

FDA *Consumer*

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

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A microscopic image showing several spherical influenza virus particles. The particles have a textured, bumpy surface and are colored in shades of green and yellow against a dark background.

Influenza: Vaccination Still the Best Protection

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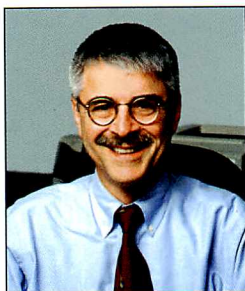
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OBSERVATIONS

Every year in the United States, an average of 5 percent to 20 percent of the population comes down with seasonal influenza, according to the Centers for Disease Control and Prevention. Of that number, more than 200,000 people are hospitalized from influenza-related complications, and about 36,000 people die from it.



Each year, the Food and Drug Administration clears a seasonal influenza vaccine formulation that protects people against the strains of influenza considered most likely to strike the Northern Hemisphere. Distribution of influenza vaccine begins in the fall. About 100 million doses of influenza vaccine are expected to be available for the 2006–2007 season—a record number.

The vaccine does not protect people against bird (avian) flu, which is caused by different strains of the virus. Scientists worldwide are working to develop vaccines that could be effective against avian influenza.

Public health officials urge those eligible for vaccination against seasonal influenza to receive it and remind people that although influenza vaccination begins in September or October each year, vaccine continues to be available in November, December, and later, and that immunization during those months is beneficial. For an in-depth look at the 2006–2007 influenza season, see our cover story titled “Influenza: Vaccination Still the Best Protection,” beginning on page 12.

The FDA regulates products that represent almost 25 percent of all consumer spending. The total includes 80 percent of the nation’s food supply and all human drugs, vaccines,

medical devices, cosmetics, tissues for transplantation, radiation-emitting equipment, and animal drugs.

In order to accomplish this challenging task, other government agencies, health care providers, regulated industry, experts at colleges and universities, and consumers contribute their expertise and experiences to help the FDA tackle complex scientific issues.

“Our collaborations are an essential part of the FDA’s long-term strategy to promote and protect the public health,” says Acting FDA Commissioner Andrew C. von Eschenbach, M.D. We take a look at how the FDA collaborates with other organizations and individuals in our feature story titled “Advancing Public Health Through Partnerships,” beginning on page 27.

Nonsteroidal anti-inflammatory drugs (NSAIDs) developed in recent years are increasingly being used to safely and effectively control symptoms of arthritis, including inflammation, swelling, stiffness, and joint pain in dogs. The FDA considers approved NSAIDs to be safe and effective when used according to the label and when dog owners are informed about common NSAID adverse reactions. For more on the use of NSAIDs in dogs, see our feature titled “Pain Drugs for Dogs: Be an Informed Pet Owner,” beginning on page 20.

We also take a look at a recent FDA survey that indicates benzene levels are not a safety concern for consumers, new measures taken by the FDA to protect people against counterfeit drugs, and a new vaccine that helps protect women against cervical cancer.

Raymond Formanek Jr.
Editor

UPDATES

Mercury and Seafood Advice Still Current

The FDA and the U.S. Environmental Protection Agency want consumers to know that a joint advisory concerning mercury in fish issued in 2004 remains current.

The advisory titled “What You Need to Know About Mercury in Fish and Shellfish” contains recommendations for women who might become pregnant, women who are pregnant, nursing mothers, and young children.

The FDA and the EPA say that women

and young children should include fish and shellfish as a regular part of their diet. Both are an important part of a healthy diet and can contribute to heart health and to children’s proper growth and development. Nearly all fish and shellfish, however, contain traces of mercury.

Women and young children can receive the benefits of eating fish and shellfish while reducing their exposure to the harmful effects of mercury by following three recommendations:

- Do not eat shark, swordfish, king

mackerel, or tilefish because they contain high levels of mercury.

- Eat up to 12 ounces (two average meals) a week of a variety of fish and shellfish that are lower in mercury, such as shrimp, salmon, pollock, catfish, and canned light tuna. Albacore tuna has more mercury than canned light tuna, so when choosing your two meals of fish and shellfish, you may eat up to six ounces (one average meal) of albacore tuna per week.

- Check local advisories about the safety of fish caught by family and

Acting FDA Commissioner Andrew C. von Eschenbach, M.D. (left), presents U.S. Health and Human Services Secretary Mike Leavitt with the Commissioner's Special Citation at the FDA's centennial celebration of the Pure Food and Drugs Act of 1906.

More than 200 people, including former Commissioners of Food and Drugs, representatives of consumer and trade groups, FDA employees, and descendants of Dr. Harvey W. Wiley, the scientist whose early support of food and drug regulations earned him the title of "Father of the Pure Food and Drugs Act," attended the June 30 event at the Harvey W. Wiley Federal Building in College Park, Md. The Centennial event also was telecast to all FDA employees nationwide.



U.S. Department of Health and Human Services/Chris Smith

friends in your local lakes, rivers, and coastal areas. If no advice is available, eat up to six ounces (one average meal) per week of fish you catch from local waters, but don't consume any other fish during that week.

- Follow the same recommendations when feeding fish and shellfish to young children, but serve smaller portions.

The FDA continues to test fish and shellfish for mercury and will update the advisory if there is a significant change in the underlying science regarding the risks from methylmercury or the benefits from eating fish.

See www.cfsan.fda.gov/~dms/admehg3.html for more information.

Increasing the Availability of Generics

The FDA has approved the first generic version of Zocor (simvastatin), an important step in the agency's effort to increase the availability of lower-cost generic medications.

Simvastatin is recommended for use,

along with a diet restricted in saturated fat and cholesterol, to treat high cholesterol and to reduce the amount of certain fatty substances in the blood such as triglycerides and other lipids.

Zocor is a member of a drug class known as statins. According to the research firm IMS Health, statins accounted for \$16 billion in U.S. sales in 2005. Zocor was the second most widely prescribed statin.

"Simvastatin is a widely-used cholesterol lowering agent, and its generic version can bring significant savings to the millions of Americans with this disease," says Gary J. Buehler, director of the FDA's Office of Generic Drugs.

Simvastatin tablets are manufactured by IVAX Pharmaceuticals Inc. of Northvale, N.J., and by Ranbaxy Pharmaceuticals Inc., Princeton, N.J.

The FDA has also recently approved the first generic version of Zoloft tablets (sertraline), as well as a liquid concentrate (sertraline hydrochloride) version of the product.

Sertraline tablets are indicated for

the treatment of major depressive disorder (MDD) in adults, and the liquid concentrate is approved for the treatment of MDD and some anxiety-related disorders. In 2005, Zoloft was the sixth highest-selling brand-name drug in the United States, with retail sales totaling \$2.6 billion.

Other first generic products recently approved by the FDA are

- Finasteride tablets (Proscar) for the treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms by reducing the size of the prostate
- Lamotrigine tablets (Lamictal) for treating patients with seizures due to epilepsy.

The economic benefits of the FDA's generic drug approval program are significant because generics can cost a fraction of the price of brand-name drugs and generic drugs represent about two-thirds of total prescription doses sold in the United States in 2004, according to IMS data on U.S. retail sales.

The FDA Approves New Over-the-Counter Sunscreen

Anthelios SX, a sunscreen to be sold over-the-counter (OTC) for the prevention of sunburn and for protection against ultraviolet B (UVB) and ultraviolet A (UVA) rays, has been approved by the FDA.

"While this product provides protection from harmful UVA and UVB rays, FDA continues to recommend that in addition to using a sunscreen, consumers protect themselves from sun exposure by limiting time in the sun and wearing protective clothing," says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research.

Anthelios SX, which has a sun protection factor (SPF) of 15, is a sunscreen product that contains a combination of three active ingredients. One of the ingredients is a new molecular

entity (NME), ecamsule. Ecamsule has not been marketed in the United States, but has been marketed in Europe and Canada as Mexoryl SX since 1993. The other two active ingredients, avobenzone and octocrylene, are generally recognized as safe and effective under the current OTC monograph for sunscreens.

The safety and efficacy data for Anthelios SX included information from 28 studies involving more than 2,500 people, ranging in age from 6 months to more than 65 years. Side effects reported

during clinical studies were infrequent and not serious. The most common side effects in patients were acne, dermatitis, dry skin, eczema, abnormal redness, itching, skin discomfort, and sunburn.

The product will be distributed by La Roche-Posay.



Getty Images

CORRECTIONS

An article titled "A Focus on Vision," on page 10 of the July–August 2006 issue, referred to "the National Contact Lens Enforcement Petition in 2003 that strongly encouraged the FDA to amend the medical device laws to include regulation of all contact lenses." This petition actually encouraged FDA to enforce the existing law more effectively, not to amend the law, which only Congress can do. In 2005, Congress amended the Federal Food, Drug, and Cosmetic Act to define noncorrective, decorative contact lenses as medical devices.

An article titled "Artificial Sweeteners: No Calories ... Sweet," on page 27 of the July–August 2006 issue, incorrectly stated that the artificial sweetener saccharin is generally recognized as safe. Saccharin was discovered in 1879 and had been considered generally recognized as safe (GRAS) until 1972, when it was removed from the GRAS list by the FDA.

Treatment for Hunter Syndrome Approved

The FDA has approved Elaprase (idursulfase), the first product for the treatment of Hunter syndrome (Mucopolysaccharidosis II, or MPS II), a rare inherited disease that can lead to premature death. Elaprase is a new molecular entity, which is an active ingredient never before marketed in the United States.

Hunter syndrome, which usually becomes apparent in children ages 1 to 3 years, is a disease in which the person's body is defective in producing a chemical called iduronate-2-sulfatase. This chemical is needed to adequately break down complex sugars produced in the body. Symptoms include growth delay, joint stiffness, and coarsening of facial features. In severe cases, patients experience respiratory and cardiac problems, enlargement of the liver and spleen, neurological deficits, and death.

Approved in July 2006, Elaprase was designated as an orphan product by the FDA. Orphan products are generally developed to treat rare diseases

or conditions that affect fewer than 200,000 people in the United States. The Orphan Drug Act provides a seven-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan product. Hunter syndrome is diagnosed in about 1 out of every 65,000 to 132,000 births.

Elaprase was approved after a randomized, double-blind, placebo-controlled study of 96 patients with Hunter syndrome showed that the treated participants had an improved capacity to walk.

Because of the potential for severe hypersensitivity reactions, appropriate medical support should be readily available when Elaprase is administered. Patients and their physicians are encouraged to participate in a voluntary Hunter Outcome Survey that has been established to monitor and evaluate the safety and effects of long-term treatment with Elaprase.

Elaprase is manufactured by Shire Human Genetic Therapies Inc., Cambridge, Mass.

Warning on Bismacine

The FDA is warning consumers and health care providers not to use a product called bismacine, also known as chromacine. The agency is investigating one report of a death and several reports of injury related to the administration of the substance.

Bismacine, an injectable product prepared by druggists, has been used by some to treat Lyme disease. But bismacine has not been approved by the FDA to treat Lyme disease or any other disease or condition.

Bismacine is not a pharmaceutical. It is suggested or administered by "alternative health" practitioners or by people claiming to be medical doctors. Bismacine contains high amounts of bismuth, a heavy metal used in some medications taken by mouth to treat a bacterium that can cause stomach ulcers (*Helicobacter pylori*). It is not approved for use by injection.

On April 20, 2006, one person died as a result of treatment with bismacine, and on March 29, 2005, another person was hospitalized after receiving a bismacine treatment. Other serious adverse events have been reported. Possible effects of bismuth poisoning include cardiovascular collapse and kidney failure.

The FDA is advising consumers and health care providers not to use bismacine. Individuals who believe they have suffered adverse events from receiving bismacine may wish to seek medical attention. The agency is evaluating the product suppliers and will take additional action as appropriate.

Adverse reactions experienced with the use of this product should be reported to the FDA's MedWatch Adverse Event Reporting program online at www.fda.gov/MedWatch/report.htm; by phone (800) FDA-1088 (332-1088); by returning FDA form 3500, which may be downloaded from www.fda.gov/MedWatch/getforms.htm; by mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787; or by fax (800) FDA-0178 (332-0178).

First Treatment for Dementia of Parkinson's Disease

The FDA has approved Exelon (rivastigmine tartrate) for the treatment of mild-to-moderate dementia associated with Parkinson's disease, a disorder of the central nervous system. Exelon was approved previously for the treatment of mild-to-moderate dementia of the Alzheimer's type.

"It's been recognized for almost a decade that the dementia of patients with Parkinson's disease differs from the dementia of patients with Alzheimer's," says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research. "But until now, there has been no treatment that has been shown to be effective specifically for the dementia associated with Parkinson's disease. Today's approval of Exelon helps to fill this medical need."

It is estimated that about 0.2 percent to 0.5 percent of people older than 65 are affected by Parkinson's dementia and experience such symptoms as impairments in executive function, memory, and attention. The approval of Exelon for the treatment of Parkinson's

son's dementia is based on the results of a randomized, placebo-controlled clinical study with 541 patients who showed symptoms of mild-to-moderate dementia two years or later after their diagnosis for Parkinson's disease. At the end of the 24-week trial, the condition of the Exelon-treated patients, as shown on a scale that measures mental processes, was significantly better than the condition of the patients on placebo.

The use of Exelon has been associated with significant gastrointestinal adverse reactions. In clinical trials, 47 percent of the patients treated with the drug developed nausea, and others on high doses of Exelon experienced significant weight loss. Other common adverse events reported by patients on Exelon include vomiting, anorexia, dyspepsia, and loss of strength (asthenia). In some patients with Parkinson's disease, treatment with Exelon was associated with a worsening of tremor.

Exelon is manufactured by Novartis Pharmaceutical Corp. in East Hanover, N.J.

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

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Treatment for Wet Macular Degeneration

The FDA has approved Lucentis (ranibizumab injection) for the treatment of people with wet (neovascular) age-related macular degeneration (AMD). Lucentis is the first treatment that, when taken monthly, can maintain the vision of more than 90 percent of people with this type of AMD, studies show.

Lucentis is a new molecular entity, meaning it contains an active substance that has never before been approved for marketing in any form in the United States. It is the first FDA-approved product to provide prescription information in a new, easy-to-read format that the agency unveiled in January 2006 for prescription drug package inserts.

"This approval is of great importance for the 155,000 Americans who are diagnosed each year with AMD, a common cause of severe and irreversible vision loss in older adults," says Acting Commissioner of Food and Drugs Andrew C. von Eschenbach, M.D.

AMD is a retinal disease and a major cause of blindness in individuals older than 55. Wet AMD, which accounts for 10 percent of all AMD, is responsible for 80 percent of the associated vision loss.

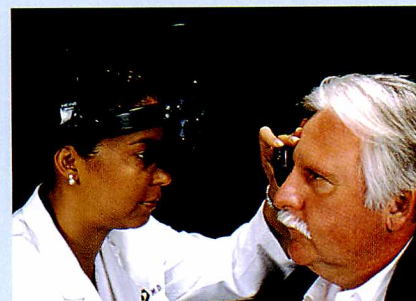
Lucentis, a biologic product, is designed to block the growth of abnormal leaky blood vessels, which cause the vision loss in wet AMD. Lucentis is administered by injection into the eye. It was shown to be safe and effective in

three multicenter, randomized studies of people representative of the population usually affected with AMD. In clinical trials, nearly 95 percent of the participants who received a

monthly injection maintained their vision at 12 months, compared with about 60 percent of patients who received the control treatment. About one-third of the trial participants had improved vision at 12 months.

The most commonly reported side effects included red eye (conjunctival hemorrhage), eye pain, small specks in vision (floaters), increased eye pressure, and inflammation of the eye. Serious side effects, which were rare and often related to the injection procedure, included severe inflammation of the interior of the eye (endophthalmitis), intraocular inflammation, retinal detachment, retinal tear, increased eye pressure, and traumatic cataract.

Lucentis is manufactured by Genentech Inc. in South San Francisco, Calif.



National Eye Institute

Campaign to Reduce Medication Mistakes

The FDA and the Institute for Safe Medication Practices (ISMP) have

launched a nationwide education campaign for health professionals aimed at reducing medication mix-ups and mistakes caused by the use of unclear medical abbreviations.

"Some abbreviations, symbols and dose designations are frequently misinterpreted and lead to mistakes that result in patient harm," says Acting Commissioner of Food and Drugs Andrew C. von Eschenbach, M.D. "This joint campaign will promote safe practices among those who communicate medical information to help avoid serious and even potentially fatal consequences of medication errors."

According to the Institute of Medicine (IOM) of the National Academies, more than 7,000 deaths a year are attributable to medication errors.

The educational campaign focuses on eliminating the use of potentially confusing abbreviations by health care professionals, medical students, medical writers, the pharmaceutical industry, and FDA employees.

