risk for hepatitis B include those who have more than one sex partner in six months. Hepatitis B can cause loss of appetite, vomiting, diarrhea, tiredness, jaundice, and pain in the muscles, joints and stomach. It can cause chronic liver damage, liver cancer and death.

To access the complete recommended schedule of adult vaccines, including information on warnings and specific high-risk groups, contact www.cdc.gov/nip/recs/adult-schedule.htm. ■

Source: Centers for Disease Control and Prevention



Osteoporosis and Men

By Carol Lewis

More than 10 million Americans have osteoporosis, according to the National Institute on Aging. Eighteen million more have lost enough bone to make them more likely to develop the disease. The majority of these 28 million are women. But men are at risk for the bone-thinning disease, too.

Osteoporosis gradually weakens bones and can lead to painful and debilitating fractures. It is characterized by low bone density (how solid bones are) and structural deterioration of bone tissue.

Often called the "silent disease," osteoporosis usually progresses without symptoms until it is diagnosed following a fracture.

Osteoporosis is seen less often in men than in women because men generally have larger, stronger bones, and because men don't usually experience the abrupt and substantial hormonal changes that women do following menopause. Also, bone loss begins later and advances more slowly in men than in women. However, the National Institutes of Health says that the problem of osteoporosis in men recently has been recognized as an important public health issue, especially in light of estimates that the number of men above age 70 will double between 1993 and 2050.

Today, more than 2 million American men have osteoporosis, and another 3 million are at risk for the disease, according to the National Osteoporosis Foundation (NOF). Each year, men suffer one-third of all hip fractures, and one-third of these men will not survive more than one year. In addition to hip fractures, men most often experience fractures of the spine and wrist due to osteoporosis.

But changing attitudes and improved technology are brightening the outlook for men with osteoporosis. Although some bone loss is expected as men age, osteoporosis is no longer viewed as an inevitable consequence of aging. Diagnosis and treatment need no longer wait until bones break. New products are becoming available specifically to treat men with osteoporosis.

Bone Life

Bones grow in length and density during a person's younger years. Bone density relates to the mineral content of the tissue. People reach their maximum height during their teens, but bone density continues to increase until about age 30. After that point, bones slowly start to lose density and strength. Throughout life, bone density is affected by heredity, sex hormones, physical activity, diet, lifestyle choices, and the use of certain medications.

In their 50s, men do not experience the rapid loss of bone mass that women have in the years following menopause. "But some men do have a hormonal drop-off in testosterone, with skeletal consequences that are similar to those seen in women following reduction of estrogen," explains Bruce Schneider, a medical officer in the FDA's Division of Metabolic and Endocrine Drug Products. Testosterone may diminish as a result of hypogonadism, a condition marked by decreased function of the testicles. Testosterone levels also may decrease naturally as a man ages. This loss of sex hormone eventually can result in accelerated bone loss. Whether bone loss at this point translates into osteoporosis, however, depends on how much bone a man has when the loss begins, and how quickly he loses it.

By age 65 or 70, men and women lose bone mass at similar rates, and the absorption of calcium, an essential nutrient for bone health throughout life, decreases in both sexes.

Prevention, Diagnosis and Treatment

In men, there are two main types of

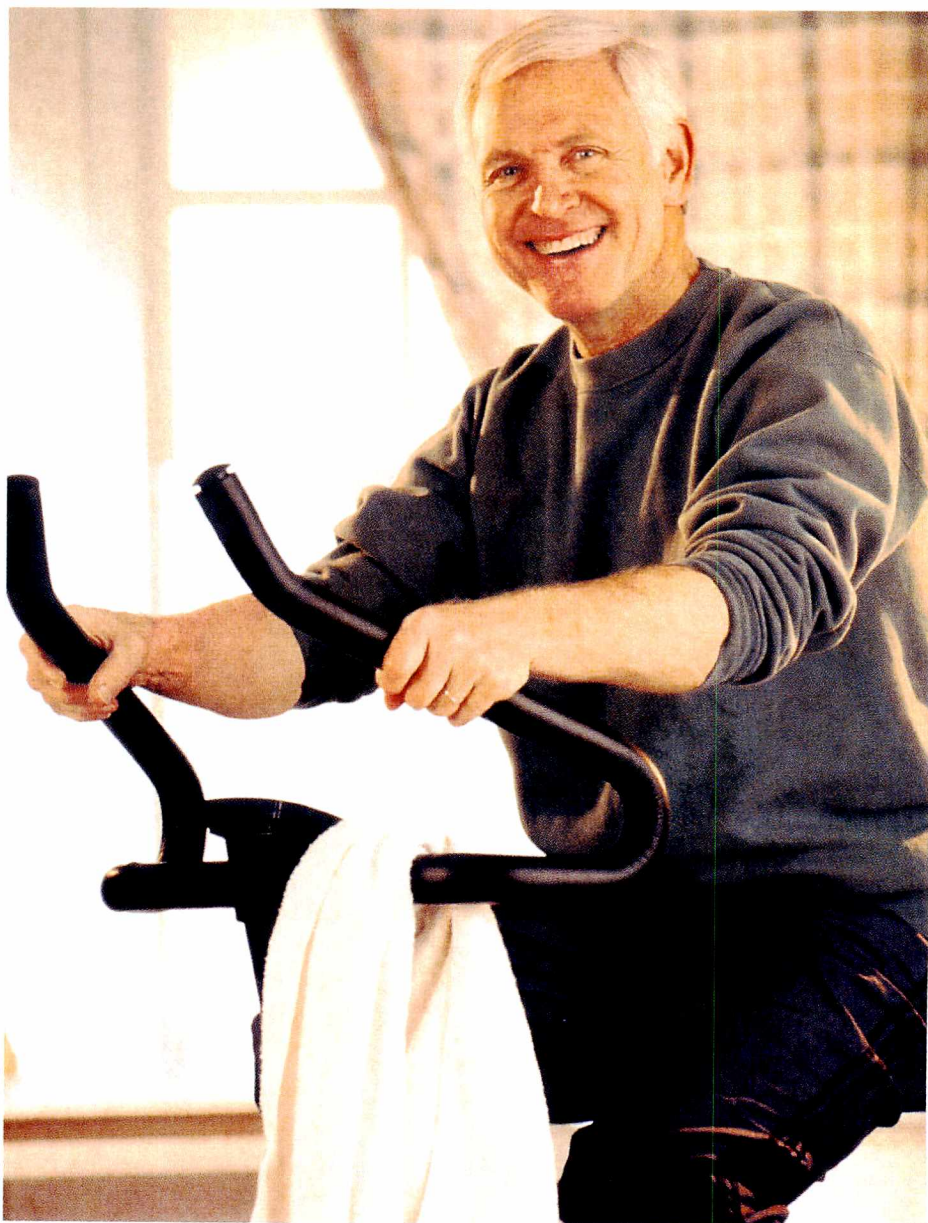
osteoporosis: primary and secondary. In primary osteoporosis, there may be no identifiable cause (idiopathic) or it may be the result of age-related bone loss. Often, these two conditions overlap, and distinguishing between them is arbitrary. Secondary osteoporosis in men can be due to a variety of causes. Low testosterone (hypogonadism), medications such as prednisone that can lead to steroid excess, and alcoholism are among the important causes of secondary osteoporosis in men.

Once bone is lost, it cannot be completely replaced using currently available therapies. Therefore, it is essential that men be evaluated and

treated before significant bone loss has occurred. Building strong bones during childhood and adolescence can be the best defense against developing osteoporosis later.

Although it cannot be cured, osteoporosis can be slowed down, and steps can be taken to help prevent the disease. A special kind of X-ray, the bone mineral density (BMD) test, is a safe, accurate, quick, painless, and noninvasive way to diagnose osteoporosis, detect low bone density, monitor the effectiveness of treatments, and predict the risk for future fractures.

Mone Zaidi, M.D., Ph.D., director of the bone program at the Mount



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Sinai School of Medicine in New York, says that men should get a BMD test if they have a bone fracture, experience lower back pain, or notice height loss.

"If one falls on an outstretched hand, that shouldn't break the wrist," says Zaidi. "If it does, there's a problem."

In 2001, the FDA approved Fosamax (alendronate) to increase bone mass in men with osteoporosis. Fosamax works by reducing the activity of the cells that cause bone loss. The drug was already approved to prevent and treat postmenopausal osteoporosis in women based on studies that indicated it not only increased BMD, but also reduced fractures related to a loss of bone mass. The study in men was designed only to examine the effect on BMD, not on fracture risk. However, it is believed that ultimate fracture benefits are likely to occur in men who experience increases in BMD with treatment, although the relationship between BMD increases and fracture benefits may differ between the genders.

More recently, a novel approach to treating osteoporosis in postmenopausal women and in men with primary or hypogonadal osteoporosis is being investigated. The active portion of human parathyroid hormone (PTH), which regulates normal calcium and phosphate metabolism in bones, has been administered by daily injections and shown to stimulate new bone formation, leading to increased bone mineral density. Postmenopausal women treated with this agent showed a reduction in the incidence of osteoporotic fractures relative to those treated with calcium and vitamin D alone. Like Fosamax, the trial of parathyroid hormone in men was not designed to test the effect of treatment on the risk of fractures. However, based on the study in women, some beneficial effect on fracture risk reduction is likely.

Until Fosamax was approved for men with osteoporosis, the FDA had approved medications only for the prevention and treatment of os-

teoporosis in postmenopausal women and steroid-induced osteoporosis in both men and women. Steroids, a class of compounds that includes prednisone and cortisone, are powerful anti-inflammatory substances that are used to treat many diseases, including rheumatoid arthritis and asthma. Steroids can cause bone to be removed faster than it is formed, and loss of bone density can occur, increasing the risk for osteoporosis and related fractures. Fosamax and Actonel (risedronate) are approved for use by men and women with steroid-induced osteoporosis.

