

# FDA Consumer

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

January–February 2007 • Vol. 41 No. 1



## Cancer Drugs

### Weighing the Risks and Benefits



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U.S. Department Of Health And Human Services

# **FDA Consumer**

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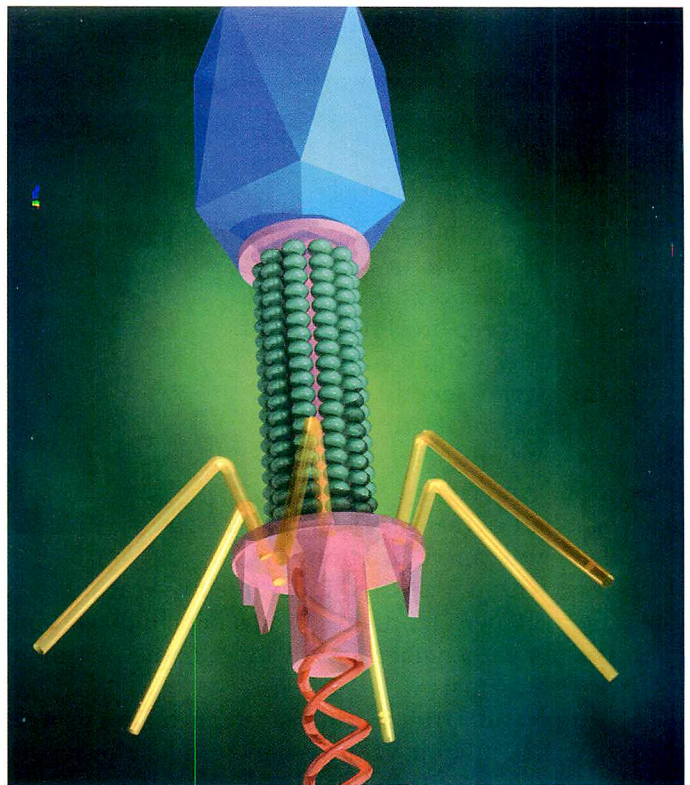
New enforcement policies crack down on the marketing of unapproved drugs.





33

The FDA is helping consumers make quick and informed food choices that contribute to lifelong healthy eating habits.



20

A bacteriophage is any virus that infects bacteria.



23

Use of the measles vaccine has led to a greater than 99 percent reduction in measles, compared with the pre-vaccine era in the United States, when about 450,000 cases were reported each year, according to the Centers for Disease Control and Prevention.

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## OBSERVATIONS

The cells in the human body usually grow and die in a controlled way. Cancer occurs when abnormal cells keep dividing and form more cells without control.

Cancer is the second most common cause of death in the United States. Only heart disease kills more Americans. Thirty years ago, half of the Americans diagnosed with cancer died from the disease within five years. Today, the five-year survival rate is up to 65 percent, thanks to advances in diagnosing cancers at an earlier stage and the development of more effective treatments.

The Food and Drug Administration has approved dozens of drugs that have been shown to be effective in destroying cancer cells by interfering with their growth and multiplying. The array of cancer drugs includes some that can block the effects of hormones in the body. Doctors also can prescribe treatment with substances that boost the immune system against cancer.

Oftentimes, drugs are part of a treatment plan that includes surgery and radiation, as well as antibodies, interleukins, and vaccines, according to the National Cancer Institute.

In recent years, the rapidly increasing research area of cancer drug development and an accelerated drug review process have produced many more treatment options. Over the past decade, the FDA has approved 43 new cancer drugs, compared with 27 during the previous decade. For more on cancer drugs, their promise—and their drawbacks—see our cover story titled “Cancer Drugs: Weighing the Risks and Benefits,” beginning on page 10.



Many adults incorrectly think that vaccines are only for young children. According to the Centers for Disease Control and Prevention (CDC), it is always better to prevent a disease than to treat it. Vaccines prevent disease in adults as well as children and help to protect people who come into contact with those who aren't vaccinated. Vaccines help to save lives and are responsible for the control of many infectious diseases that were once common in this country, including polio, measles, diphtheria, whooping cough, German measles, mumps, tetanus, and *Haemophilus influenzae* type B, the CDC says.

Our feature article titled “Keeping Up With Vaccines,” beginning on page 23, takes a look at vaccines that have been recently licensed by the FDA, along with the latest recommendations from the CDC's Advisory Committee on Immunization Practices for young children, adolescents, and adults.

We also take a look at the FDA's decision to approve the marketing of silicone gel-filled breast implants for reconstruction and augmentation, the approval of an additive that contains a bacteria-eating virus to help keep ready-to-eat luncheon meats wholesome, and a new interactive aid designed to help people make healthy nutritional choices.

Happy New Year from the staff of *FDA Consumer Magazine*!

*Raymond Formanek Jr.*  
Editor

## UPDATES

### New Skin Cancer Drug

Zolinza (vorinostat) capsules have been approved to treat cutaneous T-cell lymphoma (CTCL), a type of skin cancer, to be used when the disease persists, gets worse, or comes back during or after treatment with other medicines.

Zolinza was approved as part of the FDA's Orphan Drug program, which offers companies financial incentives to develop medications for diseases affecting fewer than 200,000 Ameri-

cans a year. Every year in the United States, about three in every 1 million people are diagnosed with CTCL.

Evidence of Zolinza's safety and effectiveness was developed in two clinical trials with 107 CTCL patients who received Zolinza after their disease had recurred following other treatments. A response, defined by improvements on a scale that scores skin lesions, occurred in 30 percent of people who received Zolinza and lasted an average of 168 days. The most com-

mon serious side effects were blood clot in the lungs (pulmonary embolism), dehydration, deep vein thrombosis, and anemia.

Zolinza is manufactured by Pantheon Inc. in Mississauga, Ontario, Canada, for Merck & Co. Inc. in Whitehouse Station, N.J.



## New Treatment for Diabetes

The FDA has approved Januvia (sitagliptin phosphate) tablets, the first diabetes treatment approved in a new class of drugs, DPP-IV inhibitors, that enhances the body's own ability to lower elevated blood sugar.

Januvia was approved in October 2006 to improve blood sugar levels in people with type 2 diabetes. Januvia can be used alone or in combination with two other commonly prescribed oral diabetes medications, metformin or a peroxisome proliferator-activated receptor gamma (PPAR) agonist, when either of these drugs alone, along with diet and exercise, doesn't provide adequate blood sugar control.

Type 2 diabetes is the most common form of the disease, accounting for about 90 percent to 95 percent of all diagnosed cases of diabetes. In type 2 diabetes, the body does not produce enough insulin, or the cells ignore the insulin. Insulin is necessary to take sugar, the basic fuel for cells, from the blood into the cells. Over time,

high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, nerve damage, and kidney damage.

Januvia prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Januvia blocks an enzyme called dipeptidyl peptidase IV, or DPP-IV, which breaks down these proteins, leading to better blood sugar control.

Januvia was examined in 2,719 people with type 2 diabetes in studies lasting from 12 weeks to more than a year. The studies demonstrated improved blood sugar control when Januvia was used alone, or with metformin or a PPAR agonist in people whose blood sugar was not managed satisfactorily with either of these drugs.

The most common side effects in studies were upper respiratory tract infection, sore throat, and diarrhea.

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

## First Generic Metronidazole Vaginal Gel

The FDA has approved the first generic version of MetroGel-Vaginal (metronidazole vaginal gel), a treatment for bacterial vaginosis.

Bacterial vaginosis is a condition in women that is characterized by vaginal discharge and results from an overgrowth of bacteria in the vagina.

"Metronidazole vaginal gel is a widely-used antibacterial preparation, and its generic version can bring significant savings to the millions of Americans with bacterial vaginosis," said Gary J. Buehler, director of the

FDA's Office of Generic Drugs, after the drug's approval in November 2006.

Metronidazole Vaginal Gel, 0.75%, is manufactured by QLT USA Inc. in Fort Collins, Colo.

## Expanded Use of Aricept

Aricept (donepezil) has been approved by the FDA for treating severe dementia in patients with Alzheimer's disease. Aricept was previously approved for the treatment of mild-to-moderate dementia of the Alzheimer's type. With this latest approval in October 2006, Aricept became the first product approved for the treatment of all degrees of severity of the disease.

Alzheimer's disease is a devastating, age-associated brain disorder that affects an estimated 4.5 million Americans. The FDA approved Aricept to treat patients with mild-to-moderate Alzheimer's disease 10 years ago after two clinical trials demonstrated that patients receiving the drug performed better than patients who received placebo.

The October 2006 approval is based on two additional randomized, placebo-controlled, 24-week clinical stud-



Photodisc

ies conducted in Sweden and Japan in more than 500 patients with severe Alzheimer's disease. In these studies, the effectiveness of treatment with Aricept was determined by evaluating the patients' cognitive functions, such as memory, language, orientation, and attention, as well as their overall functioning. The results showed that patients on Aricept performed better on both measures, compared with placebo.

Aricept is manufactured by Eisai Inc. of Teaneck, N.J.



Centers for Disease Control and Prevention

Bacteria adhering to vaginal cells.



## First Drug to Treat Irritability Associated With Autism

The FDA has approved Risperdal (risperidone) orally disintegrating tablets, an adult antipsychotic drug, for the symptomatic treatment of irritability in autistic children and adolescents. The October 2006 approval is the first for the use of a drug to treat behaviors associated with autism in children. These behaviors fall under the general heading of irritability, including aggression, deliberate self-injury, and temper tantrums.

"This approval should benefit many autistic children, as well as their parents and other care givers," says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research. "Our agency strongly encourages the development of appropriate pediatric labeling for adult drugs, and Risperdal is a welcome addition to the growing number of such products that have been shown to have an appropriate risk-benefit profile when tested in children."

Risperdal has been approved since 1993 for the short-term treatment of adults with schizophrenia, and since 2003 for the short-term treatment of adults with acute manic or mixed episodes associated with extreme mood swings.

The product's effectiveness in the symptomatic treatment of irritability associated with pediatric autistic disorders was established in two eight-week, placebo-controlled trials in 156 patients ages 5 years to 16 years. Ninety percent of the patients were ages 5 to 12 years. The results, which were evaluated using two assessment scales, showed that children on Risperdal achieved significantly improved scores for certain behavioral symptoms of autism, compared with children on placebo. The most common side effects of Risperdal included drowsiness, constipation, fatigue, and weight gain.