"We recommend that ISMP's list of abbreviations, symbols and dose designations most often associated with medication errors be considered whenever medical information is communicated," says the ISMP's President Michael Cohen.

For campaign materials and more information, see www.fda.gov/cder/drug/MedErrors and www.ismp.org/tools/abbreviations.



Photodisc

New HIV Treatment

A new HIV protease inhibitor, Prezista (darunavir), has been approved for adults whose HIV infection has not responded to treatment with other anti-retroviral drugs. Prezista is approved to be used with a low dose of ritonavir and with other active anti-HIV agents. Ritonavir, a protease inhibitor approved in 1996, slows the breakdown of Prezista in the body, thereby increasing the concentration of Prezista in the person's system.

"This approval offers new hope to HIV patients who too often urgently need new therapies in order to maintain their health," says Acting Commissioner of Food and Drugs Andrew C. von Eschenbach, M.D. "This drug

is not a cure, but when combined with other standard therapies, it presents one more major step in our effort to help patients combat the effects of the disease."

The accelerated approval was based on evidence from two randomized, controlled studies comparing the safety and effectiveness of a Prezista-ritonavir combination with other ritonavir-boosted protease inhibitor combinations. Participants in both arms of these trials also used other anti-HIV agents (nucleoside reverse transcriptase inhibitors), with or without enfuvirtide, which inhibits the virus from entering the cell.

In these studies, participants on a Prezista-ritonavir combination experi-

enced higher rates of reduction of their HIV viral load than those on other ritonavir-boosted protease inhibitor combinations. Seventy percent of those treated with the Prezista-ritonavir combination achieved a response, improving the treatment outcome, compared with 21 percent in a control group at six months.

The most common side effects reported by those on the Prezista-ritonavir regimen included diarrhea, nausea, and headache. About 7 percent of people on this combination therapy experienced skin rashes.

Prezista is manufactured for Tibotec Inc., a division of Ortho Biotech Products L.P., Raritan, N.J., by JOLL, Gurabo, Puerto Rico.

First Drug for Seasonal Depression

The FDA has approved the first drug for seasonal affective disorder (SAD). Wellbutrin XL (bupropion HCL extended-release tablets) previously was approved to treat major depressive disorder. It's now also approved to prevent major depressive episodes in people with a history of SAD.

SAD is characterized by recurrent major depressive episodes that usually coincide with the seasonal decrease of daylight during autumn and winter. The depressive episodes can last up to six months. Although patients with SAD may have depressive episodes during other times of the year, the diagnosis of SAD requires that the number of seasonal episodes substantially outnumber the non-seasonal episodes during the individual's lifetime.

A major depressive episode is defined as the presence of five or more of the nine core symptoms of major depression for at least two weeks. The symptoms include: depressed mood, loss of interest, weight loss or other weight or appetite changes, insomnia or hypersomnia, agitation or psychomotor retardation, fatigue, feelings of worthlessness or guilt, impaired concentration, and suicidal thinking or behavior. One of the five symptoms must be either depressed mood or loss of interest in activities. Another essential feature of major depression is the presence of significant distress or impairment in social, occupational, or other important areas of functioning. A seasonal major depressive episode is defined by the identical features.

The effectiveness of Wellbutrin XL for the prevention of SAD episodes was established in three double-blind, placebo-controlled trials in adults with a history of major depressive disorder in autumn and winter. In these trials, the percentage of people who were depression-free at the end of treatment was significantly higher for those on Wellbutrin XL than for those on placebo. For all three studies combined, the overall rate of patients depression free at the end of treatment was 84 percent for those on Wellbutrin XL, compared with 72 percent for those on placebo.

Wellbutrin XL's labeling includes a "black box" warning concerning the increased risk of suicidal thoughts and behavior in pediatric patients treated with antidepressant medications. As with all antidepressants, Wellbutrin XL has a Medication Guide advising that pediatric patients on antidepressants should be watched closely for these serious symptoms. It is important to note that Wellbutrin XL is indicated only for patients who meet strict diagnostic criteria of seasonal major depressive episodes. Wellbutrin XL is manufactured by GlaxoSmithKline, Research Triangle Park, N.C.



Photodisc

Drug Approved for Late-Stage Cervical Cancer

The FDA has approved a combination of Hycamtin (topotecan hydrochloride) and cisplatin for use as the first drug treatment for women with late-stage cancer of the cervix when surgery or radiation therapy is unlikely to be effective. The approval is a new indication for Hycamtin, which was approved in 1996 for treating ovarian cancer and in 1998 for small cell lung cancer.

In the United States, there are an estimated 10,000 new cases of cervical cancer and about 3,700 related deaths each year. "We are making great strides in the fight against cervical cancer, a disease that, world wide, is the second most common cancer in women," says Acting FDA Commissioner Andrew C. von Eschenbach, M.D. "This course of drug therapy is a potentially life-prolonging option for thousands of women."

The combination of Hycamtin and cisplatin is specifically indicated for women with Stage IVB (incurable), recurrent, or persistent cancer of the cervix that spreads to other organs and is not likely to respond to treatment with surgery or radiation.

Hycamtin is associated with a significant risk of neutropenia (a drop in white blood cell count), a condition which makes it more difficult for the body to fight infections. Serious side effects also include thrombocytopenia, a decrease in blood platelets that can lead to excessive bleeding and anemia. Less serious side effects include nausea and vomiting. The incidences of neutropenia, anemia, and thrombocytopenia were significantly increased among patients receiving the combination treatment, compared with those receiving cisplatin alone, as were nausea and vomiting, inflammation of a mucous membrane (mucositis), rash, and liver toxicity.

Hycamtin is manufactured by GlaxoSmithKline, Research Triangle Park, N.C.

New Safety Information on Ketek

The FDA has completed its safety assessment of the antibiotic Ketek (telithromycin) and is advising health practitioners and patients to be aware of rare but potentially serious health risks.

Ketek is indicated for the treatment of acute exacerbation of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia, including pneumonia caused by resistant strep infections. The drug has been associated with rare cases of serious liver injury and liver failure, with four reported deaths and one liver transplant after its use. The manufacturer, sanofi-aventis U.S. LLC of Bridgewater, N.J., is revising the drug labeling to address this safety concern.

Although it is difficult to determine the exact frequency of Ketek-associated adverse events on the basis of the FDA's

reporting systems, the agency has concluded that the drug's benefit to patients for the approved indications outweighs its risk, including the rare risk of liver failure, and supports its continued availability.

"We are advising both patients taking Ketek and their doctors to be on the alert for signs and symptoms of liver problems," says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research. "Patients experiencing such signs or symptoms should discontinue Ketek and seek medical evaluation, which may include tests for liver function." The signs and symptoms of liver failure include fatigue, malaise, loss of appetite, nausea, yellow skin, and dark-colored urine.

The FDA will continue to evaluate Ketek-associated safety issues and will take further action, if warranted.

Company Agrees to Correct Problems With Infusion Pumps

Baxter Healthcare Corp. and two of its top corporate executives have signed a consent decree of condemnation and permanent injunction for certain infusion pumps made by the firm. The company and executives have agreed to stop manufacturing and distributing all models of the Colleague Volumetric Infusion Pump and the Syndeo Patient Controlled Analgesic Syringe Pump within the United States until manufacturing deficiencies are corrected and until the devices are made in compliance with the FDA's current good manufacturing practice requirements and quality system regulation for devices.

Infusion pumps are electronic devices used to control the delivery of solutions and medications to patients. They are used in situations in which medication must be given intravenously or through other routes for an extended period of time.

"Infusion pumps deliver life-saving drugs and nutrition to thousands of critically ill patients," says Daniel Schultz, M.D., director of the FDA's Center for Devices and Radiological Health. "But if they don't work properly, patients are put at risk. Baxter has clearly had significant problems with some of its infusion pumps. With this action, Baxter has agreed to correct those problems. FDA's goal is to see that the necessary corrections are made, that the public health is protected, and that users have access to safe and effective pumps."

Under the consent decree, the FDA will allow the firm to continue to provide routine maintenance, or to replace components, parts, or accessories, for the Colleague and Syndeo Infusion Pumps that were already in the hands of customers before Oct. 12, 2005. Baxter also is required to submit to the FDA an acceptable detailed corrective action plan to bring these infusion pumps currently in use in the United States into compliance with the Federal Food, Drug, and Cosmetic Act. ■

Benzene in Beverages



Corbis

By Michelle Meadows

The Food and Drug Administration is working with the beverage industry to ensure that benzene levels in soft drinks and other beverages are as low as possible. Benzene is a chemical used in dyes and detergents, and in some plastics. It's also released into the air from automobile emissions and results from burning coal and oil. Benzene may be produced in soft drinks and other beverages with certain ingredient combinations. High levels of benzene in workplace air have caused cancer in workers.

The FDA has no regulatory limits for benzene in beverages other than bottled water. The U.S. Environmental Protection Agency has established a maximum contaminant level for benzene of 5 parts per billion (ppb) in drinking water. The FDA has adopted this level for bottled water as a quality standard. Based on results from a recent survey of soft drinks and other beverages conducted by the FDA's Center for Food Safety and Applied Nutrition (CFSAN), most beverage samples analyzed contained either no detectable benzene or levels below the 5 ppb limit for drinking water, and do not suggest a safety concern, says Judith

"The presence of benzoates and vitamin C as ingredients in a product doesn't mean that elevated levels of benzene have formed or will form," Kidwell says.

A Recent Survey

In November 2005, the FDA received private laboratory results reporting low levels of benzene in a small number of soft drinks that contain benzoate preservatives and vitamin C. In response to these findings, the FDA began collecting and analyzing samples of beverages with a focus on products that contain both benzoate and vitamin C.

From the start of the survey in

above 5 ppb in five of the beverage products tested: Crystal Light Sunrise Classic Orange, Crush Pineapple, Safeway Select Diet Orange Soda, Aquacal Strawberry Flavored Water Beverage, and Giant Light Cranberry Juice Cocktail.

Additional Actions

The FDA has contacted those firms whose products were found to contain more than 5 ppb benzene in the CFSAN survey. Manufacturers have reformulated the products to reduce or eliminate benzene, and some have sent samples to the CFSAN for analysis. Thus far, the CFSAN has tested a few

The FDA and industry initiated research and discovered that exposure to heat and light can stimulate the formation of low levels of benzene in some beverages that contain both benzoate salts ... and vitamin C.

Kidwell, a consumer safety officer in the CFSAN's Office of Food Additive Safety.

How Benzene May Form in Soft Drinks

In 1990, the FDA learned that benzene was present in some soft drinks. The FDA and industry initiated research and discovered that exposure to heat and light can stimulate the formation of low levels of benzene in some beverages that contain both benzoate salts, such as sodium benzoate or potassium benzoate, and vitamin C (ascorbic acid).

Sodium benzoate or potassium benzoate may be added to beverages to prevent the growth of bacteria, yeasts, and molds. Benzoate salts also are naturally present in some fruits and their juices, such as cranberries. Vitamin C may be naturally present in beverages or added to prevent spoilage or to provide additional nutrients.

November through April 2006, the FDA tested more than 100 soft drinks and other beverages. Beverage samples were collected from retail stores in Maryland, Virginia, and Michigan. The survey is not a reflection of the distribution of benzene in beverages in the U.S. food supply. The data cover a limited number of products and brands, and limited geographic areas. Even though the data are limited, Kidwell says, the FDA believes that the results indicate that benzene levels are not a safety concern for consumers. In May 2006, the FDA released results of the survey through April 20, 2006.

Almost all the samples analyzed in the CFSAN's survey contained either no benzene or levels below 5 ppb. "And benzene levels in hundreds of samples tested by other government agencies and the beverage industry are consistent with CFSAN's findings," Kidwell says.

The CFSAN found benzene levels

of the reformulated products provided by the manufacturers and found that benzene levels were less than 1 ppb; additional testing is ongoing.

The International Council of Beverages Associations and the American Beverage Association have developed guidance for all beverage manufacturers on ways to minimize benzene formation.

The FDA will continue to collect and analyze beverage samples for the presence of benzene and will continue to follow up with manufacturers as survey results warrant. "Once the FDA has completed its beverage survey we will determine whether further action is necessary to protect the public health," Kidwell says. ■

For More Information

Questions and Answers on Benzene in Beverages

www.cfsan.fda.gov/~dms/benzqa.html

In June 2006, the Food and Drug Administration's Counterfeit Drug Task Force released a new report on ways to curb the growing problem of counterfeit drugs. The report recommends measures that emphasize certain regulatory actions and the use of new technologies for safeguarding the integrity of the drug supply in the United States.

Curbing Counterfeit Drugs

"The adoption of the FDA Counterfeit Drug Task Force's recommendations will further reduce the risk that counterfeit products will enter the U.S. drug distribution system and reach patients," says Acting FDA Commissioner Andrew C. von Eschenbach, M.D. "We must remain vigilant in our efforts to ensure our nation's drug supply is protected against an increasingly sophisticated criminal element engaging in a dangerous type of commerce."

Among the new measures, the FDA will fully implement regulations related to the Prescription Drug Marketing Act of 1987, which requires drug distributors to provide documentation of the chain of custody of drug products—the so-called "pedigree"—throughout the distribution system.

The FDA had placed certain regulatory provisions on hold because of concerns raised at the time about the impact on small wholesalers. Most recently, in early 2004, the FDA delayed the effective date of certain regulatory provisions regarding pedigrees to allow the industry time to adopt electronic technology for tracking drugs through the supply chain.

On the basis of information from drug supply stakeholders, the FDA had expected this technology to be in widespread use in the drug supply chain by 2007. But it now appears that these expectations will not be met.

Furthermore, concerns raised in the past regarding the impact on small wholesalers have not been repeated. In

fact, the FDA was encouraged by most drug stakeholders to allow the hold to expire. Doing so also would provide clarity in the drug supply chain regarding who is and is not required to pass a pedigree. Continuing the hold would allow the current confusion to continue and to further allow opportunities for counterfeiting activity. The hold expires in December and will not be continued.

Consistent with recommendations of the Task Force, the FDA also announced that during 2007, its enforcement of the pedigree regulations will focus on products most susceptible to counterfeiting and diversion. The FDA intends to announce that the availability of a draft compliance policy guide for public comment describing this enforcement approach will be available in the Federal Register.

By providing guidance on the types of drugs that are currently of greatest concern to the FDA, the agency intends to give wholesale distributors a better idea on where and how to focus their initial energies to come into complete compliance with the regulations for all the prescription drugs they distribute. Under appropriate circumstances, the agency may initiate regulatory action, including criminal prosecution, for pedigree violations that do not meet the factors listed in the guidance.

The Task Force report also underlines the agency's belief that widespread use of electronic pedigrees (e-pedigrees) using electronic track and trace technology, including radio fre-

quency identification (RFID), would provide an electronic safety net for our nation's drug supply. RFID places electromagnetic chips and tags containing a unique serial number onto cartons and individual drug products. This technology creates an e-pedigree for tracking the movement of the drug through the supply chain. The report recommends that stakeholders continue to work expeditiously toward this goal, and that their implementation of RFID technology be used first on products most susceptible to counterfeiting.

The new FDA report is largely based on the Task Force's recent findings in numerous contacts with stakeholders, including a February 2006 public workshop, a request for public comment, and monitoring of the latest technological developments.

This latest report is the third in a series of documents exploring ways to ensure the safety of the U.S. drug supply. The first report, issued in 2004, outlined the framework for protecting the public from counterfeit medicines. The second report, released last year, assessed the progress toward implementing the 2004 recommendations. ■

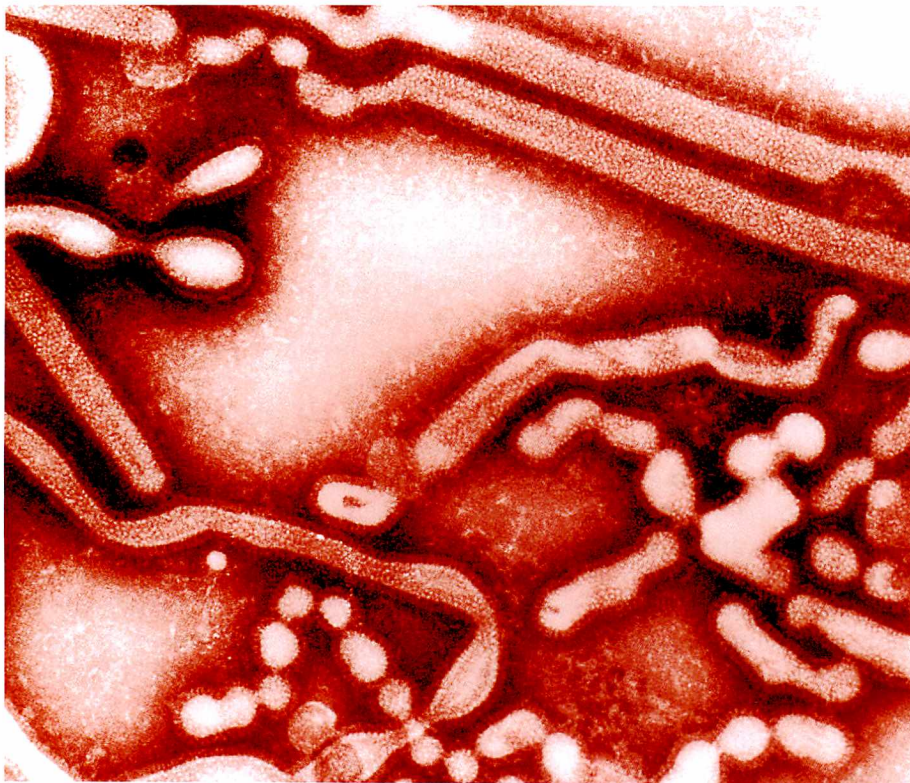
For More Information
FDA Task Force Reports
www.fda.gov/counterfeit

Influenza:

Vaccination Still the Best Protection

By Linda Bren

No one could say that the threat of bird influenza—along with talk of widespread illness, quarantines, and school and business closings— isn't alarming. The risk is real. Health officials are not downplaying it, and the nation is preparing for it aggressively at federal, state, and local levels.