Tailored to the particular reason for bone loss, the treatment plan for men with osteoporosis will include proper nutrition, exercise, and lifestyle modifications for preventing bone loss and, if needed, one of the FDA-approved osteoporosis medications. Doctors may want to monitor bone density and testosterone levels, recommending testosterone replacement as necessary, and may suggest changes to the current steroid dosage if they feel bone loss is due to steroid use. Finally, maintenance of adequate calcium and vitamin D intake is very important in the treatment and prevention of osteoporosis. ■

Risk Factors/Prevention Measures

Factors that increase the risk of osteoporosis include:

- Cigarette smoking
- Excessive alcohol consumption
- Inactive lifestyle
- Advanced age.

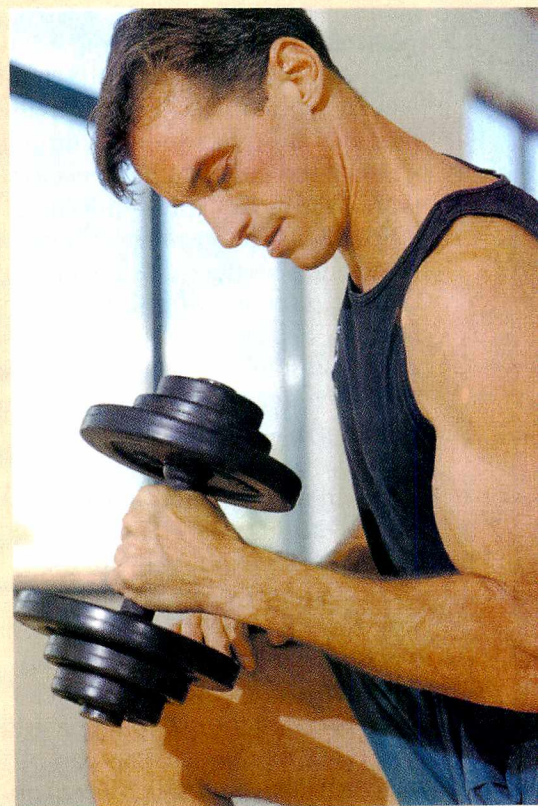
Measures to take to prevent osteoporosis include:

- Don't smoke
- Drink in moderation
- Exercise regularly, especially in weight-bearing activities
- Eat a balanced diet rich in calcium. ■

—C.L.

Osteoporosis: Facts and Figures

- About 1 out of every 2 women and 1 in 8 men over 50 will have an osteoporosis-related fracture in their lifetimes.
- More than 2 million American men suffer from osteoporosis, and millions more are at risk. Each year, 80,000 men suffer a hip fracture, and one-third of these men die within a year, generally as a result of an accompanying illness.



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- Osteoporosis can appear at any age.
- Osteoporosis is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 fractures at other sites.
- Hospitals and nursing homes in the United States spend an estimated \$14 billion each year in direct costs for osteoporosis and related fractures. ■

Source: National Institutes of Health, Osteoporosis and Related Bone Diseases-National Resource Center

Imported Drugs Raise Safety Concerns

By Michelle Meadows

Selene Seguros Rios was 18 months old in 1999 when she received two injections of a pain and fever drug called Neo-Melubrina (dipyrone) in an illegal backroom clinic in Tustin, Calif. That was 20 years after the Food and Drug Administration had banned the drug in the United States because of potentially fatal side effects, including a drop in white blood cells that hampers the body's ability to fight off infections.

Selene died soon after the shots. Her death set off a crackdown in December 2000 on smuggling drugs from Mexico and selling them at swap meets, gift stores, clothing stores, meat markets and other retail establishments in Southern California.

"We've found drugs that were stored in tin containers and car trunks," says Daniel Hancz, Pharm.D., a pharmacist with the Health Authority Law Enforcement Task Force (HALT) in Los Angeles, an organization of police officers and other law enforcement personnel with special training in pharmaceuticals. HALT was launched as part of the crackdown, and task force members have confiscated a variety of prescription drugs being sold illegally.

Experts say the problem mirrors what goes on in nearby Mexico, where easy access to prescription drugs is common. Marv Shepherd, Ph.D., director of the Pharmacoeconomic Center at the University of Texas at Austin, places drugs available in Mexico into two categories. "Plenty of drugs that require a prescription in the United States—like antibiotics, cardiac drugs, and birth control pills—are available over the counter in Mexico," he says. "Then there are controlled substances like Valium, which you do need a prescription for



Black Star/Keith Shelton

Health Authority Law Enforcement Task Force members have seized millions of dollars worth of illegally sold pharmaceuticals, including birth control pills, antibiotics, injectable anesthetics, and pain relievers. (From left to right) Pharmacist Daniel Hancz, Erick Aguilar of the Los Angeles County Health Department, and Steve Opferman and Kay Miller of the Los Angeles County Sheriff's Department.

in Mexico."

The FDA's Office of Criminal Investigations in Los Angeles has teamed with HALT to uncover major black market pharmacy rings selling Spanish-labeled pharmaceuticals. Ring members have been arrested and accused of violating the Federal Food, Drug, and Cosmetic Act (FD&C Act). Local lawmakers have stiffened penalties, and many illegal pharmacies have been shut down. Other drug sellers have taken their businesses underground, moving from storefronts to private homes in an attempt to hide.

As in Selene's case, some criminals have falsely claimed to have a medi-

cal background and not only illegally sold drugs, but administered injections. Hancz says that HALT has seized prescription drugs found mostly in Latino, Asian, and Russian immigrant communities, where some undocumented immigrants, fearing that their immigration status may be discovered, have sought health care in back rooms. The U.S. Attorney's Office in the Central District of California has indicated that legitimate or state-licensed clinics exist where immigrants can be treated safely regardless of immigration status.

The list of safety risks is long, but the principal problems involve the use of prescription drugs without a

With an unapproved drug, you can't be sure that it has been shipped, handled, and stored under conditions that meet U.S. requirements.



U.S. Customs Service/James R. Tourtellotte

Illegal steroids seized from a southern border port.

physician's supervision, and the danger of buying drugs of unknown origin and quality. "I've seen eye medications that look like they're 20 years old," Hancz says. "The drugs could be old, contaminated, or counterfeit. And if you experience some kind of allergic reaction or other side effect, it's hard to trace the problem and treat it."

Whether you're searching for a cheaper price or dodging the doctor's office, the FDA warns against using unapproved drugs. And just because a drug is approved in a foreign country, that doesn't mean it's approved in the United States. Drug standards and regulations vary from country to

country and the FDA is responsible only for those marketed and sold inside the United States.

Joe McCallion, a consumer safety officer in the FDA's Office of Regulatory Affairs, sums it up this way: "If you buy drugs that come from outside the U.S., the FDA doesn't know what you're getting, which means safety can't be assured."

Benefits of a Closed System

Under the FD&C Act, the interstate shipment of any prescription drug that lacks required FDA approval is illegal. Interstate shipment includes importation—bringing drugs from a foreign country into the United

States.

Drugs sold in the United States also must have proper labeling that conforms with the FDA's requirements, and must be made in accordance with good manufacturing practices.

As part of the FDA's high standards, drugs can only be manufactured at plants registered with the agency, whether those facilities are domestic or foreign. If a foreign firm is listed as a manufacturer or supplier of a drug's ingredient on a new drug application, the FDA generally travels to that site to inspect it.

After the FDA approves a drug, manufacturers still are subject to FDA inspections and must continue to

How the FDA Works With the U.S. Customs Service

The exact amount of imported drugs that come into the United States is hard to track, and the high volume makes it impossible to examine them all. In one pilot program last year, the Food and Drug Administration and the U.S. Customs Service examined 1,908 packages of drug products from 19 countries that came through a mail facility in Carson, Calif., during a five-week period.

The FDA estimates that a total of 16,500 packages could have been set aside if there were enough resources to handle them. Of the 1,908 packages, 721 were detained and the addressees were notified that the products appeared to violate the Federal Food, Drug, and Cosmetic Act.

The FDA's enforcement efforts focus on drugs for commercial use, fraudulent drugs, and products that pose an unreasonable health risk.

- If a bag or package arouses suspicion, customs will set it aside and contact the nearest office of the FDA or the Drug Enforcement Agency for advice on whether to release or detain the drug product.
- Even though your bag may not be checked, it is against the law not to properly declare imported medications to customs. Failure to declare products could result in penalties.
- Possession of certain medications without a prescription from a licensed physician may violate federal, state, and local laws.
- Prescription drugs should be stored in their original containers, and you should have a copy of your doctor's prescription or letter of instruction.
- If a drug is detained, the FDA is required by law to send you a written notice asking whether you can show that the product meets legal requirements. If you can't, the drug could be destroyed or returned to the sender.

For more information about the U.S. Customs Service, visit the agency's Web site, www.customs.ustras.gov. ■

—M.M.

comply with good manufacturing practices. "With an unapproved drug, you can't be sure that it has been shipped, handled, and stored under conditions that meet U.S. requirements," McCallion says.

Along with legal requirements on manufacturing, U.S. pharmacists and wholesalers must be licensed or authorized in the states where they operate, and limits on how drugs can be distributed lessen the likelihood that counterfeit or poor quality drugs will turn up. It's because of such safeguards that the process of getting drugs onto U.S. pharmacy shelves is commonly referred to as a "closed" distribution system.

Counterfeit drugs—phony replicas of pharmaceuticals—can surface anywhere. Historically, they have been more common in foreign countries than in the United States. And while the Internet has given customers the convenience of buying drugs from the privacy of their own homes, it's also opened up windows for crooks to crawl through.

In an investigation that ended in the indictment of seven people and five companies in the spring of 2002, undercover agents in the Manhattan District Attorney's Office in New York bought more than 25,000 counterfeit Viagra pills. They pretended to sell the impotence pills and uncovered four supply streams from China and India.

Some of the little blue pills arrived in the mail stuffed inside a teddy bear and stereo speakers. The exporters used a machine to punch the pills with Pfizer's logo, and intermediaries sold the pills over the Internet to brokers and consumers.

In this case, all the counterfeit pills tested had some of Viagra's active ingredient (sildenafil citrate) with varying potency, according to Barbara Thompson, a spokeswoman for the Manhattan District Attorney's Office. With fake drugs, "you could be getting some of an active ingredient or you could be getting nothing at all," she says.