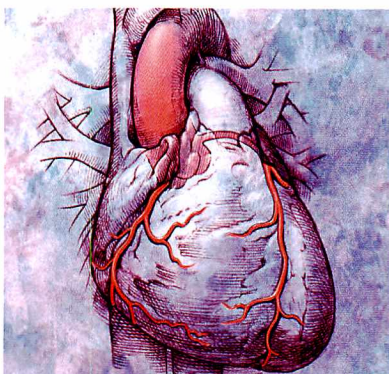
Risperdal is marketed by Janssen, L.P. in Titusville, N.J.

## Partnership on Cardiac Safety

The FDA has announced a partnership with Duke Clinical Research Institute (DCRI) to develop a new generation of tools to identify the potential effects that drugs and devices may have on the heart. The research will be conducted using a virtual electronic database of more than 200,000 electrocardiograms (ECGs) amassed by the agency from clinical trial data submitted as part of new drug applications.

The FDA and the DCRI are developing a consortium with members of academia, patient advocacy groups, other government and nonprofit organizations, and industry to coordinate and support a variety of research projects involving ECGs obtained in clinical trials.

Research shows that women are at higher risk of abnormal heartbeats (arrhythmias), but it is not known whether this difference in susceptibility is related to different responses to drugs. Among the first applied projects the consortium will address is a review of gender differences in the effects of drugs on the ECG. A second research project will evaluate current methods of measuring ECGs and develop criteria



Artville

to determine the best method to be used in a particular research study.

In October 2005, the FDA and the DCRI cosponsored the first in a series of meetings on improving the evaluation of cardiac safety during product development. This partnership is part of the FDA's Critical Path Initiative, an effort to modernize the drug development process.

## New Recommendations to Modernize Drug Manufacturing

The FDA has issued a final guidance on quality systems, a set of formalized practices and procedures to ensure quality of human and veterinary drugs and human biological drug products

during manufacturing. This guidance enhances the FDA's current requirements for ensuring manufacturing quality known as the current Good Manufacturing Practices regulation.

Following the guidance contained in the document "Quality Systems Approaches to Pharmaceutical Current Good Manufacturing Practice (cGMP) Regulations" should help manufacturers maintain consistent high quality and improve efficiency. The guidance, issued in September 2006, demonstrates to pharmaceutical manufacturers the benefits of incorporating modern quality principles, which should foster technical advancements into their manufacturing processes to better ensure the safety and effectiveness of drugs for people and animals.

The aim also is to help produce drugs more efficiently, which should help lower costs and prevent shortages of critical medicines due to manufacturing failures that can result in production stoppages and recalls.

The FDA will continue to monitor manufacturing plants through its inspection program and will continue to advance the training of its investigators in the latest technologies.



## Test to Help Diagnose HIV-1 Infection

The FDA has approved the APTIMA HIV-1 RNA Qualitative Assay, manufactured by Gen-Probe Inc. of San Diego. The APTIMA assay, which detects the RNA—the nucleic acid or genetic material—of the HIV-1 virus, is the first test approved for the detection of HIV-1 RNA to help diagnose HIV-1 infection. HIV-1 is the main virus that causes AIDS.

"This product offers medical diagnostic laboratories the ability to perform a gene-based test for HIV-1 that, until now, was only available as part of a larger kit used to screen blood and plasma donors," says Jay Epstein, M.D.,

director of the Office of Blood Research and Review in the FDA's Center for Biologics Evaluation and Research.

"This test also can detect infection with HIV-1 earlier than HIV antibody tests when used to detect primary HIV-1 infection."

Approved in October 2006, this test has important implications for medical diagnostic use because it could be a potential alternative to the traditional Western blot test now used to confirm HIV-1 infection when screening tests for HIV-1 antibodies are positive. In addition, the Western blot can, in some instances, be difficult to interpret and may not always provide a conclusive result. In such cases, the APTIMA test

may be helpful in HIV-1 diagnosis. The APTIMA test can also be used in clinical laboratories and public health facilities to detect early HIV-1 infection, before the appearance of antibodies to HIV-1.

The sensitivity of the APTIMA assay is comparable to that of FDA-approved viral load assays that measure the amount of HIV-1 virus circulating in the blood of patients with established HIV-1 infection to monitor the treatment and progression of AIDS. Unlike the viral load tests, the APTIMA test has been approved for the diagnosis of primary HIV-1 infection, as well as for the confirmation of HIV-1 infection when tests for antibodies to HIV-1 are positive.

## The FDA Approves Drugs for Colorectal Cancer, Lung Cancer

The FDA has approved Vectibix (panitumumab) to treat people with colorectal cancer that has spread to other parts of the body (metastasized) after standard chemotherapy. Vectibix, a monoclonal antibody that binds to a protein called epidermal growth factor receptor (EGFR) on some cancer cells, received an accelerated approval after showing effectiveness in slowing tumor growth and, in some cases, reducing the size of the tumor.

In the United States, it is estimated that 150,000 new cases of colon cancer were diagnosed and that 55,000 deaths occurred from colon and rectal cancer in 2006. About 70 percent of all colorectal cancerous tumors test positive for EGFR.

The approval of Vectibix was based on the results of a clinical trial of 463 people with metastatic cancer of the colon and the rectum after undergoing treatment with the chemotherapy drugs fluoropyrimidine, oxaliplatin, and irinotecan.

People in the trial who took Vectibix, on average, got worse or died 96 days later—33 days longer than in people who received the best standard supportive care. In addition, 8 percent of the people on Vectibix experienced a tumor shrinkage that in some cases exceeded 50 percent of the pre-treatment size of the tumor.

The most serious side effects in studies of Vectibix included pulmonary fibrosis, severe skin rash complicated by infections, infusion reactions, abdominal pain, nausea, vomiting, and constipation.

Vectibix is manufactured by Amgen Inc. in Thousand

Oaks, Calif.

In a separate action, the FDA approved the use of Avastin (bevacizumab), in combination with carboplatin and paclitaxel, for the initial treatment of people with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer. This approval was based on an increase in survival time when Avastin was added to a standard chemotherapy regimen.

Non-small cell lung cancer accounts for 75 percent of the 174,400 new cases of lung cancer that were expected to be diagnosed in 2006. Lung cancer is the leading cause of cancer-related death in men and women.

In a clinical trial of more than 800 patients who had not received prior chemotherapy, the median overall survival time for people taking Avastin plus carboplatin and paclitaxel was 12.3 months versus 10.3 months for those receiving only carboplatin and paclitaxel.

The most serious side effects associated with Avastin in the trial, including some that were fatal, were gastrointestinal perforation, wound healing complications, hemorrhage, blockage of the arteries, abnormally high blood pressure, albumin deficiency in the blood, and congestive heart failure.

Avastin, in combination with a specific type of chemotherapy, was previously approved for first- or second-line treatment of people with metastatic cancer of the colon or rectum.

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



## New Hepatitis B Treatment

Tyzeka (telbivudine) has been approved for the treatment of adults with chronic hepatitis B, a serious viral infection that attacks the liver and can cause lifelong infection, scarring of the liver (cirrhosis), and eventually liver cancer, liver failure, and death. Tyzeka is a new molecular entity, meaning an active substance that has never before been approved for marketing in any form in the United States.

Tyzeka, approved in October 2006, was studied in a yearlong international clinical trial in 1,367 people with chronic hepatitis B. Three-quarters of the trial participants were male, and all participants were 16 years of age or older. The trial produced evidence of antiviral effectiveness, including the suppression of hepatitis B virus (HBV) and improvement in liver inflammation comparable to Epivir-HBV (lamivudine), one of five other medications approved to treat people with chronic hepatitis B.

HBV is spread when blood from an infected person enters the body of a person who is not infected, sometimes by sexual contact or by blood contamination. Tyzeka is not a cure for hepatitis B, and long-term treatment benefits are unknown.

Most of the side effects of Tyzeka reported in clinical studies were mild to moderate. The most common were elevated creatinine phosphokinase (CPK), an enzyme present in muscle tissue and a marker for the breakdown of muscle tissue, upper respiratory tract infection, fatigue, headache, abdominal pain, and cough.

Among drugs in the same class as Tyzeka, some cases have been reported of too much acid in the body due to buildup of lactic acid (lactic acidosis) and to severe enlargement and accumulation of fat in the liver, including fatal cases.

Tyzeka is manufactured by Novartis Pharma Stein AG, Stein, Switzerland, and marketed and distributed by Idenix Pharmaceuticals Inc., Cambridge, Mass.

## New Allergy Treatment

Omnaris (ciclesonide) nasal spray was approved by the FDA in October 2006 to treat nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 12 years of age and older.

Commonly known as hay fever, allergic rhinitis is the medical term for the inflamed, runny nose that's the main symptom of allergies. Seasonal allergic rhinitis is the most common allergic disease. About 35 million Americans suffer from this condition. The ailment's classic symptoms are watery nasal discharge, fits of sneezing, and itching that can affect not just the nose but the roof of the mouth, throat,



Photodisc

and the Eustachian tubes, which connect the middle ear to the back of the throat.

Although the precise way Omnaris works is unknown, the drug is a corticosteroid. Corticosteroids are hormone-like drugs that suppress the immune response. The safety and efficacy of Omnaris nasal spray were studied in four randomized placebo-controlled clinical trials ranging in duration from two weeks to a year. The studies assessed how well Omnaris treated symptoms (runny nose, nasal itching, sneezing, and nasal congestion) in patients with hay fever. The results of these trials showed that patients treated with Omnaris nasal spray had an 8 percent to 10 percent greater reduction in nasal symptoms, compared with placebo. The difference between Omnaris nasal spray and placebo was significant.

The most common side effects of Omnaris in clinical studies were headache, nosebleeds, and inflammation of the nose and throat linings.

Omnaris is manufactured by ALTANA Pharma US Inc. of Florham Park, N.J. ■

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## Disability Among Older Americans Continues Significant Decline

Chronic disability among older Americans has dropped dramatically, and the rate of decline has accelerated during the past two decades, according to a new analysis of data from the National Long Term Care Survey (NLTCS). The study, published in the Nov. 28, 2006, issue of *Proceedings of the National Academy of Sciences*, found that the prevalence of chronic disability among people ages 65 years and older fell from 26.5 percent in 1982 to 19 percent in 2004–2005. The findings suggest that older Americans' health and function continue to improve at a critical time in the aging of the population.