Centers for Disease Control and Prevention

A photograph of influenza A virus taken through an electron microscope.

Bird (avian) influenza is caused by influenza viruses that occur naturally in wild birds. The avian influenza currently of concern, the H5N1 subtype, can be transmitted from bird to bird and, less frequently, from bird to human. The fear is that the virus will mutate into one that will spread easily from person to person, causing a pandemic—a worldwide outbreak of serious illness.

But people should not let the fear of avian influenza distract them from paying attention to the more predictable seasonal influenza, experts say.

"Clearly there's been a growing concern among Americans about a possible future avian influenza pandemic," says William Schaffner, M.D., professor and chairman of the Department of Preventive Medicine at Vanderbilt University School of Medicine in Nashville, Tenn. "There is no evidence of avian influenza [H5N1] among avians in this entire hemisphere let alone among people. But there will be influenza annually—real traditional, seasonal influenza."

Seasonal influenza is among America's most lethal killers, according to the Centers for Disease Control and Prevention (CDC), because the virus infects so many people—5 percent to 20 percent of the U.S. population every year. Most people who get this contagious respiratory illness caused by the influenza virus recover in a week or two without complications. But each year, more than 200,000 people have complications severe enough to send them to the hospital. And another 36,000 die each year from seasonal influenza—more than 250 times the number who have died in the last three years from avian influenza, reported to

be 133 by the World Health Organization (WHO) as of July 20, 2006.

Ninety percent of the deaths from seasonal influenza occur in those ages 65 and older, but the highest rates of infection occur in children. And healthy children younger than 2 years are as likely to land in the hospital because of influenza as those over 65.

"Vaccination remains the single most effective preventive measure available against influenza, and can prevent many illnesses and deaths," says Jesse Goodman, M.D., director of the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER). Yet each year, millions of Americans choose to take a chance and forgo influenza vaccination.

Public health officials urge those eligible for vaccination to receive it and remind people that although influenza vaccination begins in September or October each year, vaccine continues to be available in November, December, and later, and immunization during those months is still beneficial.

The CBER regulates vaccines for use in the United States and is responsible for their safety and effectiveness. "Ensuring an adequate, safe, and effective supply of influenza vaccine each year is one of FDA's highest priorities," says Goodman.

Who Should Get Vaccinated?

Vaccine is available this season to anyone who wants to reduce his or her chances of getting influenza, with a few exceptions, but the CDC strongly recommends it for certain people—those at high risk for serious influenza complications and those who live with or care for people at high risk, such as health care workers, nursing home

staff, and home caregivers. Groups at high risk are identified in the spring of each year by the CDC's Advisory Committee on Immunization Practices (ACIP). The CDC formally issues or reiterates the ACIP's recommendations in the summer. Influenza vaccine is not recommended for certain people, such as those allergic to eggs.

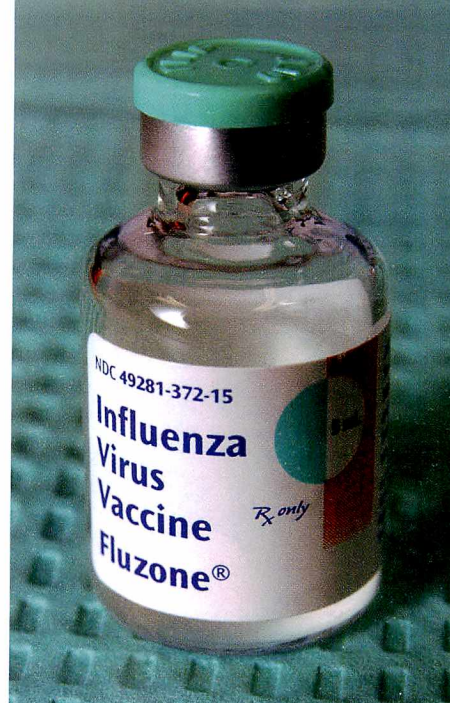
To protect more children at risk for serious influenza-related complications, the ACIP recommended in 2006 that children 6 months to 59 months of age be vaccinated. This recommendation expands the previous one to vaccinate from ages 6 months to 23 months. Children younger than 9 years receiving the vaccine for the first time need a booster dose one month after the initial dose.

Since no influenza vaccine is approved for children younger than 6 months of age, families should use a strategy known as "cocooning," says Schaffner. "They should provide a cocoon, or zone of protection, around that very vulnerable young child by vaccinating all the other people in the family, including grandma and granddad who come in for visits, and out-of-home caregivers."

How Well Does Influenza Vaccine Work?

Influenza vaccine works by stimulating our immune system to make antibodies—proteins that specifically recognize and target influenza viruses and help eliminate them from the body when we encounter them. Infection-fighting antibodies develop about two weeks after vaccination.

Studies have shown that influenza vaccine is 70 percent to 90 percent effective in healthy adults younger



Centers for Disease Control and Prevention

A vial containing the Influenza Virus Vaccine, Fluzone, distributed by Aventis Pasteur, USA.

than 65. In older people, children, and those with chronic illnesses, the vaccine may not necessarily prevent influenza, but it can reduce the severity of the symptoms and the risk of complications if they do get sick.

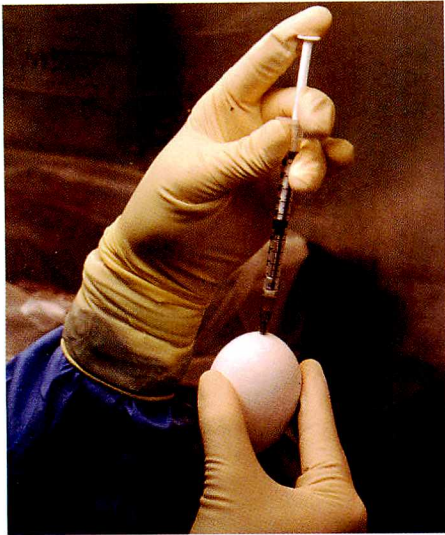
Vaccination in people older than 65 reduces the likelihood of hospitalization for influenza-related complications by 30 percent to 70 percent. And for those living in nursing homes or other long-term care facilities, the vaccine is up to 80 percent effective in preventing death from influenza.

Two Types of Influenza Vaccine

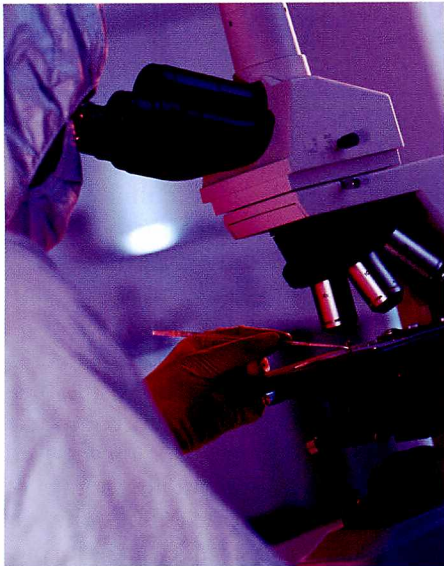
The FDA has licensed two types of influenza vaccine for use in the United States: the "shot" and the inhaled vaccine.

The shot contains inactivated, or killed, viruses and is given with a needle in the arm. The inhaled vaccine contains live viruses that are weakened, or attenuated, and is administered into the nose with a sprayer. The influenza shot can be given to those 6 months of age and older, including healthy people and those with medical conditions. The inhaled vaccine is approved only for healthy people between the ages of 5 years and 49 years, excluding pregnant women.

Production Schedule for Influenza Vaccine



Centers for Disease Control and Prevention



Artville



Centers for Disease Control and Prevention

Year-Round

Officials track influenza worldwide to help predict severity and timing for the upcoming season in the United States.

February

The ACIP/CDC issues early recommendations for vaccination for the upcoming season.

The FDA advisory committee, in collaboration with the WHO, selects three strains to be included in vaccine.

March–April

Licensed manufacturers receive reference viruses from the WHO collaborating centers, which include the FDA and the CDC.

Manufacturers generate seed viruses tested by the FDA to ensure that they are the same as the recommended strains. Viruses are injected into fertilized chicken eggs.

April–June

Manufacturers harvest and purify the virus from the eggs.

June

The ACIP/CDC meets and reiterates/updates recommendations.

May–July

The FDA provides antiserum to manufacturers to test each strain's potency.

July

Manufacturers blend three strains into one vaccine and ship sample vaccines to the FDA for release.

August

Manufacturers fill vials with vaccine and prepare to ship them.

September–November

Manufacturers ship vaccine to health care professionals for immunization; vaccine manufacturing continues.

October–November

Vaccination begins.

December–March

Influenza disease activity continues; immunization is still beneficial.

ACIP - Advisory Committee on Immunization Practices

CDC - Centers for Disease Control and Prevention

FDA - Food and Drug Administration

WHO - World Health Organization

The most common side effect of the influenza shot is soreness where the shot is given. Some people may get a mild fever, body aches, and fatigue for a few days, but you can't get influenza from the influenza shot, says Karen Midthun, M.D., the CBER's deputy director for medicine. "No vaccine is 100 percent effective. So you may get the flu soon after you received the vaccine, before it could be expected to protect you. It does not mean the shot gave you the flu."

Neither does the inhaled vaccine cause influenza in healthy people, the only group for which it's approved. "Some people may get a mild runny nose," says Goodman. Other mild side effects are nasal congestion, headache, sore throat, cough, and muscle aches.

A Year-Round Process

Preparing for the influenza season each year is a time-critical, highly orchestrated, collaborative effort between the FDA, CDC, National Institutes of Health (NIH), WHO, vaccine manufacturers, and the health community. The year-round process requires ongoing worldwide influenza disease surveillance, development of recommendations for immunization, selection of virus strains, preparation of antiserum used for standardization of new vaccine, and manufacture and distribution of new vaccine.

One of the biggest challenges in the process is to produce a new vaccine every year, says Goodman. "Because the virus mutates, each year's vaccine may be different from the preceding year."

"The manufacturing demands are tremendous," adds Goodman. "There's no other instance where a new vaccine is made every year, and actually three new vaccine components are made because there are three strains within our annual flu vaccine."

Each year, the vaccine formulation depends on the strains that are predicted to be circulating that season. The closer the match between the circulating strains and the strains that make up the vaccine, the better protection the vaccine offers.

The process begins in late January or early February when an FDA advisory

committee meets to recommend which three strains of the virus should be included in the vaccine, based on data from WHO laboratories in more than 80 countries. The FDA and the CDC collaborate with the WHO on strain selection, and the FDA makes the final decision on which strains will be included in the vaccine for the U.S. population. This season's formulation for the U.S. vaccine is identical to that recommended by the WHO, and it includes one virus from last year's vaccine and two new viruses.

Once the strains are selected, the FDA, CDC or other WHO collaborating centers can produce reference influ-

enza viruses that are adapted to high growth in eggs. The reference influenza viruses are provided to the licensed vaccine manufacturers to generate the "seed virus" for further manufacturing influenza vaccine. Following a rigorous review of safety and effectiveness data on manufacturers' vaccine products, the FDA has licensed four manufacturers to produce influenza vaccine for the 2006–2007 season.

Using an automated system, manufacturers inject the seed viruses into fertilized chicken eggs, which contain a nutrient in which the virus multiplies. "The high-growth virus generally grows well in fertilized hens' eggs,"

Influenza Drugs

Getting an annual influenza vaccination continues to be the first line of defense against seasonal influenza. But antiviral drugs—started within the first two days of experiencing influenza symptoms—can shorten the time influenza lasts.

The FDA has approved four antiviral prescription drugs to treat influenza: Tamiflu (oseltamivir), Relenza (zanamivir), Symmetrel and generics (amantadine), and Flumadine and generics (rimantadine). These drugs are in two classes, the adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir).

All four of these drugs also are approved to prevent influenza, but they are not substitutes for influenza vaccine. The Centers for Disease Control and Prevention (CDC) recommends that the drugs be used in specific circumstances, for example, in combination with the vaccine to help control influenza outbreaks in institutions such as nursing homes where people at high risk for complications from influenza are in close contact with each other. The CDC says, however, that people who receive inhaled vaccine that contains live viruses should not use antiviral drugs for at least two weeks after vaccination and should not get vaccinated within two days of stopping the use of antiviral drugs.

The drugs may be prescribed by a doctor to prevent influenza in place of vaccine in certain people, such as those who are allergic to eggs, the medium used to grow the virus for the vaccine.

Influenza viruses can rapidly develop resistance to certain drugs. Because of recent evidence that many circulating influenza viruses are resistant to amantadine and rimantadine, the CDC has recommended that these drugs not be used for influenza in the United States at this time.

The emergence of resistant strains of influenza was a catalyst for a regulation, which became effective June 20, 2006, prohibiting the use in chickens, turkeys, and ducks of the adamantane and neuraminidase inhibitor classes of human antiviral drugs for influenza, including all four approved drugs listed above. Although the FDA has not approved any veterinary drugs to treat or prevent influenza in animals, veterinarians can legally prescribe human drugs for use in animals under certain conditions, a practice known as extralabel use. The FDA may prohibit such extralabel use in animals, however, if it presents a risk to public health. ■



Getty Images

Hunein "John" Maassab, a professor of epidemiology at the University of Michigan, developed a nasal-introduced influenza vaccine called FluMist through the University of Michigan.

says Norman Baylor, Ph.D., director of the CBER's Office of Vaccines Research and Review. "Fertilized hens' eggs have been used safely and successfully to produce influenza vaccine since the late 1940s."

The manufacturer harvests and purifies the virus from the egg and applies chemical treatments to kill (inactivate) the virus so that it cannot transmit infection. These treatments are done for each of the three strains (monovalents), which are tested and retested by both the manufacturer and the CBER before being blended into the three-virus strain (trivalent) vaccine.

The CBER produces and provides manufacturers with antiserum. The antiserum is collected from sheep that have been injected with a purified influenza protein, causing the sheep to make antibodies to that influenza protein. The antiserum then is used to test vaccine potency for each influenza strain. Vaccine potency is determined by the manufacturer for each monovalent vaccine pool. "This is a critical step in the process, because you need to check the potency of each of the monovalents prior to blending," says Baylor, so that manufacturers can blend

the right amount of each monovalent into the final trivalent vaccine.

Manufacturers ship sample vials of vaccine from each lot, along with their test results, to the CBER for "lot release." The CBER reviews the test results as well as performs its own tests to ensure the accuracy of the manufacturers' tests and the vaccine's safety and effectiveness before releasing each lot for distribution.

Some lots of vaccine may be released as early as July, but manufacturing usually continues until October or later in order to produce and test the large volume of vaccine required for the U.S. population.

It takes about six months to complete influenza vaccine production—from egg to vial—each season. Throughout the process, the FDA discusses technical and manufacturing issues with the companies and inspects each company's facility and manufacturing processes while it is making vaccine.

"Each year, FDA begins working with manufacturers at the earliest stages of influenza vaccine development," says Goodman, "and we continue to assist them throughout the production phase."

Vaccine Supply and Shortages

Selecting the influenza virus strains each year, preparing the vaccine, and manufacturing and distributing millions of doses all must be precisely timed to make the vaccine available for the influenza season. Any problems encountered during the process may cause delays or shortages, says Goodman. In addition, because the number of companies that make influenza vaccine for the United States is small, a production problem with any company can substantially affect the overall supply.