That's what happened with a batch of Viagra worth \$150,000 that HALT recently seized from Los Angeles gift shops. "It looked perfect," says Hancz.

"But there was nothing there—just lactose, dye, and other filling agents."

Limits on Re-Importation

The FD&C Act also states that prescription drugs made in the United States and exported to a foreign country can only be re-imported by the drug's original manufacturer. Even when original manufacturers re-import drugs, the drugs must be real, properly handled, and relabeled for sale in the United States if necessary.

The Medicine Equity and Drug Safety Act (MEDS), enacted in 2000, would have allowed prescription drugs manufactured in the United States and exported to certain foreign countries to be re-imported from those countries for sale to American consumers. Supporters of the bill hoped that lower drug pricing in other countries would be passed along to consumers. But Health and Human Services Secretary Tommy G. Thompson responded by saying that, while he believed strongly in access to affordable drugs, he could not implement the act because it would sacrifice public safety by opening up the closed distribution system in the United States.

Though the law was enacted in 2000, before the bill can take effect, one provision requires that the HHS secretary determine whether adequate safety could be maintained and whether costs could be reduced significantly. Both Thompson and his predecessor, Donna Shalala, concluded that these conditions could not be guaranteed.

"Once an FDA-approved prescription drug is exported for sale in another country, it is no longer subject to U.S. requirements and it can no longer be monitored by U.S. regulators," Thompson wrote in a letter to Sen. James Jeffords (I-Vt.), one of the bill's sponsors. "In addition, it may not have the U.S.-approved labeling. Instead it may have labeling for the country to which it is exported."

Guidance on Personal Use

Although importing unapproved prescription drugs is illegal, the FDA's guidance on importing prescription drugs for personal use recognizes that there may be circumstances in which

the FDA can exercise discretion to not take action against the illegal importation.

The personal use guidance was first adopted in 1954, and it was modified in 1988 in response to concerns that certain AIDS treatments were not available in the United States. The guidance allows individuals with serious conditions, such as a rare form of cancer, to get treatments that are legally available in foreign countries but are not approved in the United States.

The current policy is not a law or a regulation, but serves as guidance for FDA personnel. The importation of certain unapproved prescription medication for personal use may be allowed in some circumstances if all of these factors apply:

- If the intended use is for a serious condition for which effective treatment may not be available domestically.
- If the product is not considered to represent an unreasonable risk.

- If the individual seeking to import the drug affirms in writing that it is for the patient's own use and provides the name and address of the U.S.-licensed doctor responsible for his or her treatment with the drug or provides evidence that the drug is for continuation of a treatment begun in a foreign country.

- If the product is for personal use and is a three-month supply or less and not for resale. Larger amounts would lend themselves to commercialization.

- If there is no known commercialization or promotion to U.S. residents by those involved in distribution of the product.

"While we can appreciate the cost issue, saving money on prescription drugs isn't one of the circumstances," says the FDA's McCallion. "The guidance doesn't condone the use of buying foreign-made versions of drugs available in the United States, even if they are sold under the same name," he says. "They are still unapproved products."

That means if you buy your high blood pressure or other medication from a foreign country because it's cheaper—even though a drug with the same name is approved for sale in the United States—generally the drug will be considered unapproved and the FDA's personal use guidance will not apply. The Drug Enforcement Administration has additional requirements for controlled drugs.

The Same Goes for Canada

Neena Quirion, director of the Maine Council of Senior Citizens in Augusta, has organized bus trips to Canada for her members and estimates that 25 seniors collectively saved about \$19,000 on an overnight trip in March. "Paying for drugs is a real hardship for so many people," she says. "One lady takes about 15 different medications."

Quirion says they've obtained prescriptions from a doctor who is licensed to practice medicine in both



U.S. Customs Service/James R. Tourtellotte

A U.S. Customs Canine Enforcement Team inspects arriving international mail for illegal pharmaceuticals purchased over the Internet at Dulles International Airport outside of Washington, D.C.

Potential Health Risks With Imported Drugs

- **Quality assurance concerns.** Medications that have not been approved for sale in the United States may not have been manufactured under quality assurance procedures designed to produce a safe and effective product.
- **Counterfeit potential.** Some imported medications—even those that bear the name of a U.S.-approved product—may, in fact, be counterfeit versions that are unsafe or even completely ineffective.
- **Presence of untested substances.** Imported medications and their ingredients, although legal in foreign countries, may not have been evaluated for safety and effectiveness in the United States. These products may be addictive or contain other dangerous substances.
- **Risks of unsupervised use.** Some medications, whether imported or not, are unsafe when taken without adequate medical supervision. You may need a medical evaluation to ensure that the medication is appropriate for you and your condition. Or, you may require medical checkups to make sure that you are taking the drug properly, it is working for you and that you are not having unexpected or life-threatening side effects.
- **Labeling and language issues.** The medication's label, including instructions for use and possible side effects, may be in a language you do not understand or may make medical claims and suggest specific uses that have not been adequately evaluated for safety and effectiveness.
- **Lack of information.** An imported medication may lack information that would permit you to be promptly and correctly treated for a dangerous side effect caused by the drug. ■

—M.M.

Maine and Canada and who performs a physical examination on each person before writing prescriptions. "Our feeling is that the quality of the drugs is the same," she says. "Everything's very regulated in Canada."

Greg Thompson, Pharm.D, a pharmacy professor at the University of Southern California, agrees. "Getting drugs from Canada under the doctor's orders is different than getting drugs from Mexico on your own," he says. "Regulations in Mexico aren't as strict."

But even if you obtain drugs from a place or in a manner that you consider to be safe, according to the FDA, you are almost always obtaining unapproved drugs. "The law applies evenly to all countries outside of FDA's jurisdiction," says Thomas McGinnis, Pharm.D, director of pharmacy affairs in the FDA's Office of Policy, Planning, and Legislation.

So what about the belief often mentioned in the media that drugs sold in Canada are exactly the same as drugs sold in the United States—made in the exact same manufacturing plants? Some

may be, and some may not. For example, drugs sold and distributed in Canada by Eli Lilly Canada come from the company's manufacturing facilities throughout the world—the United States, Europe, Asia, and South America.

Manufacturing facilities that make drugs for Canadians have been approved and registered by Health Canada's Health Products and Food Branch, the federal agency responsible for regulating drugs sold in Canada. This agency is responsible for approving the product labeling, which must be made available in Canada's two official languages, English and French.

But the FDA does not have authority to approve drugs sold in Canada. And if a Canadian company is selling drugs only for export to the United States, and not to Canadian citizens, Health Canada may not regulate the drugs or the company at all. Drugs coming to the United States from Canada may be coming from some other country and simply passing through Canada. The drugs could also be counterfeit, con-



Black Star/Keith Shelton

Some imported medications may be unsafe or ineffective counterfeit versions. The Health Authority Law Enforcement Task Force in Los Angeles seized counterfeit Viagra that looked perfect, but turned out to contain only filling agents.

taminated, or subpotent, among other things (see "Potential Health Risks With Imported Drugs," page 22).

FDA experts say it would be hard for you to know whether drugs sold outside of the United States meet FDA standards and have been manufactured in a plant listed on an FDA-approved new drug application. "Even if you did know," McCallion says, "existing law requires you to prove it. The burden is on the importer to prove that the drug meets legal requirements—that includes having an FDA-approved label in English." The fact also remains that a drug made in this country can only be re-imported back into this country by the original manufacturer, he adds.

Barbara Wells, executive director of the National Association of Pharmacy Regulatory Authorities (NAPRA) in Ontario, Canada, says the practice of U.S. residents filling prescriptions in Canada is an issue that her organization is concerned about. "Our members do not feel that Canadian pharmacists should be breaking laws of jurisdictions

in which their patients reside," she says.

Internet Challenges

When it comes to buying prescription drugs online, Canada is dealing with some of the same regulatory challenges that occur in the United States. In May, the Ontario College of Pharmacists announced that it laid charges against The Canadian Drug Store Inc. for operating an illegal Internet pharmacy based in Toronto. The store, which was filling prescriptions written by U.S. doctors for U.S. residents, was charged along with one of its directors with unlawfully operating an unaccredited pharmacy without registered pharmacists.

NAPRA has signed an agreement with the National Association of Boards of Pharmacy (NABP) in the United States, and recently developed a program in Canada modeled after the NABP's Verified Internet Pharmacy Practices Site (VIPPS), a voluntary certification program.

A VIPPS seal of approval indicates that an online pharmacy complies with

state licensing and inspection requirements, along with other VIPPS criteria dealing with such areas as patient rights to privacy and authentication of orders.

NABP developed the service in 1999 after consumers complained to state pharmacy boards about rogue sites posing as legitimate pharmacies. Sites can pop up overnight and disappear just as quickly, and there is little the U.S. government can do if you get swindled. The FDA suggests you steer clear of foreign Web sites. If you buy medicine from a domestic site, remember that the legitimate ones require a valid prescription.

The FDA sends warning letters over the Internet to suspicious sites. About 30 percent of Internet sites that receive the FDA's letters stop their illegal activity. The FDA also sends copies of the letters to the home governments of the Web sites when the locations can be identified.

"We seek out the cooperation of foreign governments because we have limited reach in a foreign land," says David Horowitz, director of the Office of Compliance for the FDA's Center for Drug Evaluation and Research. "That is one of the major challenges of Internet enforcement." ■



FDA/Zebulon Rogerson

Thomas McGinnis, Pharm.D., reviews the FDA's testimony on importing drugs for a Congressional hearing as part of his duties as director of pharmacy affairs in the FDA's Office of Policy, Planning, and Legislation.