The study was funded by the National Institute on Aging (NIA), a component of the National Institutes of Health (NIH). A caregiving component of the survey was supported by the Office of the Assistant Secretary for Planning and Evaluation (ASPE). All are part of the U.S. Department of Health and Human Services. Kenneth G. Manton, Ph.D., and colleagues at Duke University conducted the research.

In addition to a drop in the percentage of older Americans reporting disability, the analysis found that the average annual rate of the decline has accelerated. The decline in disability averaged 1.52 percent annually over the 22-year time span, but the rate of change shifted gradually from 0.6 percent in 1984 to 2.2 percent in 2004–2005.

"This continuing decline in disability among older people is one of the most encouraging and important trends in the aging of the American population," says NIA Director Richard J. Hodes, M.D.

The report is an eagerly anticipated

The analysis also showed the following results from 1982 to 2004–2005:

- Chronic disability rates decreased among those over age 65 with both severe and less severe impairments, with the greatest improvements seen among the most severely impaired.

The researchers note that environmental modifications, assistive technologies, and biomedical advances may be factors in these declines.

- The proportion of people without disabilities increased the most in the oldest age group, rising by 32.6 percent among those 85 years and older.

- The percentage of Medicare enrollees ages 65 and older who lived in long-term care institutions, such as nursing homes, dropped dramatically from 7.5 percent to 4 percent. The emergence of assisted-living options, changes in Medicare reimbursement policies, and improved rehabilitation services may have fueled this decrease in institutionalization.

If they continue as anticipated, the downward trends in chronic disability rates among

older adults could help bolster the Medicare program's fiscal health, the researchers suggest.

Funded through a cooperative agreement between the NIA and Duke University, the NLTCS is a periodic federal government survey of about 20,000 Medicare enrollees. Visit [www.pnas.org/cgi/content/abstract/103/48/18374](http://www.pnas.org/cgi/content/abstract/103/48/18374) to read the study. ■



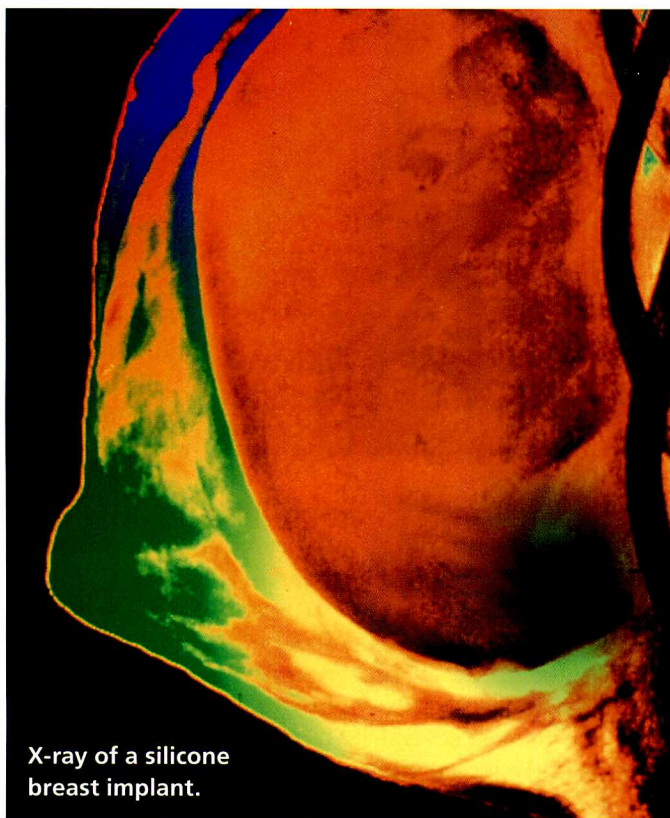
Getty Images

update of the last assessment of NLTCS data in 2001. "The challenge now is to see how this trend can be maintained and accelerated especially in the face of increasing obesity," says Richard Suzman, Ph.D., director of the NIA's Behavioral and Social Research Program. "Doing so over the next several decades will significantly lessen the societal impact of the aging of the baby-boom generation."



# Silicone Gel-Filled Breast Implants Approved

**A**fter rigorous scientific review, the Food and Drug Administration has approved the marketing of silicone gel-filled breast implants made by two companies for breast reconstruction in women of all ages and breast augmentation in women ages 22 and older. The products are manufactured by Allergan Corp., formerly Inamed Corp., of Irvine, Calif., and Mentor Corp. of Santa Barbara, Calif.



X-ray of a silicone breast implant.

Phototake

"FDA has reviewed an extensive amount of data from clinical trials of women studied for up to four years, as well as a wealth of other information to determine the benefits and risks of these products," said Daniel Schultz, M.D., director of the FDA's Center for Devices and Radiological Health after the approval in November 2006. "The extensive body of scientific evidence provides reasonable assurance of the benefits and risks of these devices."

Now that the products have been determined to be safe and effective, the FDA will continue to monitor them by requiring each company to conduct a large post-approval study following about 40,000 women for 10 years after receiving breast implants. The FDA often requires post-market studies to answer important questions that can be answered only once a product is in broader use, such as the incidence of rare adverse events.

The FDA's decision to approve these implants was based on a thorough review of each company's clinical and preclinical studies, a review of studies by independent scientific bodies, and deliberations of advisory panels of outside experts that heard public comment from hundreds of stakeholders.

Some of the complications reported in the core studies included hardening of the area around the implant, breast pain, change in nipple sensation, implant rupture, and the need for additional surgery. The majority of women in these studies, however, reported being satisfied with their implants.

In the past decade, a number of independent studies have examined whether



silicone gel-filled breast implants are associated with connective tissue disease or cancer. The studies, including a report by the Institute of Medicine, have concluded there is no convincing evidence that breast implants are associated with either of these diseases. These issues, however, will be addressed further in the postapproval studies conducted by the companies.

The package and patient labeling mandated by the FDA contain full information about the risks and benefits of the devices. The patient labeling outlines some important factors women should consider when deciding whether to get silicone gel-filled breast implants, such as the following:

- Breast implants are not lifetime devices, and a woman will likely need

The FDA approved the silicone gel-filled breast implants with a number of conditions, including requiring each company to

- conduct a large postapproval study
- continue its core study through 10 years
- conduct a focus group study of the patient labeling
- continue laboratory studies to further characterize types of device failure
- track each implant in the event, for example, that health professionals and patients need to be notified of updated product information.

The postapproval studies will continue to gather information about the safety and effectiveness of the implants. Information will be collected about rates of local complications, rates

of connective tissue disease and its signs and symptoms, rates of neurological disease and its signs and symptoms, potential effects on offspring of women with breast implants, potential effects on reproduction and lactation, rates of cancer, rates of suicide, potential interference of breast implants with mammography, and MRI compliance and rupture rates. The FDA will closely monitor the postapproval studies. The agency anticipates that data from the studies will provide important information for patients and physicians, and may lead to improvements in device labeling. ■

#### For More Information

[www.fda.gov/cdrh/breastimplants](http://www.fda.gov/cdrh/breastimplants)

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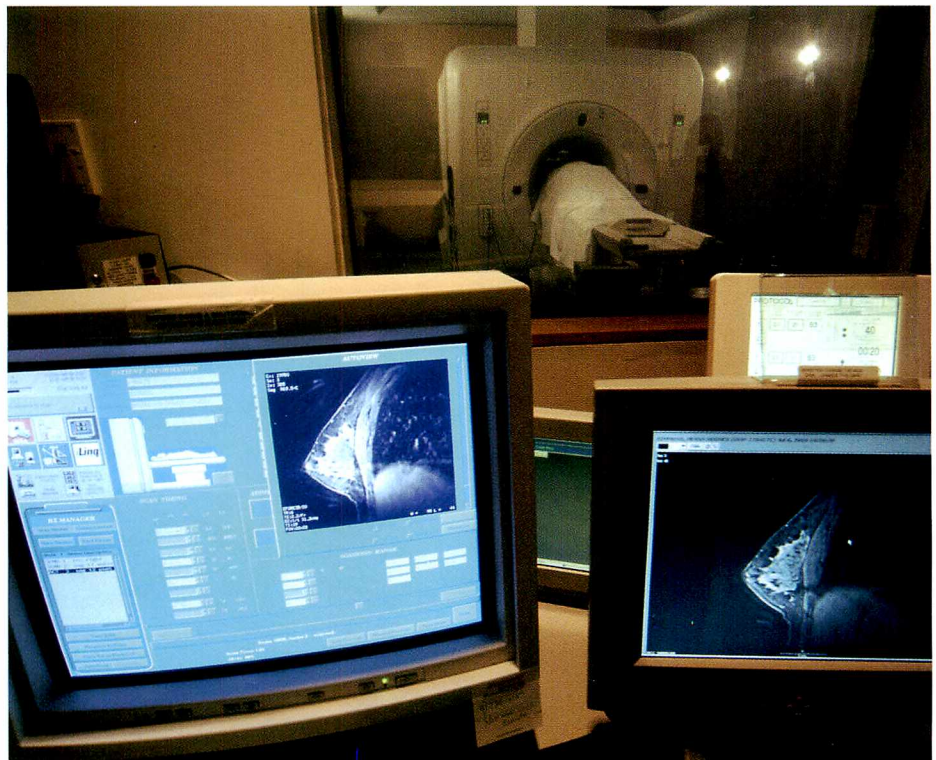
*'The extensive body of scientific evidence provides reasonable assurance of the benefits and risks of these devices.'*

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additional surgeries on her breast at least once over her lifetime.

- Many of the changes to a woman's breast after implantation are irreversible.
- Rupture of a silicone gel-filled breast implant is most often silent, which means that usually neither the woman nor her surgeon will know that her implants have ruptured.
- A woman will need regular screening Magnetic Resonance Imaging (MRI) examinations over her lifetime to determine whether silent rupture has occurred.

The labeling states that a woman should have her first MRI three years after her initial implant surgery and then every two years thereafter. The cost of MRI screening over a woman's lifetime may exceed the cost of her initial surgery and may not be covered by medical insurance. The labeling also states that if implant rupture is noted on an MRI, the implant should be removed and replaced, if needed.



Phototake

**MRI scanning of breast.**





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NAME, REBECCA

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AT 10:00 ON 05/23/06

CAIMAB INJ 425 MG

BAG 213 ML

CONC: 2MG/ML, IV BAG TOT

12.5ML

IVPB

NOT BE USED IN  
CTIONS  
ION FEDERAL (USA) LAW  
ECTS THIS DEVICE TO SAIL  
ON ORDER OF A PHYSICIAN  
HEALTHCARE CORPORATION  
NUTRITION DIVISION  
MADE IN USA

A patient receives her weekly Erbitux treatment for colon cancer.