Manufacturers have projected making about 100 million doses of influenza vaccine for the 2006–2007 season, but these projections could change as manufacturing continues. The projected supply is 16 percent more than the 2005–2006 season's 86 million doses and 40 percent more than the 2004–2005 season's 61 million doses. Demand has usually been around 70 million to 75 million doses.

"Influenza vaccine supply and distribution are very closely tied to the issue of demand," says public health researcher Christine Layton, Ph.D., M.P.H., of RTI International, a non-profit firm in Research Triangle Park, N.C. "Vaccine manufacturers produce as much vaccine as they anticipate they can sell. If they're unable to sell the vaccine, they take a loss."

A loss may mean they'll make less vaccine next season, says Layton, or they may want to get out of the influenza vaccine business altogether. "From a public health standpoint, we want to make sure that folks get flu shots so as much vaccine that is produced is used."

Government agencies monitor the vaccine market, but do not control it. Distributing and administering influenza vaccine is mostly a private sector enterprise. The CDC and state and local health departments work to influence distribution through collaborations and recommendations so that vaccine reaches the people most at risk, including older people, health care workers, nursing home residents, young children, and expectant mothers.

Vaccine distribution is a complex process, says Layton, involving manu-

facturers, wholesalers, distributors, purchasers, and providers. The providers may be private immunizers, such as doctors and nurses in private practice; community immunizers, such as visiting nurse associations; or mass immunizers, such as companies that come into a workplace or a retail establishment.

Some manufacturers sell directly to providers, others work exclusively with wholesalers, and some use both methods of distribution. In past seasons, says Layton, "where you ordered your vaccine from had a significant impact on how much vaccine you had." Since there is no coordinated system that manufacturers and distributors use to deliver vaccines, some health care providers receive their vaccine before others.

"Oftentimes, people will say, 'my own doctor doesn't have vaccine but the Costco has vaccine, or the Safeway has vaccine,'" says Layton, but that doesn't mean retailers get preferential treatment. "The retailers have not bought the vaccine. They have hired, as a customer service, a mass immunizer and have offered them space to do an onsite clinic." And the mass immunizer and the doctor's office may have purchased vaccine through different distribution channels.

Extending the Immunization Season

Sometimes, vaccine is in short supply early in the season, but there is leftover vaccine at season's end. How much vaccine is produced and distributed plays a role, says Layton, but so does timing. "The peak demand for flu vaccine is in October and November, when only about 50 percent of the vaccine has been delivered. But it's not until January, generally speaking, that all the vaccine has been available to providers."

And it's usually not until January or later that the influenza disease season peaks in the United States, according to the CDC. The FDA and the CDC support extending vaccination throughout the influenza season, into January and February.

The American Medical Association (AMA) also strongly supports an extension of the influenza immunization

season, says Ardis Hoven, M.D., an AMA spokeswoman and medical director of the University of Kentucky's Bluegrass Care Clinic in Lexington. "We know that the manufacturers cannot deliver all 100 million doses of vaccine early in the season—it's got to be staggered. For certain high-priority populations, receiving vaccination early in the season is obviously preferable. But the benefits of flu vaccine remain even when vaccinating through January and beyond, particularly if flu hasn't even hit the community yet."

Getting people vaccinated later in the season is challenging, says Schaffner, adding that there is a culture, or mindset, that needs to be changed in both vaccine providers and vaccine recipients. "From the point of view of providers, there's the sense that influ-

New Vaccines, Faster Production

The current method of influenza vaccine production uses millions of chicken eggs each year to grow the three different strains of influenza viruses—about 300 million eggs will be needed for this season's projected 100 million doses.

The process is complex and time-consuming, says Goodman. "It presents an enormous challenge for manufacturers and creates uncertainty for the vaccine supply."

Scientists and public health experts are looking for ways to boost the production of influenza vaccine and make it available more quickly to more people. And researchers are looking at new technologies that could be used to produce vaccine, not just for seasonal influenza, but for a pandemic.

Good Health Habits

The Centers for Disease Control and Prevention recommends practicing good health habits to help prevent getting influenza:

- **Avoid close contact.** Keep your distance from people who are sick.
- **Stay home when you are sick.** If possible, stay home from work, school, and errands when you are sick. You will help prevent others from catching your illness.
- **Cover your mouth and nose.** Use a tissue when coughing or sneezing. It may prevent those around you from getting sick.
- **Clean your hands.** Wash your hands frequently with warm, soapy water for about 15 seconds. It will help protect you from germs.
- **Avoid touching your eyes, nose, or mouth.** Germs are spread when a person touches something that is contaminated with germs and then touches his or her eyes, nose, or mouth. ■

enza immunization should be done by Thanksgiving."

Layton concurs that the holidays affect vaccine providers, such as stores that offer influenza vaccine clinics. "Retailers don't want to give up floor space during the holidays—they need that floor space for selling seasonal merchandise. They want to finish up shots around the end of October or beginning of November."

"I think that our patients, too, get preoccupied with the holidays," says Schaffner. "We need to persuade them that it's not too late to get vaccinated well into December, January, and even into February."

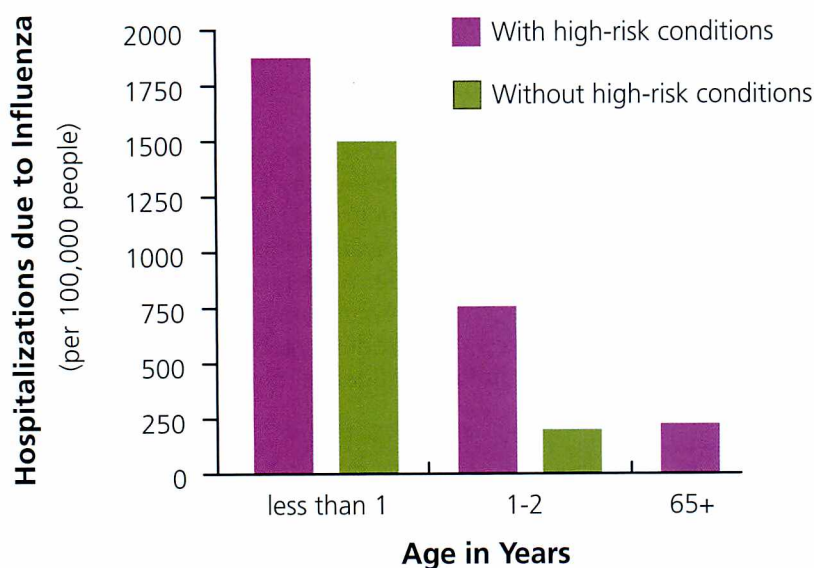
"With adequate supply and widespread immunization, we will be more likely to meet the challenge of annual influenza epidemics and future pandemics," says Goodman.

One of the technologies researchers are using is cell culture production, which allows a virus to grow and multiply in living animal cells instead of eggs. Cell-based vaccines could help meet surge capacity—making a lot of vaccine in a short time period—in the event of a shortage or a pandemic.

Making the vaccine initially in cell culture wouldn't save much time over the egg-based process, says George Curlin, M.D., M.P.H., an infectious

Influenza Causes Significant Numbers of Hospitalizations

Young children, especially those with certain underlying medical conditions, have high rates of influenza-related hospitalizations.



Centers for Disease Control and Prevention and the National Foundation for Infectious Diseases

Who Should Get Vaccinated?

The Centers for Disease Control and Prevention recommends influenza vaccination each year for the following groups of people:

- All children 6 months to 59 months of age—a new recommendation for this influenza season
- Women who will be pregnant during the influenza season
- People ages 50 years and older
- Children and teen-agers (ages 6 months to 18 years) who must take aspirin regularly and therefore might be at risk for developing Reye syndrome if they get influenza
- Adults and children ages 6 months and older with chronic heart or lung conditions, including asthma
- Adults and children who have required hospitalization or regular doctor visits during the past year because of chronic metabolic diseases (including diabetes), kidney disease, hemoglobin abnormalities, or weakened immune system (for example, caused by medications or HIV infection)
- People with any condition that makes it hard to breathe or swallow, such as brain injury or disease, spinal cord injuries, seizure disorders, or other nerve or muscle disorders
- Residents of nursing homes and other facilities that provide care for people with chronic medical conditions
- Healthy household contacts and caregivers of children up to 5 years old and people at high risk for severe complications from influenza
- Health care workers. ■

diseases researcher and adviser on vaccine clinical trials at the National Institute of Allergy and Infectious Diseases. "We'll still have to go through the annual process every year to make a match with the circulating virus. But should we need to ramp up production very, very quickly, you can use cell technology to do that faster than you can increase the availability of eggs."

With cell culture production, cells can be frozen and stored, and then thawed out and used to produce more vaccine as needed—a speedier process than acquiring millions more fertilized eggs. Like the current method of influenza vaccine production, the safety of vaccines produced in cell culture would be thoroughly evaluated by the FDA.

In May 2006, Health and Human Services Secretary Mike Leavitt announced the department's investment of more than \$1 billion in contracts with five companies to develop influenza vaccine made from cell culture. "Our current capacity of egg-based influenza vaccine production is not sufficient to meet increased demands during an emergency," said Leavitt. "Accelerating the development of this vaccine technology and creating domestic capacity are critical to our preparedness efforts."

Researchers also are looking at recombinant vaccines, made by genetic engineering, for influenza prevention. The gene from a specific influenza protein is isolated from the influenza virus, cloned, and grown in yeast or other cells to create large amounts of the protein. The protein produced is purified and then used to make vaccine. When the vaccine is injected into a person, the body's immune response to the recombinant protein protects against infection by the naturally occurring virus.

Cell culture and recombinant methods hold promise for developing new influenza vaccines, but researchers also are experimenting with substances that enhance vaccine effectiveness (adjuvants) to make current vaccines more potent. "If you could double the potency, the current technology could make twice as many doses," says Curlin, "which would make 50 percent of the doses available sooner." NIH-sup-

ported studies are under way using adjuvants as a "dose-sparing" technology.

Another area of research is a universal vaccine. This one-shot-fits-all vaccine would protect people for years against all strains of influenza anywhere in the world. "A universal vaccine would not require an annual change in the vaccine," says Curlin. "We wouldn't have to go through this annual complex, highly choreographed process which succeeds, but is a race against time every year." Although universal vaccine research has been going on for decades, says Curlin, "nothing seems like it's available right around the corner, but there are clinical trials starting."

The FDA has worked to streamline the vaccine approval and licensing process to encourage new vaccine development and to make vaccines available for use sooner. In March 2006, the agency published recommendations, in the form of two draft guidelines, to aid manufacturers in developing vaccines for both seasonal and pandemic influenza. The guidelines give specific approaches that vaccine developers can follow to show the safety and effectiveness of new vaccines, and they provide flexible, regulatory pathways for getting vaccines on the market.

One of these pathways is the accelerated approval process, which can reduce the development time for a new vaccine. For an application that does not use the accelerated approval pathway, a company must show that a vaccine actually prevents influenza, which requires waiting to see whether people in studies get sick or not. For accelerated approval, if the manufacturer demonstrates that within weeks after vaccination, adequate levels of protective antibodies are made in the blood that the FDA believes may prevent influenza, then this approach may be acceptable. If the accelerated approval approach is used, further studies are required after approval to make sure that the vaccine actually prevents influenza.

The accelerated approval pathway was critical in allowing the rapid approval in 2005 of Fluarix, a new influenza vaccine and the first vaccine of any kind approved using the FDA's

accelerated approval process.

Baylor says that because these guidelines will assist manufacturers in the development and evaluation of new vaccines for seasonal and pandemic influenza, the direction that they provide to new manufacturers, in turn, helps address the increased demand for influenza vaccine. Having additional manufacturers will enhance the capacity to produce more doses of influenza vaccine and contribute to the nation's pandemic preparedness. "Manufacturers who are already licensed for a seasonal vaccine would require limited clinical data for a new pandemic vaccine license, since the pandemic influenza vaccine would be manufactured by the same process as the seasonal vaccine," Baylor says.

In recognition of the different technologies available to researchers, the guidelines apply to specific approaches for vaccine development using cell culture, recombinant manufacturing, and newer technologies.

The FDA is committed to helping companies develop safe and effective vaccines for the seasonal influenza virus as well as assisting them with the development of a pandemic influenza vaccine when one becomes necessary. The release of the guidelines is just part of the cumulative effort that the FDA is undertaking to help in the development of vaccines. Another example includes correspondence with the major manufacturers of influenza vaccine in the world to stimulate interest in producing vaccine for the U.S. mar-

Where to Get Influenza Vaccine

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

- Contact your personal health care provider.
- Check the American Lung Association's locator at www.flucliniclocator.org for influenza clinics in your area.
- Call your local public health clinic or state health department immunization program. Or call the CDC at (800) CDC-INFO (232-4636).
- Check newspapers, radio stations, or other public information sources for specific clinics in your community.
- Check with your county medical society. ■

ket. This outreach resulted in one additional vaccine product approval for the 2005–2006 season, and the possibility for others in future influenza seasons. The FDA is also undertaking efforts to facilitate development of influenza vaccines using new technologies, including cell-based, and other novel types such as DNA and synthetic peptide. To accomplish this goal, the CBER is using various approaches to reach a broad audience, such as convening an advisory committee meeting to discuss the use of novel cell substrates for making influenza vaccine, and frequent interactions with vaccine manufacturers to provide both scientific and regulatory guidance. In addition, the CBER is participating in and leading meetings with industry, regulatory authorities of other nations, and stakeholders concerning the development of influenza vaccine. ■

For More Information

www.fda.gov/oc/opacom/hottopics/flu.html

www.cdc.gov/flu/

www.pandemicflu.gov



Pain Drugs for Dogs: Be an Informed Pet Owner

By Linda Bren

A decade ago, few drugs were available to treat pets in pain at home. Pups were spayed or neutered at the animal hospital, stitched up, and sent home without pain medication. And dogs with painful arthritis limped along without drugs that were safe and effective for long-term use.

Today, a new generation of nonsteroidal anti-inflammatory drugs (NSAIDs) is bringing relief to millions of dogs with joint problems or with pain after surgery.

"NSAIDs are extremely effective for controlling pain and inflammation in dogs," says Stephen F. Sundlof, D.V.M., Ph.D., director of the Food and Drug Administration's Center for Veterinary Medicine (CVM). "These are very valuable drugs that help many pets live to a ripe old age."

But like any drugs, NSAIDs carry a risk of side effects, or adverse reactions. Most adverse reactions are mild, but some may be serious, especially if the drugs are not used according to labeled directions. Some reactions result in permanent damage or even death.

"It's important for pet owners to be aware of the risks and benefits of all drugs, including NSAIDs, so that they can make informed decisions about their pets' health care," says Sundlof. "Owners who give their dog NSAIDs need to know the side effects to watch for that indicate their pet needs medical attention."

O.B., an Irish Wolfhound, owned by Lynne Heslip of Howell, Mich., was given NSAIDs for three years to successfully treat painful hip dysplasia.

Drugs used to control pain should be given only when necessary, and in the smallest dose that is effective.

The most common side effects from NSAIDs include vomiting, loss of appetite, depression, lethargy, and diarrhea. Serious side effects include gastrointestinal bleeding, ulcers, perforations, kidney damage, and liver problems.

"The side effects of NSAIDs are very well known and very well documented," says Michele Sharkey, D.V.M., in the CVM's Office of New Animal Drug Evaluation. But this information is not always getting to the pet owner, she says. "If the pet owner can recognize a possible reaction, stop the medication, and get veterinary help, it could mean the difference between a good outcome and a disaster."

Safety and Effectiveness

The CVM, which regulates drugs for use in animals, has approved some NSAIDs for use in dogs with pain from degenerative joint disease (osteoarthritis) or with pain after surgery. These include Etogesic (etodolac), Rimadyl (carprofen), Metacam (meloxicam),

Zubrin (tepoxalin), Deramaxx (deracoxib), Previcox (firocoxib), and Novox (generic carprofen).

NSAIDs help to control signs of arthritis, including inflammation, swelling, stiffness, and joint pain. Inflammation—the body's response to irritation or injury—is characterized by redness, warmth, swelling, and pain. NSAIDs work by blocking the production of prostaglandins, the body chemicals that cause inflammation.

The FDA considers approved NSAIDs to be safe and effective when used according to the label and when dog owners are informed about common NSAID adverse reactions.

And veterinarians are becoming increasingly aware of the advantages of recognizing and controlling pain, says Charles Lemme, D.V.M., a member of the American Veterinary Medical Association (AVMA), Clinical Practitioners Advisory Committee. "We recognize that pets are healing better and faster with pain control."

Lemme says that the emphasis on pain management may be partly because of the availability of the newer NSAIDs. "The NSAIDs we have available now are a lot safer than what we've had before and we're seeing far fewer side effects than before."