Resources: Buying Drugs Online

Buying Prescription
Medicines Online: A Con-
sumer Safety Guide
[www.fda.gov/cder/drug/
consumer/buyonline/
guide.htm](http://www.fda.gov/cder/drug/consumer/buyonline/guide.htm)

Verified Internet Phar-
macy Practices Sites
(VIPPS)
National Association of
Boards of Pharmacy
www.nabp.net/VIPPS/
1-847-698-6227 ■

Generic Drugs: What You Need to Know

When the pain reliever acetaminophen was developed in the 1950s, it was only available under its brand name, Tylenol. Today, acetaminophen can be found in many generic and store-brand versions. Similarly, many drug products, prescription and over-the-counter, have generic versions available. An estimated 44 percent of all prescriptions in the United States are filled with generic drugs.

New drugs are developed by innovator firms. Patents protect these companies' investments by giving them the sole right to sell the drug while the patents are in effect. When patents or other periods of exclusive marketing for brand-name drugs are near expiration, manufacturers can apply to the Food and Drug Administration to sell generic versions.

The law that allows approval of generic products, the Drug Price Competition and Patent Term Restoration Act of 1984, builds in certain protections for the original drug developer (including patents and marketing exclusivities), but also allows drug sponsors of identical products to apply for FDA approval without repeating the original developer's clinical trials. The law also encourages generic firms to challenge innovator patents by awarding marketing exclusivity to the first generic version challenger.

Generic drugs are safe, effective and FDA-approved. According to Gary Buehler, M.D., director of the FDA's Office of Generic Drugs, "People can use them with total confidence."

Here are some frequently asked questions about generic drugs and answers from the FDA:

Q: What are generic drugs?

A: A generic drug is a copy that is the same as a brand-name drug in dosage, safety, and strength, how it is taken,

quality, performance, and intended use.

Q: Are generic drugs as safe as brand-name drugs?

A: Yes. The FDA requires that all drugs be safe and effective. Since generics use the same active ingredients and are shown to work the same way in the body, they have the same risks and benefits as their brand-name counterparts.

Q: Are generic drugs as strong as brand-name drugs?

A: Yes. The FDA requires generic drugs to have the same quality, strength, purity and stability as brand-name drugs.

Q: Do generic drugs take longer to work in the body?

A: No. Generic drugs work in the same way and in the same amount of time as brand-name drugs.

Q: Why are generic drugs less expensive?

A: Generic drugs are less expensive because generic manufacturers don't have the investment costs of the developer of a new drug. New drugs are developed under patent protection. The patent protects the investment—including research, development, marketing, and promotion—by giving the company the sole right to sell the drug while it is in effect. As patents near expiration, other manufacturers can apply to the FDA to sell generic versions. Because those manufacturers don't have the same development costs, they can sell their product at substantial discounts. Also, once generic drugs are approved, there is greater competition, which keeps the price down. Today, almost half of all prescriptions are filled with generic drugs.

Q: Are brand-name drugs made in more modern facilities than generic drugs?

A: No. Both brand-name and generic drug facilities must meet the same standards of good manufacturing practices. The FDA won't permit drugs to be made in substandard facilities. The FDA conducts 3,500 inspections a year to ensure standards are met. Generic firms have facilities comparable to those of brand-name firms. In fact, brand-name firms are linked to an estimated 50 percent of generic drug production. They frequently make copies of their own or other brand-name drugs but sell them without the brand name.

Q: If brand-name drugs and generics have the same active ingredients, why do they look different?

A: In the United States, trademark laws do not allow a generic drug to look exactly like the brand-name drug. However, a generic drug must duplicate the active ingredient. Colors, flavors, and certain other inactive ingredients may be different.

Q: Does every brand-name drug have a generic counterpart?

A: No. Brand-name drugs are generally given patent protection for 20 years from the date of submission of the patent. This provides protection for the innovator who laid out the initial costs (including research, development, and marketing expenses) to develop the new drug. However, when the patent expires, other drug companies can introduce competitive generic versions, but only after they have been thoroughly tested by the manufacturer and approved by the FDA.

Q: What is the best source of information about generic drugs?

A: Contact your physician, pharmacist, or insurance company for information on your generic drugs. Also, visit the FDA Web site at www.fda.gov/cder/ogd/. ■

Food Freshness and 'Smart' Packaging

By Carol Lewis

JEFFERSON, Ark. — What could a roll of new carpeting possibly have in common with a slab of smelly, old salmon? They both emit chemically similar vapors—the carpet, as it's being installed; the fish, as it rots.

Chemists here at the Food and Drug Administration's National Center for Toxicological Research (NCTR) have identified "volatile amines" not only as the toxic connection between two seemingly unrelated products, but ultimately as a potential link to determining at what point a food product begins to deteriorate.

Food freshness is a key characteristic of overall food quality. And overall food quality is the result of all the desirable characteristics that make food acceptable to eat. Therefore, being able to tell when food is fresh is vitally important, at home, in a grocery store, or when dining out.

Seafood, for example, is one of the most difficult foods to keep fresh. Millions of bacteria are present on the surface, on the gills, and in the gut of virtually all seafood species. If you know when and where the fish was caught, you might be able to make an educated guess as to its freshness, provided that it's been properly stored. Inspecting the fish for color, resilience and sliminess would help. So might a check of its eyes to determine clarity and sheen. But in the end your nose might determine whether or not you buy the fish. If you're trying to determine whether to buy a piece of fish tightly wrapped in plastic and sitting on a Styrofoam tray, however, the decision might be more difficult.

The freshness and overall quality of



PhotoDisc

food depend, in large part, on the distribution and marketing systems. Any mishandling of a food along the way can have a significant impact on its overall quality. To further ensure that food retains its high quality, consumers must practice careful food storage and handling habits at home, as well.

New technologies are emerging that aim to monitor temperature and

other important variables that play critical roles in determining food freshness. It is hoped that such technologies will be useful in evaluating freshness during the movement of food from producer to supplier to consumers.

How Food Quality Deteriorates

A walk through any grocery store indicates the diversity of today's food

Food Preservation

All foods eventually spoil if not preserved. The basic idea behind the different forms of food preservation is either to slow down the activity of bacteria, or to kill the bacteria altogether. In certain cases, a preservation technique also may destroy enzymes naturally found in a food that cause it to spoil or discolor quickly. Some of the most common methods for preserving foods are:

- **Refrigeration and freezing:**

Slows bacterial action so that it takes food much longer (a week or two, rather than half a day) to spoil, or stops bacterial action altogether. Once a product is thawed, however, the bacteria can become active again, multiplying under the right conditions. Enzyme activity is slowed down but not stopped during freezing.

- **Canning:** Provides a way to store foods for extremely long periods of time. Food is first boiled to destroy bacteria and inactivate enzymes. It is then placed in an airtight container. As the food cools, a vacuum seal is formed that prevents any new bacteria from getting in. Since the food in the container is completely sterile, it does not spoil. Once the container is opened, however, bacteria enter and begin growing in the food. Any unused portions then must be refrigerated.

- **Drying (dehydration):** Removes most of the moisture from foods. This method kills or completely inactivates bacteria. Dried foods should be stored in airtight containers. This process may alter the taste and texture of some foods, but in many cases, a new and better taste has been created. Examples are powdered milk, potatoes in a box, dried fruits and vegetables, pasta, and rice.

- **Irradiation:** Exposes certain types of foods to a source of ionizing energy. Unlike canning, the taste is not altered when food is irradiated.

supply—raw vegetables, baked goods, packaged meats, seafood, and more. The selection is a chef's delight. But that diversity also contributes to the challenges of ensuring that food is healthful and wholesome. Delight can become disappointment if undesirable changes in color, flavor, odor, or texture occur. For the most part, this deterioration is caused by enzymes—either contained within the food or produced by microorganisms, such as bacteria, yeasts and molds growing in the food.

Each food type and bacterium produce different chemicals or classes of chemicals. The chemicals produced vary and include volatile bases, volatile acids, volatile aldehydes, and volatile mercaptans, or sulfur compounds.

Spoilage bacteria (rather than disease-causing "pathogenic" bacteria) usually cause food to deteriorate most quickly because of their short reproduction times. They multiply very rapidly by a process called cell replication or binary fission—one cell divides and becomes two. If conditions such as moisture and temperature are right, for example, certain bacteria can reproduce in as little as 20 minutes. Within 20 minutes, one cell can become two; in 40 minutes, there would be four, and so on. The bacteria are slow to start, but the number increases quickly.

Some bacteria need only about four hours to adapt to a new environment before they begin rapid growth and threaten the window of time that a food item maintains its taste, texture, and nutritional value, known as shelf life. When it comes to food, this means consumers can have less than four hours to make a decision about whether to cool it, heat it, or eat it.

As the bacteria grow, the amount of enzymes produced by those bacteria increases. Enzymes are a normal component of food that help speed up or slow down chemical reactions. The enzymes in a banana, for example, cause it to change color from green to yellow, and then brown to black, as it matures. The ripening and softening of other fruits, such as peaches, toma-

toes and apples, are other examples of enzyme action. Heat inactivates these enzymes, which explains why people might blanch vegetables. Cold temperatures also can inactivate enzymes, which is why you would refrigerate certain foods.

In addition, food may deteriorate as a result of chemical changes within the food itself or, more broadly, from temperature abuse.

"The odor that everyone associates with bad food is rancidity," says Dwight Miller, Ph.D., a chemist at NCTR. Rancidity, also called staleness, is caused by a chemical reaction that breaks down the molecular chains that make up fatty acids in fat to compounds called aldehydes, and may continue to smaller-sized fatty acids, resulting in the release of offensive or musty odors. So, as butter ages, it tastes stronger, just as peanuts become rancid with time.

In some cases, food deterioration may occur before flavor or odor changes are detectable. And because everyone doesn't have the same level of odor-detecting ability, Miller points out, "the untrained nose is not consistent."

A smoker, or even a woman wearing perfume, for example, can temporarily have a reduced ability to smell some odors. That's why, according to Miller, "We have to have a way that consumers can be taught to protect themselves from food that's gone—or is going—bad."

The numbers of microorganisms or enzymes present on a food product determine the degree of food spoilage. Since we cannot see them to count the number growing in our food, next to our untrained noses, we must rely on distributors, manufacturers, and grocers to provide us with some assurance that the products we purchase are fresh.

How Reliable is Current Technology?