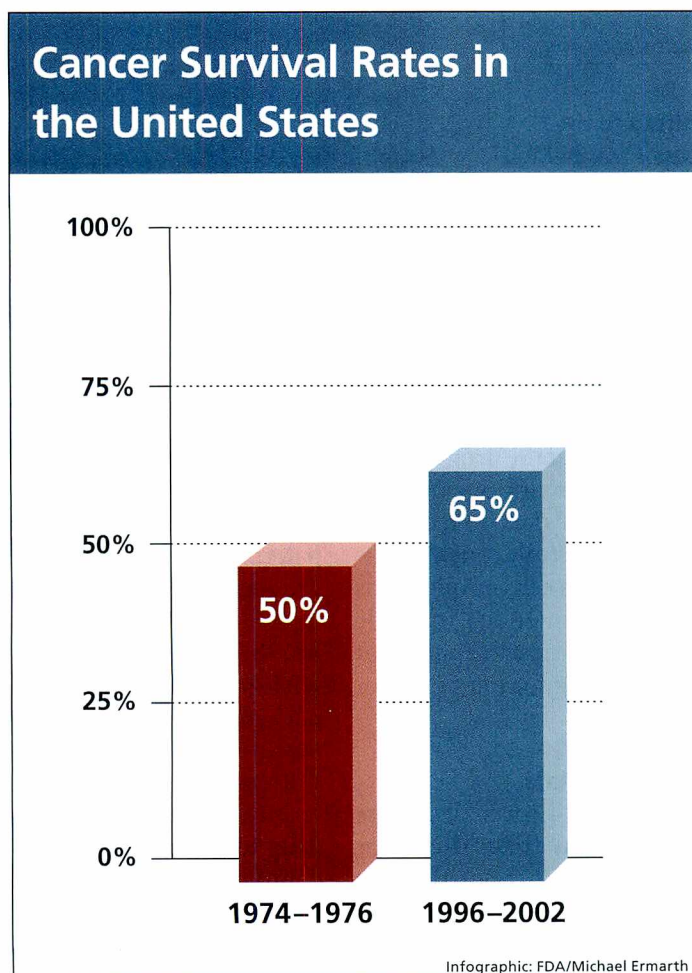


# Cancer Drugs

## Weighing the Risks and Benefits

By Linda Bren

**F**ew deliberations have greater bearing on human health than when the Food and Drug Administration weighs the risks and benefits of drugs designed to treat life-threatening diseases, such as cancer.



Source: National Cancer Institute

FDA physicians who specialize in treating cancer (oncologists), chemists, statisticians, microbiologists, pharmacologists, immunologists, and other experts work in concert to evaluate cancer drug data, weigh the risks and benefits, and reach a decision to approve or not approve. If the scale is tipped on the side of benefits, the drug is approved and allowed on the U.S. market.

Patients, doctors, caregivers, and family members must also weigh the risks and benefits of drugs to decide which treatments to use.

Cancer is the second most common cause of death in the United States, according to the American Cancer Society, exceeded only by heart disease.

Thirty years ago, half of the Americans diagnosed with cancer died from the disease within five years. Today, the five-year survival rate is up to 65 percent, credited to advances in diagnosing cancers at an earlier stage and the development of more effective treatments.

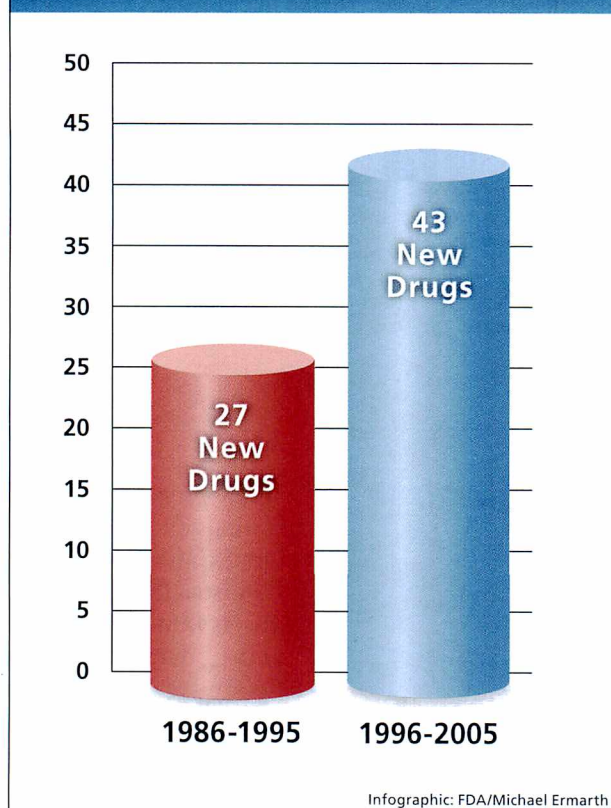
The burgeoning research area of cancer drug development and an accelerated drug review process have produced many more treatment options. Over the last decade, the FDA has approved 43 new cancer drugs, compared with 27 during the previous decade.

### Cancer Drug Review Process

Cancer drugs are regulated by the FDA under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Under the acts, the FDA



## Cancer Drug Approval Rates 1986–2005



Source: FDA

**An increase in drug applications submitted to the FDA and an accelerated drug review process have helped make more cancer treatment options available.**

than an inactive substance (placebo), but generally does not have to show that it works as well or better than other drugs on the market to treat the same illness.

Studies involving cancer drugs usually do not use placebos, says Patricia Cortazar, M.D., an oncologist in the FDA's Office of Oncology Drug Products. "Because cancer is a life-threatening illness, it would not be ethical to give placebo when something better than placebo is available." In cancer trials, a new drug is usually compared to a drug or a combination of drugs that are commonly accepted and widely used to treat the same type of cancer, known as the standard of care, or standard treatment.

"The standard of care changes over time as new drugs or drug combinations that are shown to be better become available," says Cortazar.

The FDA may approve a drug for several uses (indications). If a drug is approved for one indication, it must still be shown in clinical trials to be safe and effective before the FDA will approve it for another indication.

For example, the drug Erbitux (cetuximab) was approved in 2004 to treat colon or rectal (colorectal) cancer that had spread to other parts of the body (metastasized). In 2006, Erbitux was approved to treat patients with head and neck cancer whose cancer is inoperable.

To support a claim to treat colorectal cancer, Erbitux's manufacturer, New York-based ImClone Systems Inc., presented evidence that the drug, when given with another chemotherapy drug (irinotecan), caused tumor shrinkage in 23 percent of the colorectal cancer patients whose tumors were previously growing with irinotecan alone. For head and neck cancer, ImClone showed in clinical trials that the drug, along with radiation treatment, extended patients' lives for 20 months longer than with radiation treatment alone.

Recently, a pharmaceutical company requested that the FDA approve its drug for a second indication without conducting additional clinical trials to show an effect on cancer in this new indication. The FDA had originally approved the drug Abraxane (paclitaxel

may approve a new drug for marketing in the United States if it is supported by substantial evidence of safety and effectiveness demonstrated in adequate and well-controlled studies.

The drug's manufacturer or marketer must show this evidence by submitting an application to the FDA that includes results from studies of the drug's use in people (clinical trials).

FDA oncologists and other agency experts review cancer drug applications and evaluate the study results. When seeking outside advice regarding drug approval or drug labeling, the FDA calls upon the expertise of a group of leading cancer specialists, clinical practitioners, and patient representatives who make up the FDA's Oncologic Drugs Advisory Committee (ODAC).

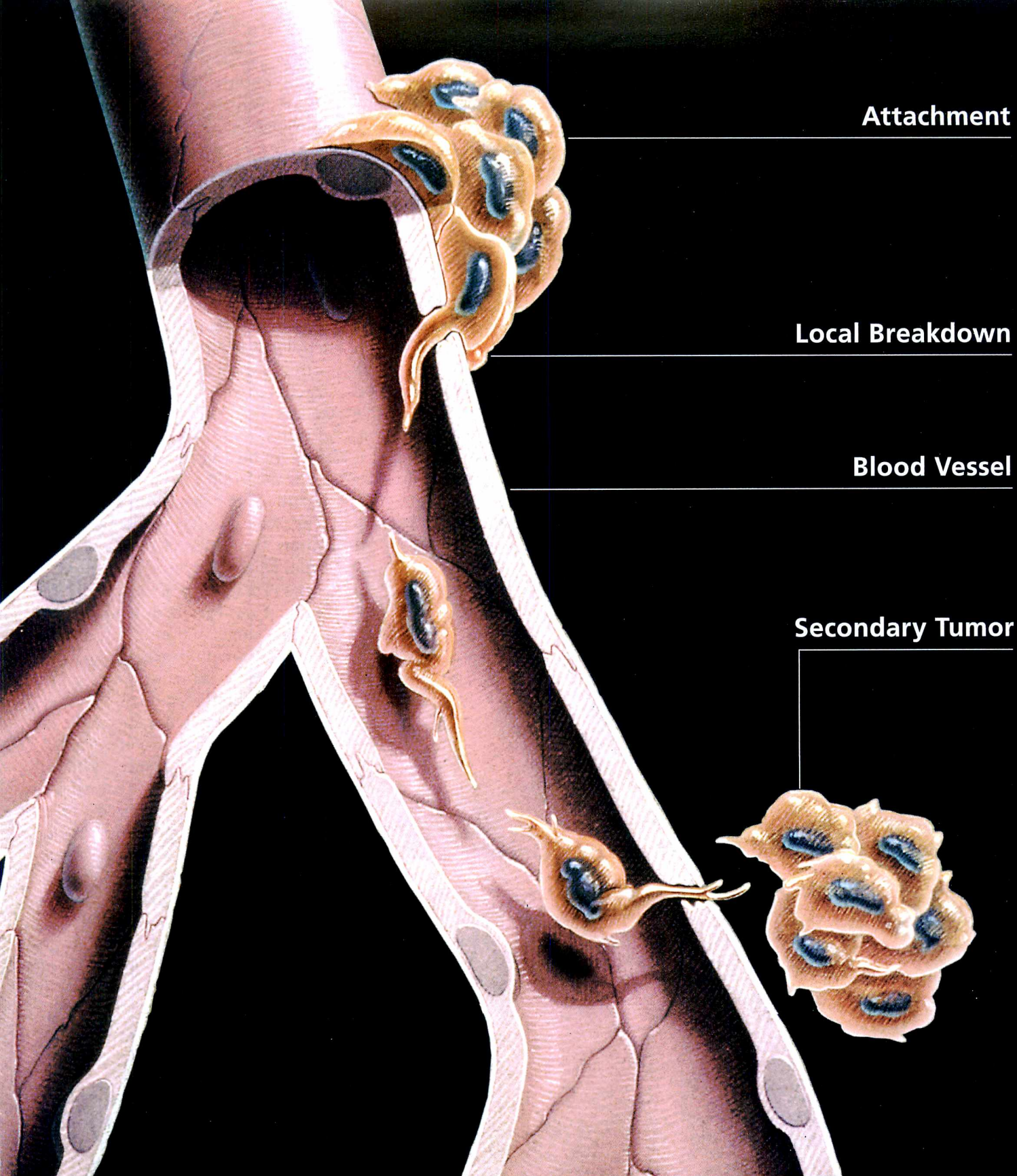
At an ODAC meeting, the pharmaceu-

tical company presents findings from clinical trials on safety and effectiveness of the drug, and FDA staff present their assessments after reviewing the drug application, which includes extensive documentation about the drug's chemistry, its proposed use for one or more specific purposes, and data from clinical trials. The ODAC carefully considers the presentations and votes on questions posed by the FDA intended to guide the agency in its decision to approve or not approve the drug for marketing or for a new claim.