Before the newer generation of NSAIDs came along, "people were using NSAIDs such as aspirin in an attempt to mitigate arthritic pain," says Michael Andrews, D.V.M., president of the American Animal Hospital Association (AAHA). "We saw the consequence of their use," adds Andrews, who recalls seeing a client who gave her dog aspirin for six weeks, two times a day. "The dog had a bleeding nose that wouldn't stop."

"NSAIDs are used in many, many dogs and the frequency of problems is quite low," says Andrews. "The duration of use makes a difference in safety. If used for a day or two, the risks often are much lower than when used over long periods of time for a chronic arthritic condition."

Drugs used to control pain should be given only when necessary, and in the smallest dose that is effective, says Sharkey. "Arthritis waxes and wanes. Some animals get worse in cold weather. If the dog seems to improve to the point of not needing the drug, the owner should discuss continued use of the NSAID with a veterinarian."

An owner should never give an NSAID to a pet, or increase the dose or frequency of a drug, without the veterinarian's instructions, adds Sharkey. "Just like different people respond differently to a drug, the way each dog responds to an NSAID varies." Because of this individual response, no one NSAID is considered more effective than another, and because every NSAID can cause adverse reactions, none is considered safer than others.

If a pet is prescribed an NSAID, the CVM recommends that pet owners take the following steps to make sure they

Medicate Under Veterinary Supervision

The FDA has approved some nonsteroidal anti-inflammatory drugs (NSAIDs) for use in dogs. In the United States, there are no oral NSAIDs approved for use in cats. Veterinarians can, however, legally prescribe human drugs to animals unless it presents a risk to the public health. This type of use is known as extralabel, or off-label, for uses not listed on the label. Extralabel use can also mean prescribing a drug to a different species, for a different condition, or in a different dosage than that for which the drug was approved. For example, a veterinarian may prescribe a lower dose of an NSAID drug approved for dogs to a cat with an inflamed joint.

But pet owners should not give their own drugs to pets or otherwise medicate their animals without veterinary supervision, says Michele Sharkey, D.V.M., in the FDA's Center for Veterinary Medicine.

Different species metabolize drugs differently, she says. "You take aspirin or Tylenol on any given day for a headache and not think twice about it, but dogs are more sensitive to aspirin than humans, and one Tylenol can kill a cat. Pet owners should always work with their veterinarians to make medication decisions." ■

are fully informed about the drug and can make the best decision for their pet's health.

Ask Questions and Tell All

Ask your veterinarian about the benefits, risks, and side effects of any medication, including NSAIDs. "An informed dog owner is the best defense against serious side effects from NSAIDs," says Sharkey. "Owners should not hesitate to ask questions and inquire about possible side effects or signs to watch for when treating a dog."

Tell your veterinarian your pet's symptoms and current medications, including prescriptions, over-the-counter drugs, vitamins, herbal supplements, and flea control products. Giving NSAIDs and other medications together could harm your pet. Aspirin, for instance, may be in a supplement you're giving to your pet, says Sharkey, and should not be used in conjunction with an NSAID.

Ask for the Client Information Sheet

Pet owners should receive a "Client Information Sheet" with every NSAID prescription. Client Information Sheets, also called "Information for Dog Owner Sheets," are user-friendly summaries that explain the results to expect from using the drug, what to discuss with your veterinarian before giving the drug, possible side effects to look for, and other important information. The FDA has helped the pharmaceutical companies who make NSAIDs for dogs develop these sheets for the owners, and the companies provide them with each NSAID they ship.

Ask your veterinarian for the sheet if you do not receive one, and read the information carefully before giving the medication to your dog. If your veterinarian can't provide the Client Information Sheet, you can get one by printing it from the CVM's Web site or by calling the toll-free number of the drug company.

Bernadette Dunham, D.V.M., Ph.D., deputy director in the CVM's Office of New Animal Drug Evaluation, explains why some veterinarians may be unable to locate the Client Information Sheet.



"They often have the role of veterinarian and the role of pharmacist," she says. Veterinary hospitals get shipments of drugs from the pharmaceutical companies or distributors. Then they may repackage the drug in their hospitals' bottles, often in smaller quantities for distributing to clients. In the repackaging process, the Client Information Sheet, which is often printed on the package insert for the veterinarian, may be tossed out inadvertently.

The FDA, the veterinary community, and the pharmaceutical companies are working together to ensure that NSAIDs are used safely and responsibly

and that owners are given the Client Information Sheets.

"The pharmaceutical companies are trying to come up with creative ideas to make it easier for busy veterinarians," says Dunham. Many companies are making the Consumer Information Sheet a tear-off sheet that can be easily separated from the drug labeling.

Some companies also are packaging drugs in smaller quantities with the Consumer Information Sheet sealed inside the package. Therefore, the veterinarian can just attach the hospital label and dosing instructions on the drug container without repackaging the drug and inadvertently discarding



Information for Dog Owners about PREVICOX™ (firocoxib) Chewable Tablets

PREVICOX™ Chewable Tablets are for control of osteoarthritis pain and inflammation in your dog.

This summary contains important information about PREVICOX. You should read this information before you start giving your dog PREVICOX tablets and review it each time your prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want to know more about PREVICOX.

What is PREVICOX?
PREVICOX is a veterinary prescription non-steroidal anti-inflammatory drug (NSAID) used to control pain and inflammation due to osteoarthritis in dogs. Osteoarthritis is a painful condition caused by "wear and tear" of cartilage and other parts of the joints that may result in the following changes or signs in your dog:

- Limping or lameness.
- Decreased activity or exercise (reluctance to stand, climb stairs, jump or run, or difficulty in performing these activities).
- Stiffness or decreased movement of joints.

What kind of results can I expect when my dog is on PREVICOX for osteoarthritis?
While PREVICOX is not a cure for osteoarthritis, it can control the pain and inflammation and improve your dog's mobility.

- Response varies from dog to dog, but improvement can be quite dramatic.
- In most dogs, improvement can be seen within days.
- If PREVICOX is discontinued or not given as directed, your dog's pain and inflammation may return.

Which dogs should not take PREVICOX?
Your dog should not be given PREVICOX if he/she:

- Has an allergic reaction to firocoxib, the active ingredient in PREVICOX.
- Has had an allergic reaction (such as hives, facial swelling, or red or itchy skin) to aspirin or other NSAIDs.
- Is presently taking aspirin, other NSAIDs, or corticosteroids.
- Is under seven pounds in body weight.

PREVICOX should only be given to dogs.
People should not take PREVICOX. Keep PREVICOX and all medications out of the reach of children. Call your physician immediately if you accidentally take PREVICOX.

What to tell/ask your veterinarian before giving PREVICOX.
Talk to your veterinarian about:

- The signs of osteoarthritis you have observed in your dog, such as limping or stiffness.
- The importance of weight control in the management of osteoarthritis.
- What tests might be done before PREVICOX is prescribed.
- How often your dog may need to be examined by your veterinarian.
- The risks and benefits of using PREVICOX. Serious adverse reactions, including death, have been associated with PREVICOX administration at doses above the recommended dose in puppies less than seven months of age.

Tell your veterinarian if your dog has ever had the following medical problems:

- Any side effects from taking PREVICOX or other NSAIDs, such as aspirin.
- Any digestive upset (vomiting and/or diarrhea).
- Any kidney disease.
- Any liver disease.

Tell your veterinarian about:

- Any other medical problems or allergies that your dog has now, or has had in the past.
- All medicines that you are giving or plan to give to your dog, including those you can get without a prescription and any dietary supplements.

Tell your veterinarian if your dog:

- Is pregnant, nursing or if you plan to breed your dog.

Merial Limited

The FDA has helped pharmaceutical companies develop Client Information Sheets for people whose dogs are prescribed NSAIDs.

FDA-Approved NSAIDs for Use in Dogs

Brand name and established name		Manufacturer/ distributor and year of FDA approval	Indication	Type of dosage	Manufacturer's telephone number for assistance or to report suspected adverse reaction
Etogesic	etodolac	Fort Dodge Animal Health, 1998	management of pain and inflammation associated with osteoarthritis in dogs	tablet	(800) 533-8536
Rimadyl	carprofen	Pfizer Animal Health, 1996 (caplet); 1999 (tablet); 2003 (injectable)	relief of pain and inflammation associated with osteoarthritis in dogs; control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs	caplet and chewable tablet; injection	(800) 366-5288
Deramaxx	deracoxib	Novartis Animal Health US Inc., 2002	control of pain and inflammation associated with osteoarthritis in dogs; control of postoperative pain and inflammation associated with orthopedic surgery in dogs ≥ 4 lbs	chewable tablet	(800) 332-2761
Metacam	meloxicam	Boehringer Ingelheim Vetmedica Inc., 2003 (oral suspension, and injectable)	control of pain and inflammation associated with osteoarthritis in dogs	drops given by mouth; injection	(866) METACAM (638-2226)
Zubrin	tepoxalin	Schering-Plough Animal Health Corp., 2003	control of pain and inflammation associated with osteoarthritis in dogs	rapidly disintegrating tablet	(800) 224-5318
Previcox	firocoxib	Merial Ltd., 2004	control of pain and inflammation associated with osteoarthritis in dogs	chewable tablet	(877) 217-3543
Novox	generic carprofen	IMPAX Laboratories Inc./Vedco Inc., 2005	relief of pain and inflammation associated with osteoarthritis in dogs	caplet	(888) 708-3326

U.S Food and Drug Administration



Lynne Heslip and her Irish wolfhound, Isabella, compete in the show ring before Isabella was diagnosed with hip dysplasia. Now retired, Isabella takes a nonsteroidal anti-inflammatory drug (NSAID) to help relieve joint pain.

Lynne Heslip

the sheet.

Through published journal articles, electronic newsletters, and information posted on their Web sites, both the AVMA and the AAHA are reinforcing the importance of client communication regarding NSAIDs, including handing out the Client Information Sheets, to their veterinary members.

Get the Recommended Tests

NSAIDs approved for use in dogs contain the following information on their labels:

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to

establish baseline blood values prior to, and periodically during, the use of any NSAID are strongly recommended.

If the veterinarian recommends a blood test before administering an NSAID to a dog, don't decline it, advises Sharkey. "There are good reasons for it." The knowledge gained from these tests could be critical in deciding whether the drug is safe to use in a dog.

Testing is particularly important with long-term NSAID use, such as to treat arthritic pain, says Andrews. "It makes sense to do some preliminary screening blood work and periodic tests to identify any problems and

monitor how well the pet is tolerating the drug over time."

Work With Your Veterinarian to Find the Best NSAID

Many NSAID choices are available, and selecting the best NSAID for a particular pet is important, says Sharkey. "Sometimes, the process of finding the best one can mean changing the prescription."

Lynne Heslip of Howell, Mich., tried several NSAIDs on her 4-year-old Irish wolfhound, O.B., who had painful hip dysplasia. "The first NSAID did not work well," she says. "Pain relief seemed to be minimal, and she had vomiting and wasn't interested in eat-

An owner should be encouraged to call his or her veterinarian with any concerns about the NSAID the dog is receiving.

ing." Heslip watched her normally outgoing dog seclude herself behind the kitchen table. "She was severely depressed. She didn't want to interact with other animals or with people."

Working with her veterinarian, Heslip stopped the NSAID, waited five days for the drug to clear out of the dog's system, and tried another NSAID. "Within one week, I noticed a drastic change for the better," says Heslip. "She was much more animated and happier." O.B. was on NSAIDs for about three years until her death. Heslip reports that her current 6-year-old Irish wolfhound, Isabella, is on the same NSAID, with very good results.

Bad Reaction? Stop Medication and Call a Veterinarian

If you suspect an adverse reaction to an NSAID, stop administering the drug and contact a veterinarian immediately. Some reactions are mild and go away after stopping the drug.

When giving a pet an NSAID, watch for these side effects, which are listed on the Client Information Sheet and on the drug label:

- Decrease or increase in appetite
- Vomiting
- Change in bowel movements (such as diarrhea or black, tarry, or bloody stools)
- Change in behavior (such as decreased or increased activity level, seizure, aggression, or lack of coordination)
- Yellowing of gums, skin, or whites of the eyes (jaundice)
- Change in drinking habits (frequency or amount consumed)
- Change in urination habits (frequency, color, or smell)
- Change in skin (redness, scabs, or scratching).

These side effects are the most common. But not all possible side effects are included on the Client Information Sheet or on the drug label. Always con-

tact your veterinarian if you have questions about your dog's medication.

What starts out as a minor problem can rapidly progress to an emergency. An owner should be encouraged to call his or her veterinarian with any concerns about the NSAID the dog is receiving. You may even call the drug manufacturer's toll-free number that appears on each Client Information Sheet. When problems are experienced with a product, the manufacturer may have specific recommendations for your veterinarian regarding tests and treatments.

Cindi Brinkley of Danville, Ill., rushed her dog to the veterinarian at the first sign of a bad reaction. Maude, a cocker spaniel-collie mix, injured herself when she was 11 months old while playing with a littermate in the house. "She slipped on the basement floor coming out of a turn, and both back legs splayed out," says Brinkley.

Maude was diagnosed with a deformed hip joint and scheduled for corrective surgery. In the meantime, the veterinarian prescribed an NSAID for pain control. "I was not told a thing about the drug other than how to give it to her," says Brinkley.

Maude had been on the drug for a month when Brinkley came home from work one day to find the dog bleeding from her rectum. "It was very, very frightening," she says. "The whole back of my dog was bright red—I thought she was bleeding to death." After treatment in the veterinary hospital and discontinuation of the drug, Maude recovered from the incident. Now more than 7 years old, "she has some vomiting and loose stools every so often," says Brinkley, who suspects the digestive problems may be a lasting effect of the drug.

Report Bad Reactions

If you or your veterinarian suspects that an adverse reaction is related to the use of an NSAID or any drug, it

should be reported to the pharmaceutical company. Usually, the veterinarian reports it, but if the veterinarian doesn't, the owner should. The company, by law, has to report all adverse reactions to the FDA, which looks for signals of increased frequency and severity of adverse reactions. The FDA works with the pharmaceutical firms to address these events and improve the ability of the product to be more safely used.

If unable to report problems directly to the pharmaceutical company, veterinarians and owners are encouraged to report veterinary Adverse Drug Experiences (ADEs) and suspected product failures to the government agency that regulates the product. Adverse experiences with NSAIDs should be reported to the FDA's CVM. ■

Michele Sharkey, D.V.M., of the FDA's Office of New Animal Drug Evaluation, contributed to this article.

For More Information

FDA Center for Veterinary Medicine
www.fda.gov/cvm

American Veterinary Medical Association
www.avma.org

American Animal Hospital Association
www.aahanet.org

Questions regarding ADE reporting should be addressed to:

Center for Veterinary Medicine
Division of Surveillance, HFV-210
7519 Standish Place
Rockville, MD 20855
(888) FDA-VETS (332-8387)

Advancing Public Health Through Partnerships



Edwin Remsberg

Andrew Kane, Ph.D., associate professor at the University of Maryland School of Medicine and director of the university's Aquatic Pathobiology Center in College Park, investigates drugs and enzyme patterns in fish.

By Michelle Meadows and Mitchell Weitzman

Whether the goal is ensuring the safety of the food supply or speeding the development of new medical treatments, the Food and Drug Administration often depends on its strong relationships with other organizations. Health care providers, regulated industry, members of academia, other government agencies, and consumers all contribute their expertise and experiences when the FDA tackles complex scientific issues.

In one example, a partnership with the National Alliance for Hispanic Health, the FDA ensures that public health alerts are available in Spanish.

"Our collaborations are an essential part of the FDA's long-term strategy to promote and protect the public health," says Acting FDA Commissioner Andrew C. von Eschenbach, M.D. "By making effective use of collective resources, each party can achieve much more than it ever would alone."

The FDA regulates products that represent almost 25 percent of all consumer spending. This total includes 80 percent of the nation's food supply and all human drugs, vaccines, medical devices, cosmetics, tissues for transplantation, radiation-emitting equipment, and animal drugs.

"In order to truly meet the emerging needs of patients and other populations that we serve, the FDA cannot function in a vacuum," von Eschenbach says. "As we carry out our

leadership role, we must remain sensitive to the changes occurring around us and work with others in the public and private sector who are also committed to building a healthier nation."

In one example, a partnership with the National Alliance for Hispanic Health, the FDA ensures that public health alerts are available in Spanish. In another, the FDA and Health Canada share analytical tools to prevent medication errors due to similar-sounding drug names. The FDA's collaborations range from informal work agreements on projects of mutual interest to financial partnerships that support state-of-the-art medical technology. Here's a look at some of the major partnerships in which the FDA is involved.