Product dating is the most widely used means for consumers to determine when to purchase or use a food product at its best quality. Dates stamped on packages also help the

store determine how long to display the product for sale. But according to the United States Department of Agriculture (USDA), these dates are not safety dates. Instead, they should be seen as more of a good-faith promise of freshness.

There is no uniform or universally accepted system of food dating in the United States. There are areas where much of the food supply has some type of readily understood calendar date (open dating), rather than a code understood only by the manufacturer and others in the industry (closed dating). Although dating of some foods is required by more than 20 states, in some areas of the country, almost no food products are dated. Except for infant formula and some baby foods, which are regulated by the FDA, product dating is not required by federal regulations.

Open dating is found primarily on perishable foods, such as meat, poultry, eggs, and dairy products. There is no regulation requiring meat products to have a calendar date, but manufacturers sometimes choose to use it voluntarily. The USDA says that if a federally inspected establishment has voluntarily placed a calendar date on meat products, some rules will apply. For example, such a date cannot be removed or changed by a retailer while the product remains in its original packaging.

Whenever a calendar date is used on meats, poultry, and eggs, the USDA also requires that it must express both the month and day of the month. The year is included on products that may be stored for longer times, such as those that are frozen. If a calendar date is shown, a "sell by" or "use before" phrase must accompany that date. (See "The Facts About Food Product Dating," page 29.)

Closed or coded dating might appear on shelf-stable products, such as canned or boxed foods. Since product dating is not used consistently on food products, this practice often confuses or misleads consumers.

A recent report on NBC's "Date-line" uncovered the questionable practice by several national grocery



Black Star/Willie Allen

Dwight Miller, Ph.D., a chemist at the FDA's National Center for Toxicological Research in Jefferson, Ark., checks the color of the dye used in a food quality indicator developed at the center to indicate the freshness of packaged foods.



Black Star/Willie Allen

Miller tests for hydroperoxides in foods, an early indicator of decomposition.

chains of extending sell-by dates on meat products. At one store, the NBC team found that labels bearing a March sell-by date were strategically placed on hams to cover up the original January sell-by date. As a result, thirty-eight days had been added to the original sell-by date. In addition, a test indicated that the hams contained six times the expected bacterial count as a result of the extended time spent on the shelf.

The take-home message? According to "Dateline": Even the sell-by promise is not always a guarantee of food freshness.

The Coming of New Technology

Dwight Miller and two other scientists at the NCTR lab, Jon Wilkes, Ph.D., and Shannon Snellings, Ph.D., used information they learned from the volatile amines detection system to develop a simple but effective way to monitor food freshness. The results? Tiny disks called "food quality indicators" that do what date stamps can't—sense the production of vola-

tile amines. Specifically, they detect the level of amines given off by certain types of seafood, such as shrimp and most types of shellfish and finfish, an indicator of the degree of decomposition.

NCTR Director Daniel A. Casciano, Ph.D., says the concept behind the food quality indicators stemmed from research already being conducted on new carpeting at the lab. The Arkansas facility routinely tests and evaluates not only the safety and hazards of food color additives, drugs, cosmetic chemicals, and other compounds within the FDA's regulatory purview, but also pesticides, airborne contaminants, plastics, synthetic fibers, industrial compounds, and more, as needed by other government agencies.

"Dwight was asked by the Consumer Product Safety Commission (CPSC) to help them identify the vapors that were coming off of new rugs," recalls Casciano. As certain building materials slowly evaporate and break down, they also release

chemicals. There are over 120 different toxic chemicals that may be emitted by carpeting, including formaldehyde, which is used as glue in carpet backing.

"After succeeding in this endeavor," says Casciano, "he theorized that the physical characteristics of the molecules in the new carpeting were similar to those in spoiled fish." Miller explains that the odor from both the carpet and the fish is known as a "volatile," a material that at normal temperatures or under the influence of heat is capable of being vaporized or becoming a gas. "If you can smell the odors," says Miller, "they're in the gas phase."

Casciano says that Miller shrunk the original desk-size analytical detection device used to test the carpet vapors down to what is now a quarter-sized food quality indicator designed to be inserted into food packaging.

The technology behind the disk is based on a dye locked in a water-repellent material and used as a dot-shaped chemical indicator that changes color as a seafood product decomposes. As the gases from the seafood move through the dot and intermingle with the chemicals, a gradual color change is produced in the disk when a sufficient level of the chemical is present.

At the supermarket, food quality indicators and other products using similar technologies would allow consumers to make rapid and informed decisions on food quality.

But Susan Ferenc, Ph.D., senior scientific adviser to the Grocery Manufacturers of America, a trade association in Washington, D.C., is somewhat skeptical.

"Unless it is very clear as to what these disks indicate," she says, "my thinking is that consumers are going to be a bit cautious—and should be, especially given the number of false positives or false negatives that could come with the technology."

At the regulatory level, Miller says that insertion of these indicators in fish products at the point of origin (during processing and packaging) could help FDA inspectors rapidly identify fish products that have



NCTR/Dwight Miller

This plastic-wrapped package of shrimp was bought at a grocery store and kept in a freezer for two days. The shrimp then were thawed in a refrigerator for 56 hours. The food quality indicator on the left was inserted into the package after thawing. Chemical gases in the package caused the indicator to change from yellow to blue in less than an hour, indicating that the shrimp were no longer fresh. The disk on the right was placed outside the package to show the indicator's color in fresh food.

Here's How Long Some Popular Foods Should Be Kept

PRODUCT	STORAGE PERIOD	
	In Refrigerator	In Freezer
Fresh Meat		
Beef:		
Ground	1-2 days	3-4 months
Steaks and roasts	3-5 days	6-12 months
Pork:		
Chops	3-5 days	4-6 months
Ground	1-2 days	3-4 months
Roasts	3-5 days	4-6 months
Fish:		
Lean (such as cod, flounder, haddock)	1-2 days	up to 6 months
Fatty (such as blue, perch, salmon)	1-2 days	2-3 months
Chicken:		
Whole	1-2 days	12 months
Parts	1-2 days	9 months
Giblets	1-2 days	3-4 months
Cured meats		
Lunch meat	3-5 days	1-2 months
Sausage	1-2 days	1-2 months
Gravy	1-2 days	2-3 months
Dairy Products		
Swiss, brick, processed cheese	3-4 weeks	*
Milk	5 days	1 month
Ice cream, ice milk	—	2-4 months
Eggs:		
Fresh in shell	3 weeks	—
Hard-boiled	1 week	—

* Cheese can be frozen, but freezing will affect the texture and taste.

Sources: Food Marketing Institute for fish and dairy products, USDA for all other foods.

The Facts About Food Product Dating

Food product dating tells people certain information about specific foods, but there is no uniform or universally accepted dating system in the United States. Except for infant formula and some baby foods, product dating is not required by federal regulations. The following definitions should help you understand the dates that are voluntarily printed on various food products:

- **"sell by":** Tells the store how long to display the product for sale. Consumers should not buy the product after this date.
- **"best if used by" (or "before"):** Tells consumers how long the product will retain its best flavor or quality. (This is not a purchase or safety date!)
- **"use by":** Tells consumers the last date that is recommended for using the product while at peak quality. The manufacturer determines this date.
- **"closed or coded":** Represents packing numbers for use by the manufacturer to track inventory, rotate stock, or locate the product under suspicion of a problem. These dates do not indicate freshness or quality of the product.

Source: Food Safety and Inspection Service
United States Department of Agriculture

deteriorated beyond acceptable limits, helping to speed inspections.

The freshness detector system is being tested on shrimp in Canada and the results are very promising, with consumer use expected to follow. But, says Miller, "Since some foods don't decompose by the same mechanisms, the technology still has a way to go." As various toxins become characteristic of one product and then another, the idea will continue to be refined

and adapted. Variations are being developed to monitor the freshness of poultry, meats, carbohydrates, and powdered baby formula.

All the new technologies in the world won't make a difference, says Ferenc, if other tried-and-true measures aren't routinely practiced. In short, regardless of technology, consumers need to choose food products carefully and handle and serve those products with care at home. ■

Treating Minor Species:

A Major Animal Health Concern

By Linda Bren

Each October, when the mountain wind begins to carry a hint of winter chill, Lyle Johnston of Rocky Ford, Colo., loads hundreds of wooden boxes containing a special cargo onto flatbed trucks. He wants those trucks and their valuable cargo—30 million honeybees per truck—to be well down the road and on their way to California before the season's wintry blasts sweep through the Rockies.

The bees are destined to be put to work pollinating the almond fields of California, the source of more than half of the world's almonds. Johnston relies on the almond industry, and the almond industry relies on him and his fellow beekeepers. "Without the bees, the growers get only 300 to 400 pounds of almonds per acre," says Johnston. "With good hives, they get 2,200 to 2,800 pounds per acre."

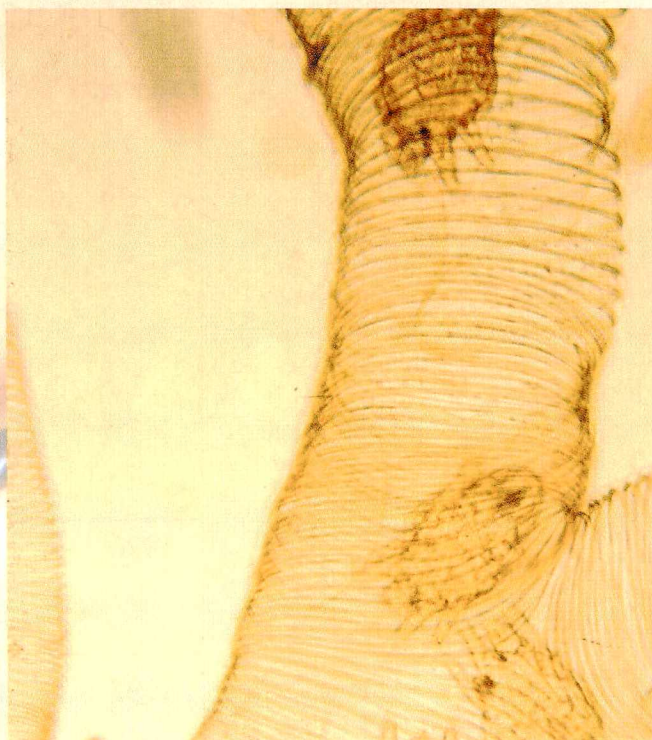
American farmers rent honeybees to pollinate almonds, apples, melons, and more than a dozen other crops, raising the value of agricultural production by more than \$14 billion per year, say entomologists at Cornell University.