### Cancer Clinical Trials

Clinical trials for cancer drugs are somewhat different from those for drugs used to treat illnesses that are less serious. For a less severe disease or condition, the commercial sponsor may show that the drug works better





National Cancer Institute

## How Cancer Spreads

Once metastatic cells are attached to the basement membrane—a physical barrier that separates tissue components—they break through with the help of an enzyme called type IV collagenase. Cancer cells then move through the bloodstream, enabling them to spread to other parts of the body. A secondary tumor may form at another site in the body.



protein-bound particles) in January 2005 for advanced (metastatic) breast cancer that had not responded to other treatments in clinical trials.

In 2006, Abraxane's manufacturer, Abraxis BioScience Inc. of Schaumburg, Ill., submitted a drug development proposal, instead of an application, for approval of Abraxane to be used in combination with chemotherapy for the indication of adjuvant treatment for breast cancer. Adjuvant treatment is a therapy given after the main treatment to lower the chance of a cancer coming back.

Abraxis proposed conducting a 30-patient study looking only at the drug's side effects instead of a large randomized clinical trial to show safety and

effectiveness of the drug. In a randomized clinical trial, participants are assigned by chance to separate groups that compare different treatments. Neither the researchers nor the participants can choose which group, so the treatments can be compared objectively. The FDA usually requires randomized clinical trials for diseases that affect a large number of people.

Abraxis argued that the drug had already been approved for metastatic breast cancer based on randomized clinical trials that compared it to the standard of care, Taxol. Abraxis stated that its drug contained the same active ingredient as Taxol, a cancer drug approved both for metastatic breast cancer and for adjuvant treatment for

breast cancer, the indication for which Abraxis was seeking approval. Taxol's approval as adjuvant treatment for breast cancer was based on the results of a randomized trial of more than 3,000 patients.

Before the FDA's ODAC on Sept. 7, 2006, Abraxis stated that a trial for effectiveness was "not scientifically necessary and would significantly delay the approval" and that "Abraxane consistently demonstrated antitumor activity that was superior to Taxol in patients with metastatic breast cancer, and there is no scientific reason to believe that Abraxane would be less effective than Taxol" as adjuvant treatment for breast cancer.

The FDA told the ODAC that Taxol and Abraxane were distinctly different. "The two drugs have different formulations and different infusion rates," said Richard Pazdur, M.D., director of the FDA's Office of Oncology Drug Products. "They have different toxicity profiles. Large randomized trials provide important information to patients in making decisions regarding which drug they should take."

Adjuvant treatments for cancer are designed to potentially cure people at risk for disease recurrence, says Cortazar. Toxic side effects that may be acceptable to treat advanced cancer, where a person is more likely to die from the disease, may not be acceptable for adjuvant treatment.

The advisory committee recommended by a vote of 13-1 that the FDA not approve Abraxane as adjuvant treatment for breast cancer without randomized clinical trials, and the FDA concurred.

### Evaluating Safety and Effectiveness

A cancer drug may be considered effective if it extends a person's life (survival), increases the probability that a person will remain alive without the disease getting worse (progression-free survival), shrinks the tumor (response rate), or relieves other symptoms. In short, FDA cancer drug reviewers ask, "Does the drug prolong life, control the disease, or relieve symptoms? And does the scientific evidence support it?"



Merck & Co. Inc.

**These before-and-after photographs were used as supporting evidence of the effectiveness of Zolinza, a drug approved by the FDA to treat a cancer that affects the skin, cutaneous T-cell lymphoma. The FDA considers visual evidence from clinical trials in its decision of whether or not to approve a drug.**



These benefits are weighed against the risks of the drug. No drug is absolutely safe—all have some risks, or potential side effects. “Safe” means that the benefits of the drug outweigh the risks for its intended use in the population the drug is intended to treat.

Cancer drugs often contain potent ingredients that kill cancer cells. “Unfortunately, most of the drugs used to treat cancer aren’t targeted,” says Cortazar. “They kill the cancer cells, but at the same time, they kill healthy cells.” The death of rapidly dividing healthy cells weakens the body’s immune system, putting a person at risk for infections and other health problems.

Yet highly toxic effects may be considered acceptable if the benefits are important and the disease is very serious or life-threatening. “With cancer drugs, you accept more toxicity in general than for drugs that are for non-lethal illnesses,” says Cortazar, since the effects of cancer can be more damaging than the treatments, and cancer drugs may extend or save lives.

For example, Nexavar (sorafenib tosylate), a drug used to treat adults with advanced kidney cancer, may cause side effects including high blood pressure, heart problems, bleeding problems, rash, diarrhea, mouth sores, and pain, swelling, or blisters on the palms of the hands or soles of the feet. The FDA considered these risks to be tolerable for a drug that had the benefit of delaying tumor growth or death nearly three months longer than in patients who received no anti-cancer therapy in clinical trials, but these risks would not be tolerated in a drug to treat a less serious condition. Nexavar is distributed and marketed by Bayer Pharmaceuticals Corp. of West Haven, Conn.

### Numbers Don’t Always Count

The FDA does not require a specific number of participants in a clinical trial, but trial size should be tailored to the risks acceptable to people with the disease and in consideration of the rarity of the disease. Similarly, the FDA does not require a specific number of patients to respond to a cancer drug, nor does it require the drug to extend



Black Star/Dennis Brack

**FDA oncologist Bhupinder Mann says that the rarity of a cancer and the other products approved to treat it are among the factors considered by the FDA in its approval of a cancer drug.**

life by a specific number of days so long as the results are convincing and clinically meaningful given the side effects of the drug and other treatment options.

“There is no hard and fast rule,” says Edwin Rock, M.D., Ph.D., an oncologist in the FDA’s Office of Oncology Drug Products. “The agency looks at the data and makes judgments about what’s

clinically significant and whether, on balance, the benefits exceed the risks.” To be considered clinically significant, a finding must show real meaning for patients, such as extending their lives or making them feel better.

For a drug to treat a common cancer, such as breast cancer, the agency would expect large clinical trials with hundreds or even thousands of partici-





Duke University Medical Center

**Philip M. Rosoff, M.D., associate professor of pediatric hematology–oncology at Duke University School of Medicine and director of the Duke Hospital Clinical Ethics Program, says children who have had cancer need to be monitored lifelong because of the potential for later health problems.**

pants. But the FDA would consider a drug for rare cancers tested in a small number of people.

The FDA approved Zolinza (vorinostat), made by Merck & Co. Inc. of Whitehouse Station, N.J., in October 2006, based on results of clinical trials conducted in only 100 patients. The drug was approved to treat skin lesions in cutaneous T-cell lymphoma (CTCL) when the disease persists, gets worse, or comes back after treatment with other medicines. CTCL is a cancer of the T-cells, a type of white blood cell, and patients who have it develop a variety of skin lesions.

It's a rare disease that has only about 1,200 new cases a year in the United States, says Bhupinder Mann, M.B.B.S., an oncologist in the FDA's Office of Oncology Drug Products. "We'd like to have large studies, but it's impractical with certain diseases," says Mann, adding that there are only two other drugs that have been approved to treat

CTCL since the late 1990s. Although only 30 percent of the study participants responded to Zolinza, "you put it in context of rarity of the disease and what is currently available," says Mann.

The FDA may approve a use for a drug if the drug shows evidence that people live longer or live without the disease getting worse for a certain period of time, even if it's just a few weeks or a few months.

For example, the FDA approved Vectibix (panitumumab), manufactured by Amgen Inc. of Thousand Oaks, Calif., in September 2006, for use in people with colorectal cancer that has spread to other parts of the body and whose tumors were no longer responding to any standard chemotherapy. In clinical trials, people who took the drug, on average, had a growing tumor or died 96 days later—33 days longer than in people who received only treatment of symptoms (supportive care).

## Physical Evidence

In addition to evaluating data from clinical trials, the FDA may look at X-rays, computed tomography (CT) scans, or even photographs that a pharmaceutical company provides to establish whether a drug is truly effective. For the review of Zolinza, the agency had asked Merck to submit before-and-after photographs of skin lesions.

"In some of the photographs, improvement is easy to see, but in others, it is difficult to evaluate," says Mann. The raised surface of a skin lesion may be evident to the touch, but not easily distinguishable in a photograph.

The photographs were considered to be supporting evidence to help assess the benefit of the drug, says Mann. The pharmaceutical company was also required to submit measurements of the lesions and classification of their severity.

## Weighing the Risks and Benefits as a Patient

The FDA weighs risks and benefits of a drug in its decision-making as a regulatory agency. But every person diagnosed with cancer, in discussions with his or her doctor, must also weigh benefits and risks before making treatment decisions as a cancer patient.

These decisions can be very difficult, especially when a person is first diagnosed, says Patty Delaney, director of the Cancer Liaison Program in the FDA's Office of Special Health Issues, and two-time cancer survivor. "You walk into the doctor's office, and you may feel fine—you walk out, and you're devastated." With some cancers, she says, "you then start the slow degradation into feeling absolutely horrible. You then slowly come to terms with your diagnosis and begin to hope that maybe you will get better—but you also know that the disease may kill you. It's terrifying."