FISH MEDICINE AND RESEARCH

Aquaculture, also called fish farming, involves raising fish in enclosed areas to be sold as food. The FDA is interested in ensuring that farmed fish are safe for human consumption, says Renate Reimschuessel, V.M.D., Ph.D., a research biologist who joined the Center for Veterinary Medicine (CVM) in 1999 to develop an aquaculture research program. "More vaccines are needed to prevent infectious diseases in fish, and more drugs are needed to treat fish that get sick," says Reimschuessel.

Examples of diseases that are a threat to the fish farming industry are infectious salmon anemia and enteric septicemia of catfish, a bacterial infection that can cause rashes and bleeding. Only seven drugs are approved by the FDA to treat diseases in farm-raised fish. And, as the aquaculture industry grows, there is a need to develop safer and more effective drugs for fish diseases.

Reimschuessel and Badar Shaikh, Ph.D., a research chemist in the CVM, are collaborating on a project with Andrew Kane, Ph.D., associate professor at the University of Maryland School of Medicine and director of the university's Aquatic Pathobiology Center in College Park.

Shaikh is leading a study at the CVM to investigate the metabolic profiles of model drugs in various fish species. The study will be used to determine the marker residues for which analytical methods will be developed to measure drug residues in aquaculture-raised fish. This research should help with regulatory monitoring so that fish destined for human consumption are safe.

Kane is looking at liver enzyme patterns in different fish

in response to the same model drugs. This research collaboration, as a potential way to spur drug development, is funded through the Joint Institute for Food Safety and Applied Nutrition (JIFSAN), a partnership between the FDA and the University of Maryland.

"We are researching profiles to characterize and predict drug residues in fish, which includes collecting data to model the relationship between the fish species and their metabolic capacity," Kane says. "We are looking closely at how the fish metabolize and excrete the drugs. And the FDA wants to make sure that drug residues in the fish don't wind up in the fillet on your plate."

The FDA has a facility in Laurel, Md., for conducting state-of-the-art aquaculture research. The facility has four fish culture rooms totaling about 4,600 square feet and a specialized aquatic research laboratory of 600 square feet. A computer system monitors the water system temperature.

There are several steps in the development of methods to test for drug residues in fish. The first step involves feeding the fish a drug, sometimes by putting capsules in gel food. Then researchers take tissues from the fish and process the samples. For example, researchers may separate the serum from a blood sample. Frequently, muscles are frozen and blended with dry ice to create a uniform powder. When samples are taken, the general health of the fish is also examined and recorded, including the clarity of the eyes, the quality of the scales, and any areas of discoloration.

Researchers then put the processed samples in an instrument to detect the drug. "The testing method depends on

the type of drug, tissue, and what kind of analytical equipment you are using," Reimschuessel says.

Kane says part of the research focuses on "species grouping"—the process of classifying species of fish based on similarities in anatomy, physiology, and drug metabolism. "Developing a new drug protocol for a single fish species costs millions of dollars, which fish farmers don't have," Kane says. "It will be beneficial if we find a new drug that could get rid of a bacterial pathogen in not only salmon, but also trout." Kane studies channel catfish, largemouth bass, rainbow trout, and other species.

The goal of the research is to improve the drug approval process and to expand the drugs available for fish production. "Having metabolic profiles may help shorten the drug approval process," Reimschuessel says. "We want to give veterinarians more choices for safe and effective treatments."

Other aquaculture studies have developed disease models in fish to learn more about diseases in humans, says Reimschuessel, who has created a research internship program at the CVM for veterinary students interested in aquaculture.

There are several steps in the development of methods to test for drug residues in fish.

Researchers have investigated infection-fighting genes in goldfish in the hopes of finding a vaccine against tuberculosis in humans, for example. "Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis*," Reimschuessel says. "So we look for mutated versions of a similar pathogen, *Mycobacterium marinum*, in fish. This could help create an *M. marinum* vaccine to keep fish disease-free and create a tuberculosis vaccine that would reduce the disease in people." ■

ACADEMIC ALLIANCES FOR FOOD SAFETY

Every year, foodborne diseases cause about 76 million illnesses and 5,000 deaths in the United States, according to the Centers for Disease Control and Prevention. Since 2000, a program called the Good Agricultural Practices (GAPs) International Training Program has been working to minimize microbial food safety hazards for produce during production, packing, and transportation.

Bacteria, parasites, and viruses can contaminate produce in many ways. The improper use of manure, water, and soil are just a few. "By teaching GAPs principles to U.S. trading partners, we want to prevent microbiological contamination of fresh produce," says Chris Walsh, Ph.D., the Joint Institute for Food Safety and Applied Nutrition (JIFSAN) international training coordinator and a professor of horticulture at the University of Maryland in College Park. Over the past six years, GAPs has been taught in Brazil, Mexico, Thailand, Chile, El Salvador, Trinidad, Puerto Rico, Honduras, and Korea.

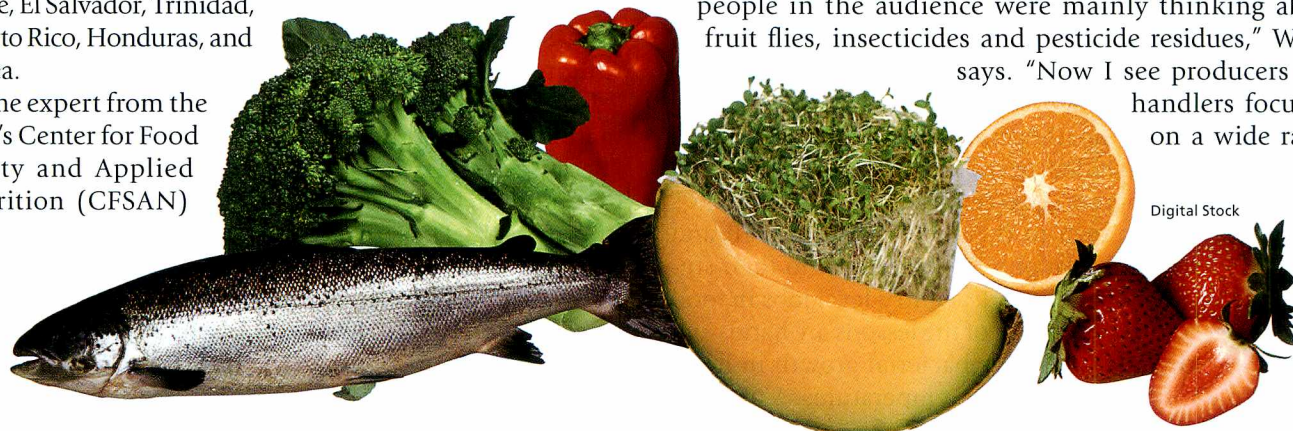
One expert from the FDA's Center for Food Safety and Applied Nutrition (CFSAN)

and three university representatives lead the GAPs five-day training programs. Sometimes, the scientists come from the same university, or they might come from three different universities. Most of the people who take the trainings work with either farmers or food packaging houses, and they in turn train others. Both basic and advanced levels are offered.

Participants break into small groups and work on case studies covering hygiene, water quality, proper packaging, proper collection and disposal of farm waste, and other food safety issues. They work as a team to give presentations and participate in a field trip where they can see how to apply what they've learned.

Since the inception of the GAPs program, Walsh says he has seen food safety and microbial contamination rise to the top of people's minds in exporting countries. He cites Mexico as one example. "When we first started this, most people in the audience were mainly thinking about fruit flies, insecticides and pesticide residues," Walsh

says. "Now I see producers and handlers focusing on a wide range



Digital Stock

of sanitary microbial issues. We can see the progress when we make repeat visits to a site. We might see a whole new sanitation facility or new signs about hand washing."

GAPs is a major program of JIFSAN, a partnership between the FDA and the University of Maryland that was established in 1996 to advance food safety research, education, and outreach.

CFSAN scientists are involved with many academic collaborations, including other formal academic partnerships, says Elizabeth Calvey, acting director of the Academic Liaison Staff in the CFSAN's Office of Science. For example, the National Center for Food Safety and Technology in Chicago is a research consortium founded in 1988 as a collaboration involving the CFSAN, the Illinois Institute of Technology, and the food industry. "Here, the emphasis is

on ensuring food safety and security through research on both novel and conventional food processing and packaging technologies," Calvey says.

The CFSAN also has an agreement with the University of Mississippi's Thad Cochran National Center for Natural Products Research. Established in 2001, the center helps the FDA assess the safety of botanical dietary supplements. For example, the center provided collections of more than 20 different species of ephedra from around the world, which assisted the CFSAN and the FDA with their evaluation of dietary supplements containing ephedrine alkaloids. Dietary supplements containing ephedrine alkaloids were banned in 2004 because of concerns over their health risks such as cardiovascular effects, including elevated blood pressure, irregular heart rhythm, and strokes. ■

BRINGING FOOD SCIENCE TO TEENS

Twenty-one people in one county have become ill with similar symptoms: nausea, vomiting, diarrhea, cramps, and fever. All of them became ill within the last month, and all have tested positive for the *Shigella* bacterium. What steps should be taken to investigate this case? What questions need to be answered?

This scenario is one kind of activity found in *Science and Our Food Supply*, a curriculum used in a professional development program in food science. The program is a partnership between the FDA's CFSAN, the U.S. Department of Agriculture Graduate School, and the National Science Teachers Association (NSTA).

Each year, 25 middle school and 25 high school science teachers are selected to attend a week of immersion training in food safety. In a six-day summer program, teachers work on experiments, hear presentations by CFSAN experts, and tour a seafood processing plant, among other activities—all without cost to the participants.

"Workshops include activities that allow teachers to more fully understand how pathogenic bacteria can grow in food that is not stored, handled, or cooked properly," says Louise Dickerson, the program's project officer at the CFSAN.

"Teachers then return to their schools in the fall and teach this very important public health topic to their students, many of whom will work at entry-level jobs in food service," Dickerson says. Many of the lessons are hands-on, like having students record the bacterial growth in hamburgers that they cook to various temperatures. A two-day



Family Photo

Seventh-grader Kaleb Thomas says a class experiment indicated that dairy foods improved the growth rate of rats.

conference in December allows those who have been through the program to share teaching strategies.

So far, 340 teachers from all 50 states, the District of Columbia, the U.S. Virgin Islands, Guam, and Puerto Rico have participated in the program, which began in 1999. As part of their agreement to complete this summer training, participants train other teachers. This development effort has reached more than 6,000 teachers nationwide, Dickerson says. As of May 2006, the program had reached more than 1.7 million students.

The *Science and Our Food Supply* curriculum kit includes middle school and high school teaching guides, an A-Z glossary of food safety terms, and a video called "Dr. X and The Quest for Food Safety." Dr. X is a food scientist who leads students on a journey through the food supply chain. In 2001, the video won an Emmy from the National Academy of Television

Arts & Sciences in the category of Outstanding One Time Children's Television Programming.

In 2005, the summer program was updated with information on the latest Dietary Guidelines for Americans. "Because of the rising problem of obesity, the program is expanding to cover not only food safety, but also nutrition information," Dickerson says.

"My seventh grade class loved the labs, and they were fairly easy to implement," says Nancy Miller, a science teacher at the Potter-Dix Schools in Potter, Neb., who participated in the program in 2005. In June 2006, Miller was named one of two Nebraska Agriculture in the Class-

room Teachers of the Year by the Nebraska Farm Bureau Federation.

"Students had to design their own handwashing experiment," Miller says. "Some tested hot versus cold water to wash their hands in 20 seconds in one group and 20 seconds in another group. They liked the 'glo germ' and black light which showed how well their hands were washed."

It's always fun to carry out labs instead of only doing book work, says Kaleb Thomas, a seventh grader who participated in Miller's class. Kaleb says he particularly enjoyed an experiment in which they fed rats to see whether dairy foods helped growth. "One rat was fed foods from all food groups and the other was fed all food groups except dairy. I learned that the dairy foods helped the one rat grow bigger," he says. "I liked playing with the rats, but did not like cleaning the cages."

Some new additions will make the program even more successful, says Al Byers, assistant executive director for government partnerships and e-learning at the NSTA. "We are really emphasizing a blended approach to professional development that combines both face-to-face and online opportunities for learning."

The new features include an FDA-NSTA symposia that will allow teachers to have opportunities to interact with each other and receive training from education specialists, as well as interactive Web seminars that deliver science content. Two soon-to-be-released resources, NSTA SciGuides

*Each year, 25 middle school
and 25 high school science
teachers are selected to attend
a week of immersion training
in food safety.*

and SciPacks, also will give teachers interactive learning experiences and include ready-to-use lesson plans. "These new tools from NSTA will help educators incorporate the Web-based resources into their classrooms," Byers says.

"The challenge is that there are 2 million teachers of science in the United States. So it will be great to expand the reach of food science curriculum material. These online food science resources will be available to any science teacher anywhere." ■

FOSTERING THE CRITICAL PATH INITIATIVE

The FDA's critical path initiative aims to bring medical discoveries to patients faster by modernizing product development. This modernization effort includes creating new tools to assess new drugs and medical devices.

For example, cutting-edge imaging techniques hold potential for staging cancerous tumors and for assessing response to therapy. New imaging technologies may also contribute to powerful new biomarkers for drug distribution and metabolism. Biomarkers are biologic indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests and tests on blood, tissue, and other biologic samples.

"As we improve product development, we also want to make sure that we are protecting people who participate in clinical trials that test new therapies," says Isaac Montoya, Ph.D., clinical professor in the University of Houston's College of Pharmacy. In April 2005, Montoya coordinated and moderated a conference titled "The Critical Path to New Medical Products: The Challenges in Protecting Human Subjects."

The national conference was cosponsored by the FDA, the University of Houston's College of Pharmacy, and the Office of Human Research Protections of the U.S. Department of Health and Human Services. More than 150 researchers and other health experts explored topics such

as research ethics, informed consent, data collection, and federal regulations.

Montoya calls the conference a community effort, citing the involvement of experts from his neighboring colleges at the Texas Medical Center—the University of Texas Health Science Center, Baylor College of Medicine, and M. D. Anderson Cancer Center. "Interest in the conference was high," Montoya says. "We have had a number of follow-up requests from other institutions who are eager to learn more about these topics."

Researchers had a good opportunity to learn more about the FDA's oversight, says Elisa Harvey, D.V.M., Ph.D., director of Investigational Device Exemption and Humanitarian Device Exemption Programs in the FDA's Center for Devices and Radiological Health (CDRH). Harvey gave a talk about FDA regulations for medical devices.

The critical path conference was part of a larger collaboration between the FDA and the University of Houston that began in 2003. The CDRH is the lead FDA center for the partnership, and the College of Pharmacy is the lead institution for the University of Houston.

"Pharmacy professionals bring knowledge to FDA that is useful in reviewing drug-device combination products," says Michelle Chenault, Ph.D., associate director for the Medical Device Fellowship Program in the CDRH. "Many

This modernization effort includes creating new tools to assess new drugs and medical devices.

home care technology products such as glucose meters, pregnancy tests, contact lens solutions, and blood pressure devices are often provided by the pharmacy and neighborhood drugstore."

Other University of Houston colleges that are part of the partnership include the Cullen College of Engineering, the College of Optometry, and the College of Technology. "We are encouraging University of Houston experts to experience training at FDA, and FDA experts can also

take advantage of training opportunities at the university," Chenault says.

"Because of our distance from the Washington, D.C. area, we feel like our collaboration with the FDA has offered us a way to close the distance gap," Montoya says. "It makes securing product approval a lot less intimidating. Rather than learning about drug and device approvals through textbooks, students now have opportunities to get hands-on experience in a regulatory environment." ■

INTERNATIONAL COMMUNICATIONS

In September 2003, the FDA entered into a confidentiality arrangement with the European Commission (EC) and the European Medicines Agency (EMA). The EC is composed of representatives from the 25 member countries of the European Union, including Spain, France, Germany, Italy, Sweden, and the United Kingdom. The EMA coordinates the evaluation and supervision of most new drugs throughout the European Union.

"This confidentiality arrangement covers human drugs, biologics, and veterinary products, and helps improve public health by strengthening our interactions," says Matthew Eckel, staff director for Europe, Harmonization, and Trade in the FDA's Office of International Programs. "It gives us an avenue to exchange nonpublic information and perspectives to assure that we both have as much information as possible when making regulatory decisions. We may develop shared approaches, if appropriate." This type of cooperation promotes global harmonization—a movement to harmonize information and requirements between regulatory authorities in different countries.

The agreement provides for the exchange of otherwise nonpublic information between the FDA and the EMA during the review of drug and biologic applications and after drugs and biologics get on the market. Examples of documents that may be exchanged are draft guidance papers, impending regulatory actions, inspection reports, and adverse event reports.