Even so, the honeybee industry is dwindling. "It's a tough game right now," says Johnston, a third-generation beekeeper whose grandfather started the business in 1908. Bees are declining in number, largely because of the destructive efficiency of parasitic mites and American foulbrood, a bacterial disease that infects the young bee larvae and is killing off bee colonies across the nation.

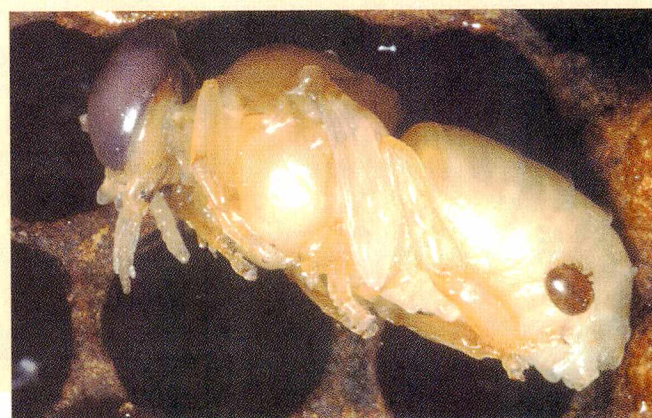
Photos courtesy of the USDA Agricultural Research Service



Blood-sucking Varroa mites cause honeybees to become sick and deformed, killing off entire hives over time.



Microscopic tracheal mites clog the windpipes of adult honeybees, causing death by suffocation and blood loss.



Varroa mites attack both the adult bee (left) and the developing larva or pupa (above).

Currently, there are no drugs approved by the Food and Drug Administration to treat the blood-sucking Varroa mites or the suffocating tracheal mites, and the one FDA-approved drug to treat American foulbrood is more than 40 years old. "Consequently, the bacteria have become resistant to treatment across large parts of the United States," says Mark Feldlaufer, Ph.D., research leader at the U.S. Department of Agriculture's (USDA) Bee Research Laboratory in Beltsville, Md.

But through the efforts of the Beltsville Bee Research Lab, the FDA, and a national research program called the USDA Minor Use Animal Drug Program, two more antibiotics to treat foulbrood may soon be available, and studies of a drug to treat Varroa mites will soon begin.

Despite their importance to agriculture, bees are considered a "minor species," and drugs to treat them are included in a category known as "minor use" drugs. There are few FDA-approved drugs available for minor use, but efforts to increase their number are being pursued on two fronts: through new legislation and through research partnerships. These partnerships among government agencies, minor species animal interest groups, universities, public hatcheries, and pharmaceutical companies are producing the data needed to support drug approvals.

A minor species is any animal species other than cattle, horses, pigs, chickens, turkeys, dogs, and cats, which are classified as major species.

Minor species include a wide variety of land animals such as sheep, goats, game birds, deer and elk, bison, emus, ostriches, rabbits, free-ranging wildlife, and zoo animals. They also include birds, ferrets, guinea pigs, and reptiles that are kept as pets. Aquatic animals, such as finfish, turtles, crustaceans, and mollusks, also qualify as minor species.

In addition to treating minor species, minor use drugs can also refer to those used in a major species to control a disease that occurs infrequently or in limited geographic areas. An ex-

ample of a minor use in a major species is a drug to treat the parasitic infection babesiosis in dairy cattle in tropical regions of the United States.

The MUMS Bill

Only one or two drugs a year, on average, are approved for minor species, says Meg Oeller, D.V.M., the FDA's liaison to the USDA Minor Use Animal Drug Program. "It's a small number compared to the need."

But this number could increase with passage of the Minor Use and Minor Species Animal Health Act, known as the MUMS bill. In response to a con-

gressional mandate under the 1996 Animal Drug Availability Act, the FDA proposed legislative and regulatory changes to improve the availability of drugs for minor uses. Building upon these FDA proposals and with the FDA's technical assistance, a coalition of animal health groups drafted the MUMS bill.

The bill would create a program similar to the FDA's human orphan drug program, which has dramatically increased the availability of drugs to treat rare human diseases. The human program encourages drug companies to seek approval of drugs for rare hu-

Minor Use and Minor Species Animal Health Act Legislative and Regulatory History



1996	Congress passes Animal Drug Availability Act (ADAA) that requires the FDA to propose ways to improve the availability of drugs for minor uses and minor species
1997	The FDA seeks public comment on documents including "Discussion Draft: Proposals to Increase the Availability of Approved Animal Drugs for Minor Species and Minor Uses"
1998	The FDA concludes federal statutes should be amended in report "Proposals to Increase the Legal Availability of Animal Drugs for Minor Species and Minor Uses"
1999-2000	MUMS Coalition established; uses FDA proposals and technical assistance to develop draft legislation
2001	The Minor Use and Minor Species Animal Health Act is introduced in Congress, but doesn't pass
2002	The Minor Use and Minor Species Animal Health Act is reintroduced in Congress

Source: American Veterinary Medical Association

Infographic by Renée Gordon

man diseases and conditions by offering companies help with study design and by giving financial incentives, such as tax relief, grants, and extended periods of marketing exclusivity. Similar incentives might encourage animal drug developers.

The MUMS bill also would provide the FDA some options such as conditional approval when reviewing drugs for minor uses. However, "The bill does not circumvent the need for public health and animal safety standards to be met," says Randy MacMillan, Ph.D., chairman of the MUMS Coalition and president of the National Aquaculture Association. "It would still have the mechanisms in place to address antibiotic resistance concerns, public safety concerns, and environmental concerns."

The MUMS bill was introduced in Congress in 2001 and again in 2002. "We continue to work with ... congressional people to get the MUMS bill passed as expeditiously as possible," says MacMillan.

Cooperative Research

Drugs to treat minor species used in agriculture are getting a boost from the Minor Use Animal Drug Program. This USDA program, officially known as National Research Support Project No. 7 (NRSP-7), funds and oversees many of the costly studies required to obtain FDA approval of an animal drug. The results of these studies are made public, and a drug company can then use them without cost to complete the process of applying to the FDA for drug approval. Once approved, the drug can be labeled, marketed, and made available for minor use.

The Minor Use Animal Drug Program works through the cooperation of many organizations. A drug manufacturer agrees to sponsor the drug; state agricultural research services, universities, and veterinary schools conduct studies; animal producers do field testing; and the FDA's Center for Veterinary Medicine (CVM) advises on the requirements needed for drug approval and reviews study results and other data.

Most of the program's efforts in-

volve drugs already approved in a major species. For example, a drug approved for cattle may be studied for its safety and effectiveness in sheep.

"With the sponsoring drug company's consent, we can use their toxicology and other data so we don't have to duplicate studies," says Stephen F. Sundlof, D.V.M., Ph.D., director of CVM. "This reduces some of the data requirements and saves a tremendous amount of money."

The program prioritizes and selects projects from requests made by animal producers, veterinarians or researchers. Current funding allows for about 1 in 6 requests to be researched.

Animal Drug Shortages

The continued shortage of minor use drugs not only poses a serious threat to the health of animals—it also may set in motion a chain of events that could adversely affect nearly every American.

First, American farmers could find their livelihoods threatened, since unhealthy animals create significant losses to producers. Second, the American economy could face a worsening trade deficit, since more food animal products would need to be imported to make up for the loss. And third, American consumers could be exposed to a poorer quality of some imported food, since certain animal

Few Drugs for Wild Animals, Pets

Few FDA-approved drugs are available for animals considered to be "minor species." These include wildlife, exotic animals, endangered species, and pets such as birds, rabbits, reptiles, and guinea pigs.

Veterinarians who treat these animals often must rely on unapproved animal drugs or drugs approved for humans or other animals. Sometimes a drug approved for one animal can be used with confidence in another animal with a similar metabolism, says Stephen F. Sundlof, D.V.M., Ph.D., the director of the FDA's Center for Veterinary Medicine. "But when it comes to exotic animals, there is no formula for extrapolating between one species and another—it's a big gamble."

More animal drugs could be available if the Minor Use and Minor Species Animal Health Act is passed by Congress. The "MUMS bill" would establish several new ways to lawfully market new animal drugs while maintaining the rigorous public safety requirements of the FDA. ■

— L.B.



USDA Agricultural Research Service

products originate in countries whose safety and environmental laws may be less stringent than U.S. standards.

So why the shortage of minor use drugs? "There is no economic incentive for pharmaceutical companies to get approval for these drugs since they affect a small population," says Sundlof. "Companies may feel that the size of the market doesn't justify the drug development costs."

Animal drugs must be approved for each species they are intended to treat. Just to add a new species to the label of an existing drug costs \$2 million to \$8 million. To get a brand-new drug approved, it costs a drug company an estimated \$20 million and 8 to 10 years of concentrated research efforts.

Focus on Fish

Fish farming, or aquaculture, is one of the fastest growing segments of American farming, says the USDA. Yet to satisfy America's taste for seafood, the United States imports over \$9 billion worth of fish each year—more than three times as much as it exports.

"The task for domestic producers is to supply a superior quality product at

a reasonable cost," says MacMillan.

"What the U.S. aquaculture industry needs is improved health-management systems. We need more vaccines and we need to be able to prevent infectious diseases. In the interim, we need methods to treat sick fish."

The USDA estimates losses of more than \$100 million each year, attributable to 50 different fish diseases.

Aquaculture organizations and government agencies are investing heavily in drug research to help ease future losses to industry. The International Association of Fish and Wildlife Agencies, U.S. Fish and Wildlife Service, U.S. Geological Survey, USDA Minor Use Animal Drug Program, and commercial aquaculture operations are among those working in partnership to increase the availability of treatments for fish diseases.