Patients who don't respond to the standard of care treatments also are faced with hard decisions, says Delaney. "Sometimes there's not very strong data in the literature on what to do." The doctor asks the patient what he or she wants to do, and the patient doesn't know what to choose, she says.



"People want to be in a partnership with their doctor, but they're often left with making a hard choice with little information."

"You can have your doctor choose for you," adds Delaney. "There is nothing wrong with that."

Philip Rosoff, M.D., agrees. "People have different ways of grappling with a situation when they have lost control," says Rosoff, an associate professor of pediatric hematology-oncology at Duke University School of Medicine and director of the Duke Hospital Clinical Ethics Program in Durham, N.C. "When they're faced with something like cancer, some people think that they do have control and want to run things. But for most, their universe is upended. Most want to be told what to do—they find it very comforting."

Rosoff notes an emphasis in society on autonomous decision-making that doctors are often afraid of impinging upon. "We've abandoned our roles as advisors and healers. We give patients this smorgasbord of options: A, B, C, and D—then ask, what do you want to do? Instead of giving A, B, C, and D, and saying, 'this is what I would do.' We do a disservice to patients when we don't use our expertise to give advice and to make recommendations to them."

When a number of treatments have been tried and failed and the person is dying, doctors may discourage further treatment, says Delaney, but patients don't want to run out of options. "Most don't want to hear that they aren't going to get treatments. Some of these drugs are like atom bombs going off in front of you, but a patient is often willing to take many more risks. People have a survival instinct. The mindset of people with cancer is, 'just give me anything and everything.'"

"But lately, some patients and families are stopping treatment because they are beginning to question the advisability of continuing drug treatment when death is imminent," says Delaney. "And now, with the cost of cancer drugs rising precipitously, patients and families are asking if continued treatment is affordable when we do not know whether it will add to a patient's life."

David Kelly did not want to stop treatment. He had a very strong survival instinct, and he underwent numerous toxic treatments and surgeries for his cancer, according to his fiancée, Patricia Davis, of Greenbelt, Md. In January 2004, 59-year-old Kelly was diagnosed with "metastatic carcinoma of unknown origin."

"At the first appointment, we were told it was in the liver and it was stage 4 cancer," says Davis. The doctors told Kelly his chances were less than 1 percent that they could completely rid his body of cancer and less than 5 percent that it would go into remission and, if it did, it would come back.

"Dave said, 'I'm not ready to die—I want to fight this,'" says Davis.

The doctors were very good about laying it all out, Davis says, adding that they informed them of serious risks, such as blood clots and heart failure, in addition to providing information sheets and brochures outlining the treatments and risks. Despite the risks, "Dave was willing to try anything to eradicate the cancer."

Over 18 months of treatment, Kelly had several courses of chemotherapy infusions in the hospital, numerous oral medications to take at home, three

back surgeries when the cancer spread to the spine, and a partial hip replacement when it spread to the pelvis.

As cancer cells multiply and spread to the bone, the pain is said to be excruciating. "The only way to alleviate the pain was to operate," says Davis, adding that the surgeon cut out some of the cancer and bone, then reconstructed the bone and followed up with radiation. "They couldn't cut out all the cancer because it was too close to the spine."

After the partial hip replacement, the hospital sent Kelly home in an ambulance when he protested going into a hospice facility. "Even then, Dave said, 'when I get better, I want to come back here and get more treatment,'" Davis says. "But at the end, cancer was going through his bones faster than they could operate or radiate."

Kelly died in September 2005.

## Access to Investigational Cancer Drugs

The FDA recognizes that many patients, like Kelly, run out of options and are willing to risk taking unproven treatments. The agency has put in place a number of regulatory programs and works with manufacturers so that seriously ill patients can get access to promising, but not fully evaluated, products.

**Clinical trials.** One of the most common methods to get an unapproved drug is to enroll in a clinical trial. More than 10,000 cancer clinical trials are ongoing in the United States. People interested in clinical trials should talk with their doctor, check out available trials at [clinicaltrials.gov](http://clinicaltrials.gov), or call the National Cancer Institute's (NCI's) Cancer Information Service at (800) 4-CANCER (422-6237).

If a person does not meet the criteria to participate in a clinical trial, usually because he or she has other serious medical conditions, an investigational new drug sponsor can make an exception to treat the patient. The patient's data would not be analyzed with the primary data from the original trial, but would be evaluated separately. Usually, such exceptions occur in the same institutions that are conducting

## Treatment Decisions

The American Cancer Society (ACS) stresses the importance of having frank, open discussions with your cancer care team and getting answers to all your questions to help you understand your specific condition and your options so that you can actively participate in your treatment decisions.

The ACS offers free interactive tools on its Web site to help people with cancer make informed decisions about their treatment. The tools provide details specific to a condition, a breakdown of treatment options and side effects, personalized reports with pros and cons of treatment, and questions to ask the doctor.

See [www.cancer.org](http://www.cancer.org)





Family Photo

**Patricia Davis of Greenbelt, Md., with fiancé, David Kelly, in a family photo four months before Kelly was diagnosed with "metastatic carcinoma of unknown origin."**

the original trial, where investigators are familiar with the drug.

**Single-patient, or emergency, investigational new drug.** If enough is known about an investigational drug's side effects and there is some evidence of effectiveness, the FDA may allow a patient to receive a drug in his or her own specifically designed study. Although the FDA's requirements are relatively simple, setting up this kind of access for an individual patient is not, and involves the following:

- The pharmaceutical company must be willing to provide the new drug to the patient. This provision can be expensive and time-consuming for the company since it must track shipments of the drug, create special instructions for its use, and devise a way to collect information on toxic side effects for each patient.
- The study treatment and an informed consent document must be approved by the local institutional review board,

a panel of scientists and non-scientists in hospitals and research institutions who ensure the safety and well-being of human subjects involved in research.

- The patient must give informed consent, understanding that the drug is not approved and may cause known and unknown side effects ranging from mild to fatal.
- The patient's physician must be willing to take responsibility for treating the patient and agree to collect information about the effects of the drug.

#### **Treatment investigational new drug.**

A promising new drug can be distributed outside of clinical trials under a treatment investigational new drug if

- the drug is intended to treat a serious or immediately life-threatening disease
- there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population
- there is presumptive evidence that

the drug may offer some benefit to certain patients

- proper clinical trials are well under way to see whether the drug really does offer patients any benefit.

The FDA cannot force a pharmaceutical company to give an individual patient an investigational drug outside of its planned clinical trials. The drug manufacturer makes the final decision to provide an experimental treatment to a patient. The company may consider many factors, including the amount of information available about the drug, the amount of drug available, and how best to use its resources to optimize development of the drug. In some cases, the company is unwilling to provide the product outside of clinical trials.

#### **Children and Cancer Drugs**

As with drugs for adults, the FDA weighs the risks and benefits of drugs for children based on clinical trials. "But it's hard to do clinical trials in children for many drugs—not just cancer drugs—because it's difficult to get a large number of patients enrolled," says Karen Weiss, M.D., pediatric oncologist and deputy director of the FDA's Office of Oncology Drug Products.

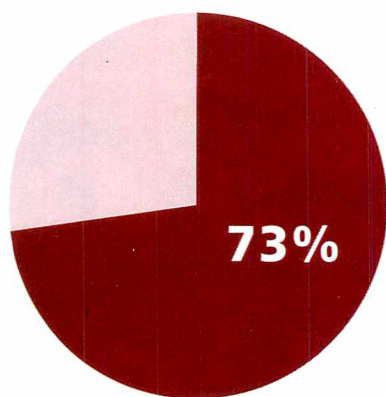
Even the most common cancer in children, leukemia, strikes only one-tenth as many children—about 3,200—as adults each year in the United States, according to the NCI. "Acute leukemia has an 85 percent survival rate, so to show that a new drug improves survival, a sponsor would need a large study and it would take many years," says Weiss.

Sometimes, in lieu of conducting randomized trials in children to demonstrate the effectiveness of a drug, the FDA may extrapolate findings from adult trials of a drug that might also be promising for children. This action may be taken when the disease being treated is similar between adults and children.

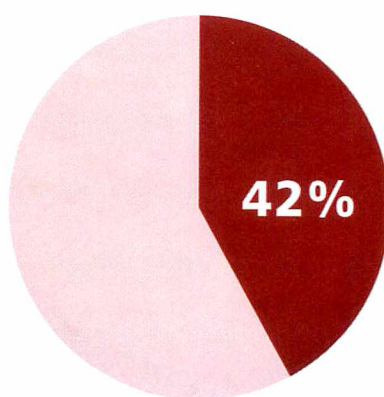
For example, in 2003, the FDA approved Gleevec (imatinib mesylate) for the treatment of children who have a rare, life-threatening form of leukemia. This approval, the first for a new cancer drug for children in more than a decade, was based on evaluating results



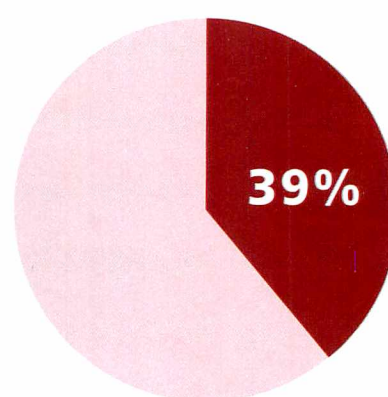
## Childhood Cancer Survivors With Health Conditions Later In Life



**Chronic Condition**



**Severe or  
Life-Threatening  
Condition**



**Multiple Conditions**

Infographic: FDA/Michael Ermarth

The Childhood Cancer Survivor Study found that children who were treated for cancer in the 1970s and 1980s have a high rate of illness as adults due to organ damage caused by chemotherapy and radiation during cancer treatments. The authors note that lifelong monitoring is an important part of overall health care.

Source: Kevin C. Oeffinger, M.D., et al., "Chronic Health Conditions in Adult Survivors of Childhood Cancer," *New England Journal of Medicine*, Oct. 12, 2006

from Gleevec-treated adults with the same leukemia together with good responses in a small number of children. As a condition of approval, the manufacturer, Novartis Pharmaceuticals Corp., agreed to conduct pediatric studies after approval to confirm that the drug improves survival or provides other clinical benefits in children. These trials are ongoing.