"We use this mechanism to give each other advance notice of significant regulatory actions that are of mutual interest," Eckel says. "So confidentiality is important." There may also

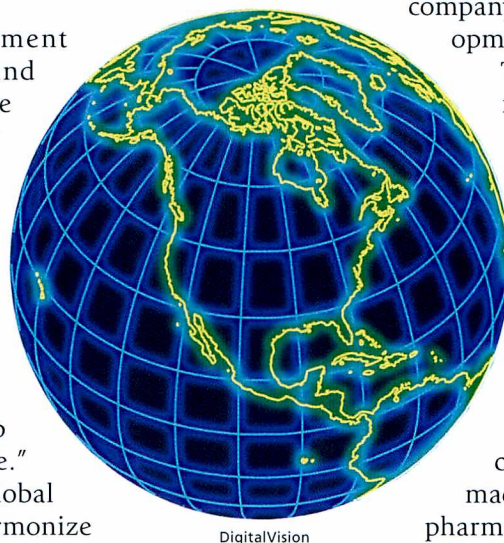
be occasions when experts will visit each other's agencies and have access to nonpublic information.

One pilot program under the agreement allows companies to obtain parallel scientific advice from the EMA and the FDA. "This gives the EMA and the FDA a way to communicate with sponsors simultaneously and exchange views between all three parties (the EMA, the FDA, the company) on scientific issues during the development of new products," Eckel says.

The EMA-FDA confidentiality arrangement was reviewed at a meeting in Brussels, Belgium in March 2006, and all parties deemed the arrangement a success. The confidentiality arrangement was extended through 2010. At the same meeting, the parties agreed to intensify trans-Atlantic cooperation by adding a new focus on vaccines, including preparedness for flu, medicines for children, medicines for rare diseases, drugs that treat cancer, and pharmacogenomics. Pharmacogenomics is the blending of drugs—

pharmacology—with genomics. It's a science that allows researchers to predict the probability of a drug response, both good and bad, based on a person's genetic makeup.

In May 2006, the EC, the EMA, and the FDA announced that they agreed to a procedure for joint FDA-EMA meetings with sponsors after voluntary submission of pharmacogenomic data. These joint voluntary submissions are important for regulatory agencies to ensure that evolving policies are based on the best science, to help develop common approaches to genomics in drug development, and to encourage the use of pharmacogenomic tests during global drug development. ■



MANAGING DRUG SAFETY RISKS

Manufacturers are required to report side effects to the FDA through the agency's Adverse Event Reporting System (AERS). Health care professionals and consumers send in adverse event reports related to drugs, biologics, devices, and dietary supplements voluntarily through the MedWatch program. When a potential "safety signal" is spotted, FDA experts evaluate how the product is being used in clinical practice.

The FDA's Office of Surveillance and Epidemiology routinely monitors adverse events for all drugs, and also taps into outside resources. One such collaboration involves Harvard Pilgrim Health Care Inc., a large health insurer based in Wellesley, Mass.; the Kaiser Foundation Research Institute in Oakland, Calif.; Vanderbilt University in Nashville, Tenn.; and Ingenix Inc., a division of UnitedHealth Group, another large health insurer based in Eden Prairie, Minn.

Each of these organizations maintains databases that contain information on outpatient prescription drug use, and medical claims from physician visits, hospital admissions, health maintenance organizations, state Medicaid programs, and other sources. Together, the databases contain data on 23.5 million people.

Judy Staffa, Ph.D., R.Ph., an epidemiologist with the FDA's Office of Surveillance and Epidemiology, says that once the FDA identifies a safety signal of concern, the collaborating organizations may be asked to determine whether an epidemiological study is possible. This approach helps experts learn more about the problem and how it can be managed. In many instances, these studies require going back to individual medical records to put pieces of the puzzle together. Records are kept confidential.

Drugs that treat attention deficit hyperactivity disorder (ADHD) are being studied under this collaboration. ADHD is the most commonly diagnosed mental health disorder in children. There are several FDA-approved drugs for children with ADHD who are ages 6 and older, including Adderall (amphetamine-dextroamphetamine) and Ritalin (methylphenidate).

In September 2003, during a review of Adderall for a possible adult indication, FDA scientists identified a cardiovascular safety signal. Several advisory committee meetings were held to discuss potential warnings on the product label, as well as the need for further research on cardiovascular events in children.

That's where the FDA's collaborators come in. "We realize that we are in a nearly unique situation in being able to follow large populations of members in whom we can identify both drug exposures and possible consequences while protecting patient confidentiality," says Joe V. Selby, M.D., M.P.H., director, Division of Research for Kaiser Permanente in Northern California.

Selby says he hopes that research on ADHD drugs will give "a much clearer idea of whether there is a risk for sudden cardiac death associated with use of drugs that treat



Black Star/John Troha

Judy Staffa, Ph.D., R.Ph., is an epidemiologist with the FDA's Office of Surveillance and Epidemiology.

ADHD, whether any such risk varies by the choice of drug, and, if there is a risk, what the size of that risk really is. In that way, parents and patients may make more informed decisions about whether to start or continue the drug."

Richard Platt, M.D., director of research for Harvard Pilgrim Health Care and a professor at Harvard Medical School, says the collaboration is highly consistent with his institution's interest in conducting research that supports public health. "We have longstanding interests in developing the science of pharmacovigilance," Platt says. Pharmacovigilance is the detection, assessment, understanding, and prevention of adverse effects of medicines.

"One of the best things about this collaboration," says Staffa, "is the chance to work with some of the top epidemiologists in the country." This relationship helps the FDA in its mission to quickly identify drug side effects and keep consumers informed about the risks and benefits of their medicines. ■

THE IMPACT OF ADVERTISING

When the volume of ads consumers see each day on television, the Internet, and in print is considered, direct-to-consumer (DTC) ads have become the “face” of medicine for many Americans. So the public health stakes are high to ensure that these ads accurately convey information about the risks and benefits of prescription medications.

The FDA has conducted its own research on DTC ads, and has also formed relationships with groups outside of government, including *Prevention* magazine, a monthly consumer health publication with 11 million readers.

The FDA's most recent survey findings, released in November 2004, indicate that DTC advertising has both positive and negative effects. For example, DTC advertising seems to increase consumer awareness of conditions and treatments and to motivate patients to ask their doctors better questions. But both

patients and physicians indicated that DTC advertisements often overstate the effectiveness of a drug and do not present a fair balance of benefits and risks.

The FDA and *Prevention* magazine surveys have a somewhat different focus, which adds to the complementary nature of the relationship. *Prevention's* survey measures consumer awareness and understanding of DTC advertising; the FDA survey focuses on how DTC ads affect the doctor-patient relationship.

The relationship between the FDA and *Prevention* began in 1997 when the magazine's corporate parent, Rodale Inc., informed the FDA about the results of a national survey that included questions on consumer perceptions of DTC ads. Since then, the *Prevention* survey team has routinely met with the FDA to refine its survey instrument and to discuss trends that arise from the survey findings.

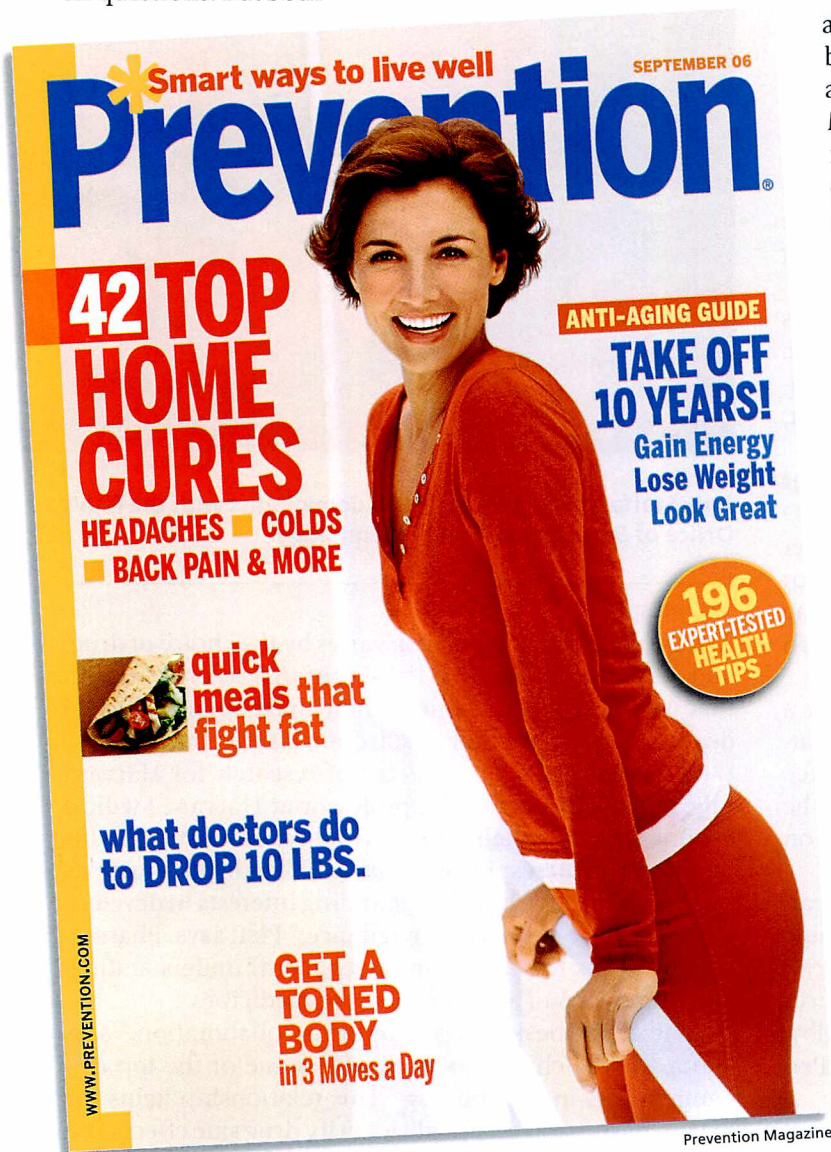
“The *Prevention* survey data have afforded us valuable additional resources we might otherwise not have been able to obtain easily,” says Kathryn Aikin, Ph.D., a social science analyst with the FDA's Division of Drug Marketing, Advertising, and Communications. “A current issue of interest is how the inclusion of a celebrity or doctor in an ad impacts consumer behavior,” Aikin says. Adding to the complexity of the issue, she notes, “What if the ‘doctor’ is an actor?”

According to Edwin Slaughter, a former director of marketing research at *Prevention*, there was a void in research on consumer perceptions of DTC advertising. “*Prevention* wanted to help fill that void.”

The relationship with the FDA has been a boon for *Prevention*, helping to create a leadership position for the publication on the DTC issue. For example, *Prevention* was invited to brief Congress on its survey findings. It's a case of “doing well by doing good,” says Slaughter, who is now a manager of consumer marketing at Merck & Co. Inc., Whitehouse Station, N.J.

Some commonly held beliefs have now been dispelled about the effect of DTC advertising, Slaughter says, such as the notion that DTC ads significantly contribute to rising health care costs. “Survey results showed that DTC ads, while effective as a marketing tool, were not causing people to run to their doctors,” Slaughter says. “Americans don't want to be sick and take medicines.”

Both the FDA and the current director of marketing research at *Prevention*, Cary Silvers, expect their relationship to continue. For his part, Slaughter has brought the spirit of collaboration with the FDA to his new position at Merck. The company will work with the FDA on a study to evaluate patient recollection and understanding of risk-benefit information in broadcast television ads. ■



ADVANCING GENE THERAPY

Few endeavors in health care have generated more excitement than gene therapy. Its promise to cure, not just treat, diseases such as cancer, diabetes, and cystic fibrosis fuels boundless optimism. Yet much about gene therapy is still unknown; its short- and long-term risks are still the subject of considerable study.

To help manage some of the unknowns, the FDA and the National Institutes of Health (NIH) launched the Genetic Modification Clinical Research Information System (GeMCRIS) in 2004. This Web-accessible database on gene therapy gives the public information about ongoing clinical trials and encourages the reporting and analysis of adverse events connected to those trials.

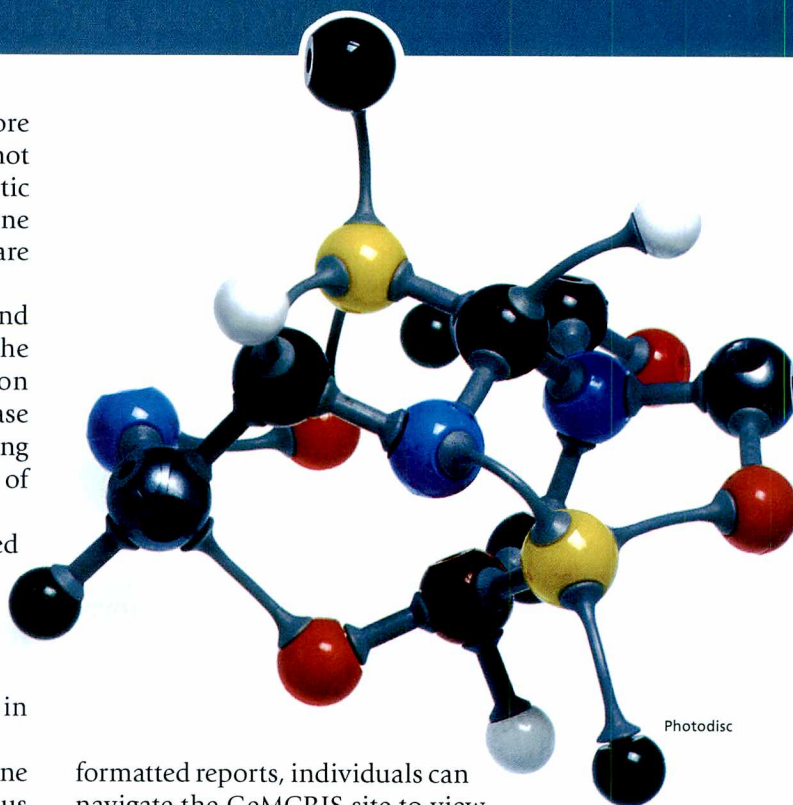
Human genes are small pieces of information recorded on a molecule called deoxyribonucleic acid (DNA). Genes determine certain physical characteristics such as eye color, and can also play a role in some diseases. Gene therapy involves the use of normal genes or genetic material to replace or cancel out the “bad” or defective genes in a person’s body that are responsible for a disease.

For example, a person with cystic fibrosis has a faulty gene for handling lung development leading to excess mucous in the lungs, chronic coughing, and respiratory infection. A successful gene therapy procedure would involve injecting a “normal” gene into a patient’s bloodstream to replace the faulty gene to help the lungs function properly.

Because the study of gene therapy is still new, scientists, industry, and government must be vigilant in minimizing risks to clinical trial participants. In 1999, an 18-year-old boy who suffered from a rare metabolic disorder died from unexpected complications due to his gene therapy trial. The case received national media attention and spurred efforts for closer collaboration among all those involved in the field.

The FDA and the NIH have complementary responsibilities with respect to gene therapy. Both agencies review proposed gene therapy studies. The FDA’s primary job is to ensure that manufacturers produce safe gene therapy products and that these products are properly studied in human subjects. The NIH’s primary job is to evaluate the quality of the science involved in gene therapy research and to fund the scientists who invent and refine the tools used for clinical studies.

GeMCRIS enables patients, researchers, scientists, product sponsors, and the public to become better informed about gene therapy research. Through drop-down menus and pre-



Photodisc

formatted reports, individuals can navigate the GeMCRIS site to view information on particular characteristics of clinical gene therapy trials. For example, GeMCRIS users can learn where trials are taking place, which diseases or health conditions are being studied, and what investigational approaches are being taken. Those conducting gene therapy trials can report adverse events using a secure electronic interface. Because toxicities can occur well after administration of a gene therapy product, monitoring adverse events is important.

While the FDA and the NIH have their distinct areas of focus, “the development of GeMCRIS was truly collaborative,” says Stephanie Simek, Ph.D., acting deputy director of the FDA’s Office of Cellular, Tissue, and Gene Therapies. For example, she notes that the two agencies worked closely together to develop a common vocabulary for the computer systems so that multiple users would have standardized inputs and outputs. “Having similar vocabulary allows sponsors or investigators to report potential adverse events to both the NIH and the FDA using comparable medical terminology and similar report forms,” Simek explains.

The FDA has not approved any gene therapy products yet, but there are numerous clinical studies ongoing, Simek says. “We are hopeful that a gene therapy product will be approved in the U.S. in the near future.” ■

The FDA and the NIH have complementary responsibilities with respect to gene therapy.