Japan, a major seafood producer, has more than two dozen drugs or combinations of drugs approved for use in its aquaculture industry, according to the American Veterinary Medical Association. The United States has just six drugs approved for use in food fish.









"Water quality in many developing countries is not as good as ours," says Roz Schnick, who helps producer groups and pharmaceutical and chemical companies work together to gain drug approvals. "This creates more stress on the animals, and with stress comes disease so they have to use more drugs," says Schnick. "In the United States, we don't need a lot of drugs—just a basic medicine chest that we are currently attempting to achieve through proper approval procedures."

Schnick reports that through the efforts of federal and state government agencies and a consortium of aquaculture organizations, the medicine chest will soon fill up—four new aquatic animal drug applications and two supplemental applications are close to being submitted to the FDA for approval.

Additional aquaculture drug research may be expedited through "species grouping." In aquaculture, where there are hundreds of species, it is not practical to test a drug on all of them, says the FDA's Oeller. Researchers are trying to group similar species of fish in order to test drug effectiveness,

How Meats Measure Up

(based upon 3 oz. of cooked, trimmed/skinless servings)

Nutrients	Daily Dietary Rec. ¹	 Ostrich ² (top loin)	 Emu (loin)	 Venison (loin)	 Bison (sirloin)	 Elk (rib/loin)	 Beef ³ (loin)	 Chicken ³ (breast) (thigh)		 Pork ³ (loin)
Calories (kcal)	1600-2800	132	123	128	146	141	182	140	178	173
Protein (gm)	50	24	25	26	24	26	29	26	22	26
Total Fat (gm)	<65	3.3	2.7	2.0	4.8	3.3	8.6	3.0	9.2	6.6
Saturated Fat (gm)	<20	1.0	0.7	1.0	2.1	1.6	3.3	0.9	2.6	2.3
Cholesterol (mg)	<300	79	75	67	73	64	65	72	81	68
Iron (mg)	8 for males; 18 for females	2.8	4.3	3.5	3.0	3.4	2.1	0.9	1.1	0.7

(gm=grams, mg=milligrams, kcal=kilocalories)

1 Based on the U.S. Department of Agriculture (USDA) Recommended Dietary Allowances for a 2,000 calorie diet, and the Institute of Medicine's Dietary Reference Intakes for iron

2 Ostrich Meat Industry Development final Reports (1993 and 1996), Texas A&M University

3 USDA Nutrient Database for Standard Reference

Source: Dennis Buege, Ph.D., University of Wisconsin-Madison, and Juliet Howe, Ph.D., USDA Nutrient Data Laboratory

safety in target animals, and safety in human food. This grouping may yield representative species whose data can be used to support including similar species on the label of a new animal drug.

Fish are not the only animals that can benefit from species grouping research, says Oeller. Other groups may include game birds (pheasants, partridges, quail), deer (white tail, red deer, elk), and ratites (ostriches, emus). "It may be that the research will show that the species are not similar, or are not similar for some classes of drugs," says Oeller. "Learning what is and is not suitable for grouping will be very valuable in making drug approval for minor species more efficient."

Alternative Meat Animals

Although much of its minor species research centers on aquatic animals, the Minor Use Animal Drug Program also is investigating the needs of other animals used in agriculture. Some of this research is motivated by the needs of American farmers seeking healthful alternatives to the traditional red-meat market.

Meats from ostriches, emus, bison, deer, and elk have some nutritional benefit over other red meats, according to a USDA-funded study con-

ducted at the University of Wisconsin-Madison. "These alternative meats, like traditional meat and poultry, are high in protein," says Dennis Buege, Ph.D., lead study researcher. "Their cholesterol content is similar to the other meats and poultry. However, they tend to be lower in fat than beef, pork and dark meat chicken, and higher in iron than beef, pork, and light and dark meat chicken." (See "How Meats Measure Up," page 34.)

The Minor Use Animal Drug Program has conducted research to support the approval of a drug for bison, and several projects are in progress for deer and elk. As yet, there are no drugs approved to treat flightless birds known as ratites, but the program recently has received several requests from this growing industry.

The program is researching treatments for diseases in sheep and goats, also minor species. A number of drugs to treat these animals have been approved, but more are needed, particularly to aid America's declining sheep industry.

Sustaining the Sheep Industry

The U.S. sheep population has been steadily decreasing since the 1940s—from its peak at 56 million in 1942 to less than 7 million in 2002, says the USDA.

The lack of approved drugs for sheep is one factor contributing to the decline, says Oeller. The sheep industry loses about \$45 million worth of sheep each year from diseases for which drugs are unavailable.

In addition to disease-treating drugs, American sheep ranchers are lacking another important tool: "the capability to manipulate reproduction," says Oeller. In other countries, such as Australia, sheep ranchers can use progesterone implants to manipulate the reproductive cycle. "This gives them spring and fall breeding of sheep, while we are limited to one breeding season in this country," says Oeller.

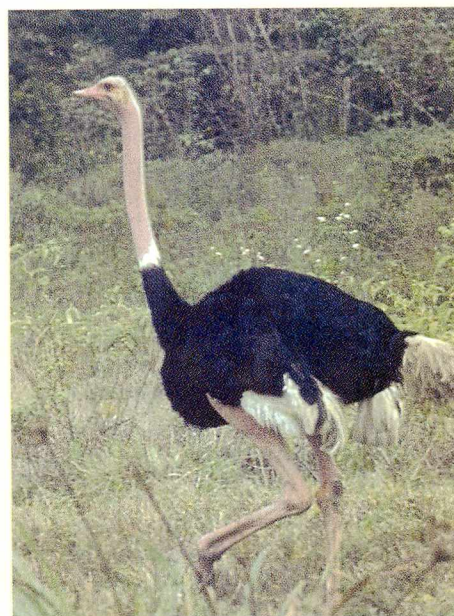
In response to the industry's need, the Minor Use Animal Drug Program is currently researching a vaginal progesterone for sheep and goats.

Big Birds

Powell Anderson, D.V.M., splits his time between his veterinary hospital in Dillwyn, Va., and his ostrich ranch next door. An ostrich breeder since 1996, Anderson sees the future of agriculture and the rebirth of small farms in businesses like his. It's a healthy and environmentally sound alternative to some other forms of animal food production, says Anderson, who doesn't use growth hormones or antibiotics in his birds.



PhotoDisc



Dr. Lloyd Glenn Ingles, California Academy of Sciences

Anderson sells the low-fat ostrich meat, which he compares to filet mignon in taste, to local restaurants. He incubates the fertile eggs during mating season and sells them for food in the mating off-season. "You can't taste the difference between scrambled ostrich eggs and chicken eggs," says Anderson, who plans to be eating ostrich eggs for a very long time. "The females lay eggs for 40 years and live to be 70."

With no FDA-approved drugs to treat ostriches, Anderson must rely on his own knowledge of veterinary medicine, an ostrich encyclopedia, and trial and error. Luckily, his birds have been pretty healthy, he says, but when one is sick, it goes down quickly. "You can't tell they're sick until they're almost dead."

Sharyn Felts, owner of one of the largest emu ranches in California, also considers herself blessed that most of her 800 emus have been disease-free. The six-foot tall, 150-pound birds, second in size only to ostriches, are very hardy, she says.

In addition to their meat, the emus are valued for their oil as an emollient used in moisturizers, shampoos and soaps. Their feathers are used by fishermen to tie flies, and their hides serve the leather industry. The dark green emu eggs are prized by artists, who carve or paint them.

Off-Label Use and Medicated Feed

The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 eased the scarcity of animal drugs somewhat by allowing veterinarians to use approved animal and human drugs "extra-label," or "off-label." This means that under certain circumstances, veterinarians can use drugs approved for other species, for other diseases and conditions, or at different dosage levels from those listed on the drug label.

This flexibility of drug use may help to ease animal suffering, but the different metabolisms of some species make the effective dosage a guessing game, says Oeller. The benefit of having a drug approved for a specific species is that "you can

count on a specific withdrawal time and know the correct dosage," Oeller says.

Although the AMDUCA allows off-label use of drugs, it prohibits off-label use in animal feed. But medicated feed often is the best route of getting a drug into certain animals, such as fish and game birds. Injecting an individual fish with a drug may be feasible for some types of brood stock, says MacMillan. "But such injection is not feasible for a large population of farm-raised aquatic animals such as trout, catfish, tilapia or bait fish."

Bill Mac Farlane, who owns one of the nation's largest pheasant farms, located in Janesville, Wis., says he needs medicated feed for his pheasants and other game birds, particularly to treat coccidia, a deadly parasite that infests the intestines. The alternatives to medicated feed don't work very well, says Mac Farlane. It's not practical to catch each bird and give them a shot every day, nor is adding a drug to the water effective. "They don't like the taste of the medicated water. They drink out of the puddles after a rain instead, so they don't get their medication."

To meet the requirements of the fish and bird industries, the Minor Use Animal Drug Program has shifted much of its focus to the approval of medicated feeds, says Oeller. The program is currently test-

ing several medicated feeds for pheasants to treat bacterial infections and coccidia and other parasites, and Mac Farlane's pheasant farm is participating in the study trials.

Keeping Animals Healthy

Currently, the Minor Use Animal Drug Program is working on more than two dozen projects, and continues to review requests for treatments to keep animals healthy. Among the active projects are drugs to treat diseases in game birds, goats, sheep, deer, rabbits, bees, and a variety of fish.

"It's never a good idea to have unhealthy animals," says Oeller. "You don't want the risk of products from unhealthy animals entering the human food supply, you don't want them exposing other agricultural animals to disease, and you don't want wildlife transporting disease-carrying ticks into areas frequented by people. Both from a public health and an animal welfare standpoint, you're better off having healthy animals."