Because of early diagnosis and successful cancer treatments, about three-fourths of children with cancer are cured and able to live into adulthood, according to the NCI. Although the cure rate is encouraging, the recently reported results of a study of survivors of childhood cancer are disturbing.

The Childhood Cancer Survivor Study found that survivors appear to have a high rate of chronic health conditions later in life due to organ damage caused by chemotherapy and radiation during cancer treatments.

The study tracked more than 10,000 children diagnosed with cancer from 1970 to 1986 and compared their health with the health of 3,000 siblings. The researchers reported in the

Oct. 12, 2006, issue of the *New England Journal of Medicine* that 30 years after a diagnosis of cancer, almost three-fourths of survivors have a chronic health condition, more than 40 percent have a serious health problem, and more than one-third have multiple conditions.

Doctors and patients need to be aware of the potential for later health problems, says Rosoff, who authored an editorial in the same journal. He emphasizes the importance of monitoring children who survive cancer as they grow up. "We need to try to convince people they need to be vigilant lifelong."

When it comes to treating cancer, Rosoff adds, "A concern about late effects is a luxury of cure. No physician or patient would sacrifice a percentage point of cure for a percentage point of late effects."

Once a medication is approved, the FDA monitors the medication and collects information on side effects including late effects, rare effects, and long-term effects. This postmarketing surveillance program is an impor-

tant complement to the premarketing assessment because the agency cannot anticipate all possible effects of a drug during clinical trials that precede a drug's approval. Through its continuous monitoring of medical products, the FDA ensures that new safety information is quickly communicated to medical professionals and patients. ■

### For More Information

Approved cancer drugs  
[www.fda.gov/cder/cancer/druglistframe.htm](http://www.fda.gov/cder/cancer/druglistframe.htm)

How to get investigational cancer drugs

The FDA's Office of Special Health Issues

Cancer Liaison Program  
(301) 827-4460

[www.fda.gov/oashi/cancer/cancer.html](http://www.fda.gov/oashi/cancer/cancer.html)

The NCI's Cancer Information Service

(800) 4-CANCER (422-6237)

<http://cis.nci.nih.gov/>





Agricultural Research Service / U.S. Department of Agriculture

# Bacteria-Eating Virus Approved as Food Additive

By Linda Bren

**N**ot all viruses harm people. The Food and Drug Administration has approved a mixture of viruses as a food additive to protect people. The additive can be used in processing plants for spraying onto ready-to-eat meat and poultry products to protect consumers from the potentially life-threatening bacterium *Listeria monocytogenes* (*L. monocytogenes*).



The viruses used in the additive are known as bacteriophages. Bacteriophage means "bacteria eater." A bacteriophage, also called a phage (pronounced fayj), is any virus that infects bacteria.

Consuming food contaminated with the bacterium *L. monocytogenes* can cause an infectious disease, listeriosis, which is rarely serious in healthy adults and children, but can be severe and even deadly in pregnant women, newborns, older people, and people with weakened immune systems. Pregnant women are about 20 times more likely than other healthy adults to get listeriosis, according to the Centers for Disease Control and Prevention (CDC). Listeriosis can cause miscarriage, stillbirth, premature delivery, or death of a newborn baby.

People with listeriosis have fever and muscle aches, and sometimes an upset stomach, nausea, and diarrhea. If the infection spreads to the nervous system, headache, stiff neck, confusion, loss of balance, or convulsions can occur.

The CDC estimates that about 2,500 people become seriously ill with listeriosis each year in the United States. Of these, about 500 die.

Cooking can kill *L. monocytogenes*, but many ready-to-eat foods, such as hot dogs, sausages, luncheon meats, cold cuts, and other deli-style meats and poultry, may become contaminated within the processing plant after cooking and before packaging. Unlike fresh meat and poultry, the ready-to-eat products can be consumed without reheating, so the *L. monocytogenes* survive and are ingested.

"*L. monocytogenes* can continue to thrive even in refrigerated conditions," says Capt. Andrew Zajac, a food safety expert and acting director of the Division of Petition Review within the FDA's Center for Food Safety and Applied Nutrition (CFSAN). "If a food product contaminated with *L. monocytogenes* is bought by a consumer and brought home and refrigerated, the bacteria can continue to multiply."

### How Bacteriophages Work

Bacteriophages are found in the environment. "We're routinely exposed to

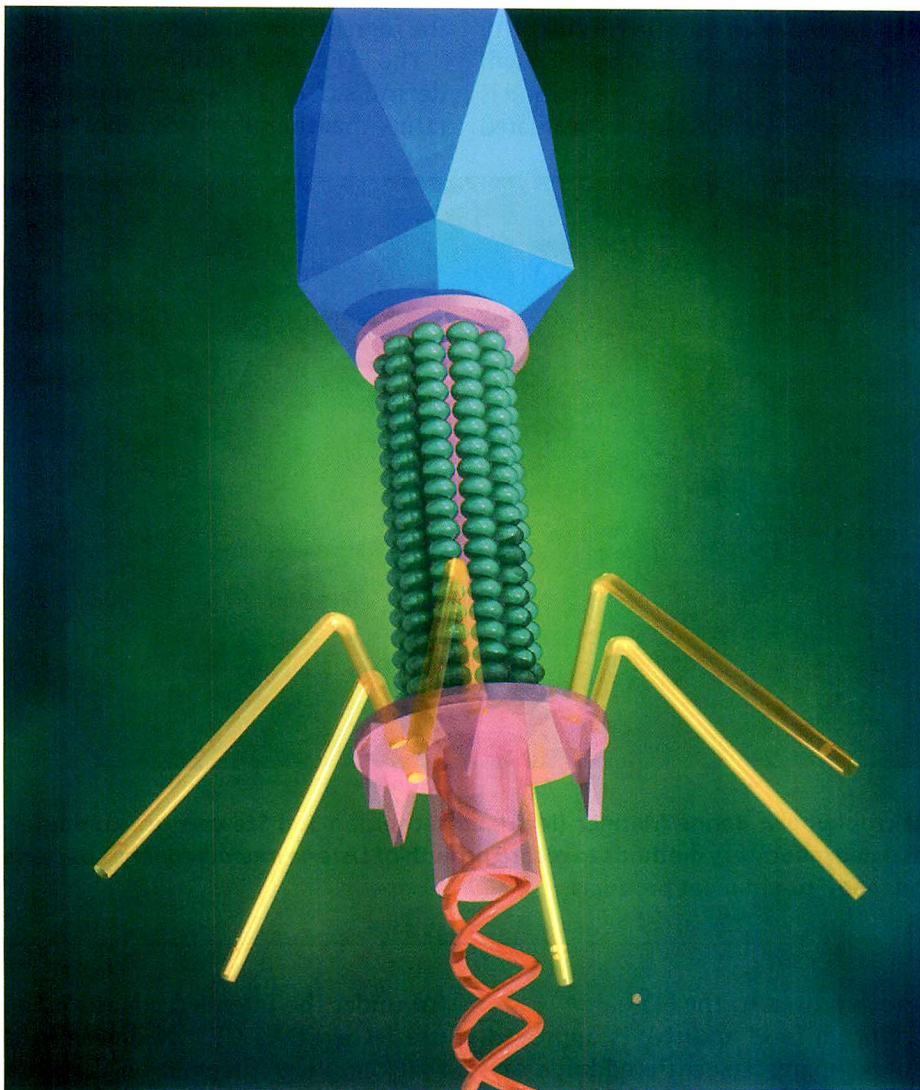
bacteriophages," says Zajac. "They are found in soil and water, and they are part of the microbial population in the human gut and oral cavity."

Bacteriophages infect only bacteria, says Zajac. "They don't infect plant or mammalian cells." Thousands of varieties of phages exist, and each one infects only one type or a few types of bacteria. The particular phages approved as a food additive are very specific to *Listeria*, says Zajac. "They'll only thrive if *Listeria* are present."

The type of phage that was approved is lytic, which means that the phage destroys its host during its life cycle

without integrating into the host genome. This type of phage works by attaching itself to a bacterium and injecting its genetic material into the cell. The phage takes over the metabolic machinery of the bacterium, forcing it to produce hundreds of new phages and causing the bacterial cell walls to break open. This process kills the bacterium and releases many new phages, which seek out other bacteria to invade and repeat the cycle.

"The process continues until all host bacteria have been destroyed," says Zajac. "Then the bacteriophages cease replicating. They need a host to multi-



Phototake

## Bacteriophage

The head (blue) stores genetic material, which is released through the corkscrew-like tail (pink) into a bacterium, forcing the bacterium to produce hundreds of new bacteriophages. The bacterial cell walls break open, killing the bacterium and releasing many new bacteriophages that seek out other bacteria to invade and repeat the cycle.



ply and will gradually become inactive when they lose the host."

### Approval Process for Food Additives

To market a new food additive, a manufacturer must petition the FDA for its approval. The petition must provide convincing evidence that the proposed additive performs as it is intended and will not cause harmful effects when consumed.

If an additive is approved, the FDA issues a regulation that includes information on the types of foods in which the additive can be used and maximum amounts to be used. The regulation also provides the additive's identity and specifications on purity, which will ensure that the additive used in food is the same substance that was evaluated

The preparation combines six different phages that have been shown to be effective against 170 different strains of *L. monocytogenes*. Multiple phages are used so that if the *L. monocytogenes* develop resistance to several phages, the remaining ones can still destroy the bacteria.

The FDA must approve any additive before it can be used in food. When an additive is to be used on meat or poultry products, as with this one, both the FDA and the U.S. Department of Agriculture (USDA) are involved in the approval. The FDA evaluates the safety of the ingredient for its intended use. At the same time, the USDA evaluates the ingredient's suitability.

The FDA's food additive regulations define safety as "a reasonable certainty that the substance is not harm-

a substance is effective in performing the intended purpose of use and at the lowest level necessary for particular types of products," says Robert C. Post, Ph.D., director of the FSIS' Labeling and Consumer Protection Staff. In addition, suitability is an assurance that the use of the additive will not result in a product that is unfit for human consumption (adulterated) or one that misleads consumers. Consumers would be misled if, for example, the additive makes a product "appear to be a better value than it actually is or it masks spoilage," says Post.

The FSIS evaluated data submitted by the petitioner to ensure suitability for a number of ready-to-eat products, such as sausages, turkey, soups, stews, hot dogs, bologna, Vienna sausage, and cooked ham and turkey.