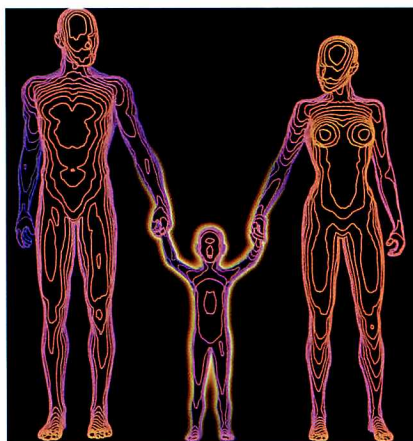
MEDICAL DEVICES: REDUCING RADIATION EXPOSURE

In the not-too-distant future, scientists will determine radiation exposure from the next generation of magnetic resonance imaging (MRI) machines and other sources of electromagnetic waves, not by probes and prods into the body, but via computer-generated models.

Dubbed the "Virtual Family," the development behind the scientific advances is already taking place under a research agreement between the FDA and the Foundation for Research on Information Technologies in Society (IT²S), says Wolfgang Kainz, Ph.D., an electrical engineer with the FDA's Office of Science and Engineering Laboratories. Based in Zurich, Switzerland, the IT²S is a leading research organization engaged in assessing the impact of electromagnetic exposure on health and in developing information technologies for diagnostic and life-supporting systems.

The origins of the joint project began, oddly enough, not in a health care setting, but with cell phones. The cell phone industry has long been cognizant of safety issues associated with the electromagnetic fields cell phones emit. In fact, a cell phone industry organization, the Mobile Manufacturing Forum, has provided funding for the FDA-IT²S collaboration.

Currently, good computer models of humans that could serve as a proxy for testing radiation exposure are rare. By creating more sophisticated computer models, engineers and scientists can assess electromagnetic exposure for such common procedures as MRIs and computed tomography (CT) scans without invasive probing. New practice guides



Fotosearch

could be drafted, and new products could be developed.

How could this technology impact consumers? Consider, for instance, that a patient with an implanted pacemaker may not be able to undergo an MRI because the metal in the pacemaker may be affected by the MRI fields. By using a computer model, engineers and scientists can test and improve a pacemaker's design to minimize such exposure.

The Virtual Family is one of the keys to potential advances in this area. It is a set of four high-resolution, anatomical, whole-body computer-aided design

(CAD) models, consisting of an average man, woman, and two children (ages 3 to 6 and 7 to 14 years).

In the past, computer-generated anatomical models hardly resembled humans. And there were no accurate anatomical models for children, frustrating efforts to measure their electromagnetic exposure. The latest generation of models more precisely defines individual organs and can help evaluate adult and child radiation exposure in both medical and non-medical environments. The Virtual Family models being developed by the FDA and the IT²S promise even greater sophistication.

Kainz's IT²S counterpart, Niels Kuster, Ph.D., is optimistic. "Working with FDA has allowed us to broaden the scope of our work," Kuster says. "We bring to the table the computer modeling expertise, while FDA obviously brings the health care expertise." The relationship promises rich dividends for public health in the United States and around the world. ■

For More Information

Fish Medicine and Research
www.fda.gov/cvm/aqualibtoc.htm

Academic Alliances for Food Safety
www.jifsan.umd.edu/

The National Center for Food Safety and Technology
www.ncfst.iit.edu/main/home.html

The Thad Cochran National Center for Natural Products Research
www.olemiss.edu/depts/pharmacy/ncnpr/index.html

Bringing Food Science to Teens
www.foodsafety.gov/~fsg/teach.html

Fostering the Critical Path Initiative
www.fda.gov/oc/initiatives/criticalpath/

International Communications
www.fda.gov/oia/homepage.htm

Managing Drug Safety Risks
www.fda.gov/cder/Offices/ODS/default.htm#Other%20Resources

The Impact of Advertising
www.fda.gov/cder/ddmac/researchka.htm
www.prevention.com

Advancing Gene Therapy
www.gemcris.od.nih.gov/
www.fda.gov/cber/genetherapy/gttrack.htm

Medical Devices: Reducing Radiation Exposure
www.fda.gov/cdrh/index.html
www.itis.ethz.ch/itiswelcome.html

New Vaccine Prevents Cervical Cancer

The Food and Drug Administration has approved Gardasil, the first vaccine developed to prevent cervical cancer and precancerous genital lesions and genital warts due to certain types of human papillomavirus (HPV). The vaccine is approved for use in females ages 9 years to 26 years. Gardasil was evaluated and approved in six months under the FDA's priority review process—a process for products with potential to provide significant health benefits.

HPV is the most common sexually transmitted infection in the United States. The Centers for Disease Control and Prevention estimates that more than 6 million Americans become infected with genital HPV each year and that more than half of all sexually active men and women become infected at some time during their lifetimes. On average, there are 9,710 new cases of cervical cancer and 3,700 deaths attributed to it in the United States each year. Worldwide, cervical cancer is the second most common cancer in women and is estimated to cause over 470,000 new cases and 233,000 deaths each year.

For most women, the body's own defense system will clear the virus, and infected women do not develop related health problems. Some HPV types, however, can cause abnormal cells on the lining of the cervix that can turn into cancer years later. Other HPV types can cause genital warts. The vaccine is effective against HPV types 16 and 18, which cause about 70 percent of cervical cancers, and against HPV types 6 and 11, responsible for about 90 percent of genital warts.

"This vaccine is a significant advance in the protection of women's health in that it strikes at the infections that are the root cause of many cervical cancers," says Acting FDA Commissioner Andrew C. von Eschenbach, M.D. "The development of this vaccine is a product of extraordinary work by scientists as well as by FDA's review teams

to help facilitate the development of very novel vaccines to address unmet medical needs."

Gardasil is given as three injections over a six-month period. Immunization is expected to prevent most cases of cervical cancer due to HPV types included in the vaccine. Females, however, are not protected if they have been infected with the HPV types prior to vaccination. Also, Gardasil does not protect against less common HPV types not included in the vaccine; therefore, regular Pap screening remains critically important to detect precancerous changes in the cervix to allow treatment before cervical cancer develops.

Four studies, one in the United States and three multinational, were conducted in 21,000 women to examine how well Gardasil worked in women ages 16 to 26 by giving them either the vaccine or an inactive injection (placebo). In women who had not already been infected, Gardasil was nearly 100 percent effective in preventing precancerous cervical lesions, precancerous vaginal and vulvar lesions, and genital warts caused by infection with the HPV types against which the vaccine is directed. While the study period was not long enough for cervical cancer to develop, the prevention of these cervical precancerous lesions is believed highly likely to result in the prevention of those cancers.

The studies also evaluated whether the vaccine can protect women already infected with some HPV types included

in the vaccine from developing diseases related to those viruses. The results show that the vaccine is only effective when given prior to infection.

Two studies were also performed to measure the immune response to the vaccine among younger females ages 9 years to 15 years. Their immune response was as good as that found in 16 to 26 year olds, indicating that the vaccine should have similar effectiveness when used in younger females.

The safety of the vaccine was evaluated in about 11,000 individuals. Most adverse experiences in study participants who received Gardasil included mild or moderate local reactions, such as pain or tenderness at the site of injection.

The manufacturer Merck & Co. Inc. of Whitehouse Station, N.J., has agreed to conduct additional studies to further evaluate general safety and long-term effectiveness. Merck also will monitor the pregnancy outcomes of women who receive Gardasil while unknowingly pregnant. Also, the manufacturer has an ongoing study to evaluate the safety and effectiveness of Gardasil in males. ■

For More Information

www.fda.gov/cber/products/hpvmer060806.htm

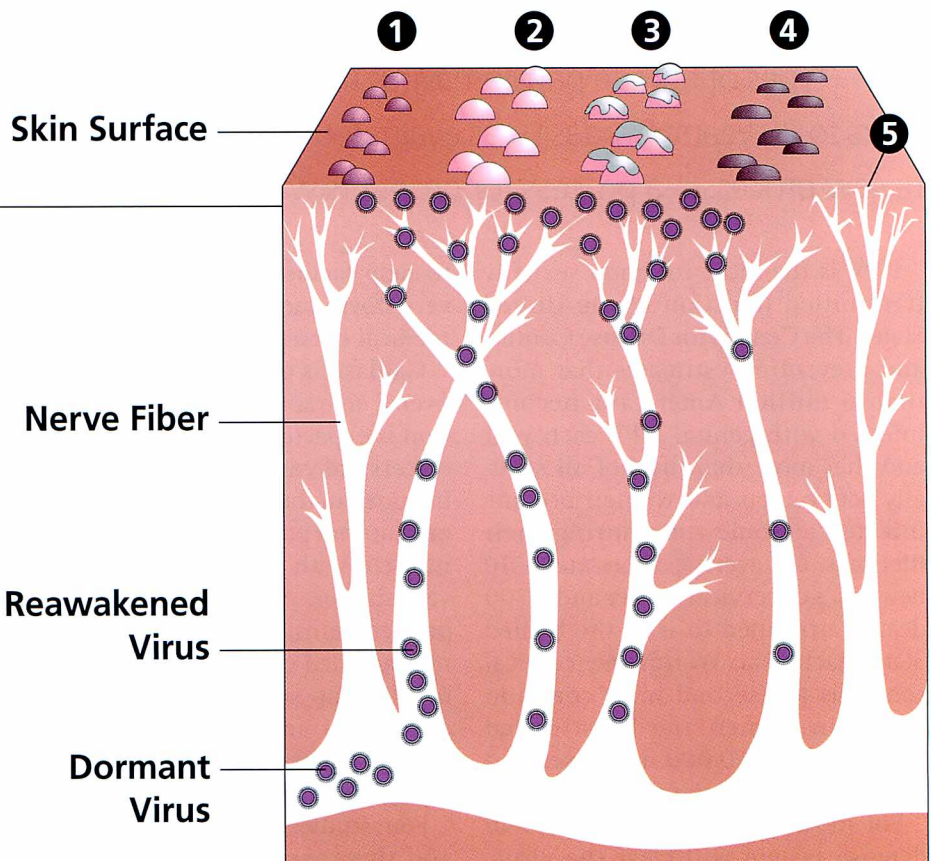
www.fda.gov/womens/getthefacts/hpv.html

Vaccine Approved for Shingles in Older People

Shingles

People who have had chickenpox (varicella) in their youth can develop shingles (herpes zoster) in later years. During an acute attack of the chickenpox virus, most of the viral organisms are destroyed, but some survive, travel up nerve fibers along the spine, and lodge in nerve cells where they may lie dormant for many years. A decrease in the

body's resistance can cause the virus to reawaken decades later. It then travels back down the nerve fibers to the skin's surface. The reawakened virus generally causes a vague burning sensation or tingling over an area of skin. A painful rash usually occurs two to five days after the first symptoms appear. A cluster of small bumps ❶, turns into blisters ❷, that resemble chickenpox lesions. The blisters fill with pus and break open ❸, crust over ❹, and finally disappear. This process takes four to five weeks. A painful condition called post-herpetic neuralgia can sometimes occur. This condition is thought to be caused by damage to the nerves ❺, and can last from weeks to years after the rash disappears.



A new vaccine called Zostavax is available to reduce the risk of shingles (herpes zoster) in people ages 60 and older.

"This vaccine gives health care providers an important tool to help prevent an illness that affects many older Americans and often results in significant chronic pain," says Jesse L. Goodman, M.D., director of the FDA's Center for Biologics Evaluation and Research.

Shingles is a disease caused by the varicella-zoster virus, the same virus that causes chickenpox. After an attack of chickenpox, the virus lies dormant in certain nerve tissue. As people age, it is possible for the virus to reappear in the form of shingles, which is estimated to affect 2 out of every 10 Americans during their lifetimes. Evidence of shingles includes clusters of blisters, which develop on one side of the body and can cause severe pain that may last for weeks, months, or even years after the virus reappears.

Zostavax, a live virus vaccine, has been shown to boost immunity against varicella-zoster virus. This is thought to be the mechanism by which the vaccine protects against zoster and its complications. The vaccine is given as a single injection under the skin, preferably in the upper arm.

Zostavax was studied in about 38,000 individuals 60 and older throughout the United States. Of these people, half received Zostavax, and half received a placebo. All study participants were then followed for an average of three years to see whether they developed shingles and, if they did, how long the pain lasted.

At the conclusion of the study, researchers found that, overall, the vaccine reduced the occurrence of shingles by about 50 percent in people ages 60 and older. It reduced occurrence by 64 percent in those ages 60 to 69.

The vaccine not only prevented approximately half of the cases, but also slightly reduced the duration of pain after the onset of shingles in people who developed the disease despite

At the conclusion of the study, researchers found that, overall, the vaccine reduced the occurrence of shingles by about 50 percent in people ages 60 and older.

being vaccinated with Zostavax.

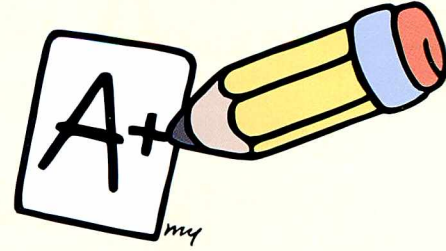
The most common side effects in people who received Zostavax were redness, pain and tenderness, swelling at the site of injection, itching, and headache. The percentage of significant adverse events observed in the study did not differ among those who received the vaccine and those who received the placebo.

As part of the vaccine development program, a smaller study was conducted to closely examine the vaccine's safety. In this smaller study, serious adverse events for all age groups were noted more frequently in those who received Zostavax than those who received placebo. Although the FDA has concluded that the available data do not establish that these events are related to the vaccine, the manufacturer will perform a Phase 4 (postmarket) study to provide additional safety information.

Zostavax is manufactured by Merck & Co. Inc., of Whitehouse Station, N.J. ■

Take the FDA Consumer Quiz

How many drugs are approved by the FDA to treat diseases in farm-raised fish? What virus causes the painful condition called shingles? The FDA has approved nonsteroidal anti-inflammatory drugs to treat what conditions in dogs? How many doses of influenza vaccine are manufacturers expected to deliver during the upcoming influenza season? To find out how much you know about these and other health-related topics, take our quiz.



Hint: The answers to all of these questions can be found in the September–October 2006 issue of FDA Consumer (and at the bottom of this page).

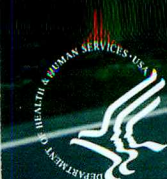
1. The FDA has licensed which two types of influenza vaccine for use in the United States?
 - a. the "shot" and the inhaled vaccine
 - b. the "shot" and the flu patch
 - c. the inhaled vaccine and the flu patch
 - d. the "shot" and the flu "sugar cube"
 - e. the "shot" and the chewable flu tablet
2. Influenza vaccine manufacturers have projected making how many doses of vaccine for the 2006–2007 season?
 - a. 65 million
 - b. 75 million
 - c. 100 million
 - d. 150 million
 - e. 200 million
3. The FDA has approved some nonsteroidal anti-inflammatory drugs (NSAIDs) for use in dogs for what conditions?
 - a. Lyme disease and ehrlichiosis
 - b. allergies and respiratory problems
 - c. osteoarthritis and pain after surgery
 - d. distemper and parvo
 - e. ear and eye infections
4. NSAIDs work by blocking the production of which body chemicals?
 - a. prostaglandins
 - b. estrogens
 - c. testosterone
 - d. vitamins B6 and C
 - e. vitamins D and E
5. Every NSAID approved for use in dogs comes with a user-friendly summary for the pet owner, called
 - a. NSAID Information Summary
 - b. Pet Owner Data Sheet
 - c. Customer Data Sheet
 - d. Client Information Sheet
 - e. Patient Information Sheet
6. The FDA has recently approved Gardasil. What is Gardasil?
 - a. a drug to treat acne in teen-agers
 - b. a vaccine to prevent cervical cancer due to certain types of human papillomavirus
 - c. a new pesticide to repel fleas and ticks in dogs
 - d. a new insecticide to keep mosquitoes at bay in humans
 - e. a new treatment for HIV infection
7. How many drugs are approved by the FDA to treat diseases in farm-raised fish?
 - a. 3
 - b. 7
 - c. 25
 - d. 42
8. How many people suffer from foodborne illnesses each year?
 - a. 26 million
 - b. 52 million
 - c. 76 million
 - d. 102 million
9. Shingles is a disease caused by the same virus that causes
 - a. flu
 - b. AIDS
 - c. virus
 - d. chickenpox
10. In a recent survey, the FDA found benzene levels above 5 parts per billion in how many of the beverage products tested?
 - a. 2
 - b. 5
 - c. 15
 - d. 22

Answers:

1. a, 2. c, 3. c, 4. a, 5. d, 6. b, 7. b, 8. c, 9. d, 10. b

Check the Medicine Label... To Make Sure You're Able

- you may get drowsy
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- use caution when driving a motor vehicle or operating machinery





FDA/Michael Ermarth

The Food and Drug Administration's Counterfeit Drug Task Force has released a new report on ways to curb the influx of counterfeit drugs. Page 11.

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