For more information on the Minor Use Animal Drug Program, see the program's Web site at www.nrsp-7.org and the FDA's Web site at www.fda.gov/cvm/index/mums/minortoc.htm. ■



George W. Robinson, California Academy of Sciences

By John Henkel

Don't Be Blind to Blindness

More Americans than ever are facing blindness from age-related eye disease, according to "Vision Problems in the U.S.," a recent report by the National Eye Institute (NEI). Currently, the institute says, more than 1 million Americans 40 and over are blind, and 2.4 million more are visually impaired. These numbers are expected to double over the next 30 years as the baby boomer generation ages.

But these staggering statistics can be reduced, experts say, with early detection and treatment—and with basic knowledge about the various eye disorders. On its Web site at www.nei.nih.gov, the NEI tells you who's at risk for eye problems and what you can do about them. The site's features include:

- photographs simulating what vision looks like to those with disorders such as glaucoma, age-related macular degeneration, cataracts, and diabetic retinopathy
- a clinical studies database that catalogs the many eye studies in progress and shows how to join studies that are open
- the full "Vision Problems in the U.S." study
- an interactive quiz that tests how much you know about glaucoma.

Some Hot Tips for Writing School Reports

So school has started and you need some ideas for writing a term paper or school report? The FDA understands and can help with "Student Resources," a Web site that suggests topics for school reports and gives tips on how to do a solid job of putting a report together. For example, the site advises: "Use the facts to write your own report, don't copy word-for-word."

The site can help get you started with topics such as cosmetics, foodborne illness, health fraud, nutrition, and pesticides. For history or government class, there's information about how laws are made and a page showing milestones in FDA history. And for civics class, there's a section on being a good citizen and consumer.

For a head start on your next school report project, go to www.cfsan.fda.gov/~comm/students.html. The page was created by the FDA's Center for Food Safety and Applied Nutrition.

Learning More About Asthma

Asthma affects nearly 15 million people in this country, 5 million of whom are under age 18, according to the National Heart, Lung and Blood Institute (NHLBI). Although asthma-related mortality in the United States is among the lowest in the world, the disease still kills about 5,000 people domestically each year.

To help consumers understand better what asthma is and how to treat and manage it, the NHLBI has created the Asthma Management Model System, an interactive Web site loaded with useful information. The model has three main features:

- Education—provides access to an electronic library, patient education materials, and teaching/learning tools.
- Communication—allows registering for e-mail updates and online forums and discussions.
- Research—links to several searchable databases related to asthma research.

The site, at www.nhlbisupport.com/asthma/, also includes an online tutorial that explains how to best search the model.

Finding Feds and Others

If you're looking for someone who works for the government, there's a good chance you can locate that person through a Web page called the U.S. Government Telephone and E-Mail Directories. Sponsored by *FirstGov*, the page is a gateway for contacting elected officials (including senators, representatives, governors, and state legislators), federal employees, and military personnel. The site links to the National Contact Center, which points the way to information on topics such as Social Security, foreign travel, and savings bonds. Also featured is a gallery of congressional photos. Check the directory out at www.firstgov.gov/Contact/Directories.shtml. ■

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



Jack Pardue

Illustration by Jack Pardue

Love and Illegal Drugs on the Internet

By Linda Bren

Anton F. Pusztai in Australia and Anita Yates in Alabama not only met on the Internet, they also found a love and business connection. Some, however, may call them luckier in love after their illegal Internet business landed them in jail.

After chatting online, Pusztai and Yates met in person in New York, and Pusztai later moved in with Yates in her Clanton, Ala., home. Through a Web site called Norfolk Men's Clinic at *Viagra.au.com*, the couple offered consumers prescription "lifestyle" drugs such as Viagra, Propecia, Celebrex and Xenical.

But their "virtual pharmacy," operated from Yates' home and a storefront in Clanton, was not licensed and consumers did not have valid prescriptions written by a licensed medical practitioner. In addition, customers were charged a fee for a non-existent medical consultation after they completed a health questionnaire and were told that a doctor had reviewed and approved it.

Pusztai and Yates hired employees throughout the world, and agents from the FDA's Office of Criminal Investigations (OCI) built a case against the conspirators with the help of law enforcement offices in Alabama, West Virginia, Australia, Romania and Germany.

In September 1999, Clanton police informed the FDA that Yates was bragging about making a lot of money selling drugs over the Internet, according to FDA Special Agent Robert J. West, of OCI's Nashville, Tenn., office. After making covert buys through the Web site, FDA agents searched Yates' residence and business in October 1999. They found hundreds of empty prescription drug bottles and cases of unpacked prescription drugs.

Yates and Pusztai had been ordering drugs from a local pharmacy in Alabama and a drug wholesaler, Yvan Degomme, in Miami. The couple wrote phony prescriptions bearing the names of doctors in Romania and Australia. They then enlisted a local doctor, Roger Eiland, to rewrite the prescriptions so they could be filled in the United States. The couple and their employees then removed the drugs from their original bottles, repackaged them in plastic sleeves, and shipped them out to customers in the United States and elsewhere.

After FDA investigators informed Pusztai and Yates of the illegality of their Clanton operation, the couple moved their business to Weirton, W.Va. "They tried to make it smell legitimate," says the FDA's West. "They

opened up a pharmacy, got a pharmacist on board, and got licenses." But they continued to write prescriptions bearing names of foreign physicians.

West flew to Australia and Romania to interview the doctors whose names appeared on the prescriptions. Neither doctor had authorized his name to be used, nor had they reviewed any consumer questionnaires.

After property searches in West Virginia and Clanton on Aug. 7, 2000, FDA agents confiscated numerous drugs, questionnaires and records. On the same day, they arrested Anita Yates in Clanton.

Pusztai, who was in Romania at the time of Yates' arrest, promised to return to the United States. "We waited until it was apparent that he was not coming back any time soon," says West, who initiated a Wanted Notice for Pusztai that went out to all Interpol agents. Pusztai, unaware of the Wanted Notice, flew to Germany in January 2001, where he was arrested and jailed. In April 2001, Pusztai waived extradition and was transported by U.S. Marshals to the United States and jailed in Montgomery, Ala.

The couple began their illegal business as early as October 1998 and continued through July 2000, according to evidence presented at trial.

On Feb. 16, 2002, a jury convicted Pusztai and Yates of all 23 counts brought against them. Charges included conspiracy to commit violations of the Federal Food, Drug, and Cosmetic Act, conspiracy to commit money laundering, mail fraud, dispensing misbranded drugs, and operating a drug repackaging facility not registered with the FDA.

Pusztai was sentenced to 15 years, 8 months in prison, 3 years supervised probation, and was fined \$2,300. Yates was sentenced to 6 and a half years in prison, 3 years supervised probation, and was fined \$2,225. The judge entered a final order of forfeiture of \$373,000 in company assets.

Eiland was acquitted at trial and Degomme entered into a plea agreement that resulted in his conviction.

"The Internet is a great tool and there are legitimate sites that sell pharmaceuticals," says West. "But if you don't go to a doctor and are depending on someone on the other end to make a decision, you're taking your life in your hands. You don't even know if you're getting legitimate drugs." ■

FDA: A Science-Based Agency

By Daniel A. Casciano, Ph.D.



The National Center for Toxicological Research (NCTR) is one of six centers within the FDA. It is the only center that does not have consumer product regulatory authority. Our primary function is to develop and modify standards that can be applied in the regulatory environment and to anticipate future research needs of the FDA. We are sometimes asked

why the FDA does research, because it is generally recognized that research is the purview of the National Institutes of Health (NIH). The NIH supports "basic research," that is, new knowledge that may or may not have a direct impact on protecting the public health.

Research done at the NCTR and other FDA centers is "translational" in nature. This means that basic information derived from an NIH-sponsored study is further modified to apply to a specific question that is relevant to the FDA's mandate to protect the public health. An example of this is the basic research developed to create a mutant mouse or rat. FDA scientists use the technology and apply it to specific mouse or rat strains to help them assess the safety of a human or animal drug, or to understand the mechanism of action of a particular food additive or medical device. Sometimes the conversion of basic information to applied information that would be useful to the FDA takes several years.

The article "Food Freshness and 'Smart' Packaging," in this issue of *FDA Consumer*, is an example of the journey of an FDA scientist's idea as it wends its way toward consumer use. The scientist, Dwight Miller, Ph.D., was asked to determine whether the odors released from new carpeting may be harmful to the consumer. Using methodology developed from basic research, he first identified the chemical class that was entering the vapor phase and sensitizing our sense of smell. Upon identification of the chemical class, he reasoned that these chemicals are similar to those emitted by decomposing fish. Realizing the direct application of this information to a consumer need, he set out to develop the "food quality indicators" described in the accompanying article (see page 25). Progressing from the initial idea to the present encompassed several years. However, the effort was well spent because he is now working on technologies that

can detect spoiling beef and poultry. In another seemingly unrelated twist, Miller also is using the applied knowledge to identify the presence of explosives. These efforts have the potential of being beneficial to consumers.

Other translational research efforts ongoing at the NCTR include:

- development and modification of research standards by which those involved in toxicological research can identify cancer-causing agents in model animal systems
- assessment of potential toxic reaction of sunlight and cosmetics or some dietary supplements on the skin of model animal systems
- development of tools that will help identify certain populations at risk to products regulated by the FDA using technologies that were derived from the sequencing of the human genome (a process funded by the NIH)
- evaluation of specific anti-viral strategies developed through NIH funding to prohibit the transmission of the HIV virus to offspring of infected females.

FDA employees are proud to be in a science-based agency whose decisions are supported by sound science. A strong scientific presence within the FDA is represented by regulatory reviewers and scientists who have:

- state-of-the-art scientific knowledge within their specific disciplines
- access to the latest scientific knowledge and instrumentation so that an enforcement decision results from risk-benefit judgment, balancing the safety of the public health and the potential economic impact of the decision, and
- the task of developing and validating scientific methods as well as anticipating the FDA's future research needs.

It is extremely important that the FDA maintain its ability to make quality decisions based on sound science. This is more important now because of the quickened pace of discovery by the industries that the FDA regulates. In order to avoid becoming a bottleneck to the process of moving these newly developed products to the consumer, a strong internal scientific presence is essential in the FDA. ■

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