### Labeling

Under the Federal Meat Inspection Act and the Poultry Products Inspection Act, both administered by the USDA, the use of the phage preparation must be declared on labeling as an ingredient. Consumers will see "bacteriophage preparation" on the label of meat or poultry products that have been treated with the food additive.

If consumers have any concerns about what they're getting at the deli counter, says Post, "they always have the ability to ask for the label of the product being prepared or sliced to see what it contains."

### A Phage First

This approval marks the first time that the FDA has regulated the use of a phage preparation as a food additive. Phages are currently approved in the United States for pesticide applications, such as spraying on crops.

Scientists continue to be interested in other uses for phages, such as to prevent food products from contamination with other types of harmful bacteria and to act as possible treatments for bacterial infections in people. ■

### For More Information

FDA Bacteriophage Questions and Answers

[www.cfsan.fda.gov/~dms/opabacqa.html](http://www.cfsan.fda.gov/~dms/opabacqa.html)



Agricultural Research Service/U.S. Department of Agriculture

**Microbiologist Benne Marmer (left) and technician Tod Stewart use computer-assisted laboratory methods to record growth of *Listeria monocytogenes* bacteria on ready-to-eat meat products.**

and approved by the FDA.

Once a food additive is approved, any company can use the additive, says Zajac, as long as it meets the conditions in the regulation.

In response to a petition submitted by industry, the FDA published a regulation in August 2006 permitting the use of a *Listeria*-specific bacteriophage preparation on ready-to-eat meat and poultry products.

ful under the intended conditions of use." The FDA's CFSAN determined that the phage preparation does not pose any safety concerns based, in part, on published reports submitted by the petitioner on the results of the use of phages in animal and human studies.

The USDA's Food Safety and Inspection Service (FSIS) evaluated the bacteriophage preparation's suitability. "Suitability establishes that the use of



Deborah Dohne, a college professor, took a semester off to recover after developing whooping cough (pertussis) in May 2006.



Black Star/Michael Greenlar

# Keeping Up With **VACCINES**

*By Michelle Meadows*

**D**eborah Dohne, 42, a college professor in Syracuse, N.Y., didn't think much of it when she developed a mild fever and sore throat in mid-May 2006. "I thought maybe I had a cold and kept going about my business," she says. But two weeks later, she wasn't getting any better. By the third week, she started vomiting and her throat became so swollen she could barely swallow.



She went to the emergency room where physicians suspected strep throat and performed a throat culture. The test came back negative, but they said there was still a chance she could have strep throat and they gave her an antibiotic.

Four weeks into her illness, Dohne felt even worse. She developed a loss of appetite, sinus congestion, chest tightness, fatigue, and a relentless cough. "I took cough medicines, but nothing helped," she says. "When I

talked or laughed, it made me cough even more." Doctors suggested that her symptoms could be caused by an infectious disease, such as mononucleosis, or allergies.

After the cough persisted for three more weeks, Dohne's primary care physician performed a blood test to check for whooping cough (pertussis). That test came back positive, and Dohne began seeing an infectious disease specialist. "I had never even heard of pertussis," Dohne says. "I had heard

the term 'whooping cough,' but I didn't think anybody got that anymore." Dohne had received a vaccination against whooping cough as a child.

Whooping cough is a bacterial respiratory illness characterized by severe spasms of coughing that can last for weeks or even months. In September 2006, Dohne experienced soft tissue damage in her back from coughing so hard. Severe coughing has also given her bloodshot eyes. "I've had dreams where I'm just coughing and coughing and coughing," she says. "It's a scary feeling—you feel like you'll be coughing forever."

Because of her illness, Dohne took an entire semester off from teaching. "In addition to the cough, fatigue has been an incapacitating problem," she says. Dohne suspects that she contracted whooping cough from a student who may have been ill, but she isn't sure. The disease is spread by close contact with respiratory tract droplets that are released when a person coughs or sneezes.

The introduction of a whooping cough vaccine in the 1940s led to a marked decline in cases and deaths from whooping cough in the United States. But as with other vaccine-preventable diseases, whooping cough still exists. That's why continued vaccination is so important. Vaccines help create antibodies, an important element in the body's defense against foreign substances.

According to the Centers for Disease Control and Prevention (CDC), rates of whooping cough have been on the rise in all age groups in the United States since the 1980s. In the pre-vaccine era, people were frequently exposed to the bacteria that cause whooping cough, providing periodic boosts to their immunity. But with the elimination of most of the natural infection, the chance of immune boosts lessened. As a result, many adolescents and adults were without antibodies to the infections. This situation was compounded by the absence of a vaccine against whooping cough that could be used in people ages 6 years and older.

In 2005, the Food and Drug Administration licensed two whooping cough vaccines for use in adolescents and



Centers for Disease Control and Prevention

**A young boy shown with measles. Vaccination has led to a 99 percent reduction in the incidence of the disease in the United States, according to the Centers for Disease Control and Prevention. The MMR vaccine is a live, weakened (attenuated), combination vaccine that protects against the measles, mumps, and rubella viruses.**



adults that will allow these groups to have immunity again against the infection. Both vaccines are combination boosters that protect against tetanus, whooping cough, and another respiratory disease called diphtheria.

"Vaccines aren't only for young children," says Norman Baylor, Ph.D., director of the Office of Vaccine Research and Review in the FDA's Center for Biologics Evaluation and Research (CBER). "We want to get children off to a healthy start by giving them the recommended series of vaccinations, and adolescents and adults should also know that they need certain vaccinations to remain protected throughout their lifetime. Serious illness and deaths from many infectious diseases have declined because of vaccination. But if we stopped vaccinations, we would see disease epidemics again."

Here's a look at vaccines that have been recently licensed by the FDA, along with the latest recommendations from the CDC's Advisory Committee on Immunization Practices (ACIP) for young children, adolescents, and adults. The ACIP consists of 15 experts, as well as liaison members from other parts of government including the FDA, who advise the CDC's director and the Secretary of the U.S. Department of Health and Human Services on the control of vaccine-preventable diseases. The ACIP's key role is to make recommendations on immunization practices in the United States, including which FDA-licensed vaccines will be recommended for routine use in children in the United States. The ACIP provides practice of medicine recommendations based on different criteria from those which the FDA must use for vaccine approvals/licensure, so some recommendations on the CDC's Web site may differ from a vaccine's label.

### For Young Children

By ages 4 years to 6 years, children should have received vaccinations that protect them from a string of diseases, including influenza, diphtheria, tetanus, whooping cough, chickenpox (varicella), hepatitis A and B, polio, pneumococcal diseases, measles, mumps, German measles (rubella),



Associated Press

**Nurse Mike Hart gives vaccines to Gino Pastore, 11, at the Washington Neighborhood Health Clinic in San Jose, Calif.**

diseases due to *Haemophilus influenzae*, and rotavirus.

In September 2006, the CDC announced that immunization rates for children 19 months to 35 months of age remain at or near record highs. About 80 percent of 19-month to 35-month-old children in the United States received all the vaccinations in the recommended series. And there have been significant increases in the percentage of young children receiving the chickenpox vaccine and childhood pneumococcal vaccine.

More good news is that for the first time in the past 10 years, immunization rates for the full series of vac-

cines did not vary significantly by race and ethnicity, says Robert Baltimore, M.D., professor of pediatrics and epidemiology at Yale University School of Medicine in New Haven, Conn. "This shows great progress in closing some significant gaps," he says. Previously, immunization rates for white children far exceeded those for black and Hispanic children.

"But there are still pockets of people across the country who are refusing vaccinations and putting their children at risk," Baltimore says. "Some people think they are protected from disease because they live in an area where most of the other people around them are



# Recommended Childhood and Adolescent Immunization Schedule

United States • 2006

Vaccine ▼	Age ►	Birth	1 months	2 months	4 months	6 months	12 months	15 months	18 months	24 months	4–6 years	11–12 years	13–14 years	15 years	16–18 years
Hepatitis B	HepB		HepB	HepB	HepB	HepB	HepB	HepB	HepB	HepB Series					
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	DTaP	Tdap	Tdap			
<i>Haemophilus influenzae</i> type B			Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib	Hib
Inactivated Poliovirus			IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV	IPV
Measles, Mumps, Rubella							MMR	MMR	MMR	MMR	MMR	MMR	MMR	MMR	MMR
Varicella							Varicella	Varicella	Varicella	Varicella	Varicella	Varicella	Varicella	Varicella	Varicella
Meningococcal												MCV4	MCV4	MCV4	MCV4
Pneumococcal			PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PPV	PPV	PPV	PPV	PPV
Influenza							Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)
Hepatitis A										HepA Series	HepA Series	HepA Series	HepA Series	HepA Series	HepA Series

Source: Centers for Disease Control and Prevention

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of Dec. 1, 2005, for children through age 18 years. Any dose not administered at the recommended age should be administered at any subsequent visit when indicated and feasible.      indicates age groups that warrant special effort to administer those vaccines not previously administered. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the FDA for that dose of the series. Providers should consult the respective ACIP statement for detailed recommendations. Footnotes for these recommendations can be found at [www.cdc.gov/nip/recs/child-schedule.htm](http://www.cdc.gov/nip/recs/child-schedule.htm) on CDC's Web site.

     Range of recommended ages           Catch-up immunization           11- to 12-year-old assessment

vaccinated, but it doesn't always work that way." Children who are unvaccinated are vulnerable.

Recent changes affecting young children include an expanded age range for annual flu vaccination, a recommendation for a second dose of the chickenpox vaccine to further boost immunity, and the licensing of a vaccine to prevent inflammation of the stomach and intestines (rotavirus gastroenteritis) in infants.

**Vaccine against rotavirus.** In February 2006, the FDA licensed RotaTeq, a live virus vaccine and the only vaccine approved in the United States that can help protect against rotavirus, a viral infection that causes diarrhea, vomiting, and fever, which may lead to serious dehydration. According to the

RotaTeq label, the vaccination series consists of three doses given by mouth starting at 6 weeks to 12 weeks of age, with subsequent doses given at four- to 10-week intervals. The ACIP recommends that rotavirus vaccine be given at 2 months, 4 months, and 6 months of age. The vaccine can be given with most other childhood vaccines.

Rotavirus infection results in about 55,000 hospitalizations of young children each year in the United States. Though death from rotavirus is rare in the United States, more than 500,000 children worldwide, especially in developing countries, die from the infection each year.

In one of the largest vaccine safety studies ever conducted, more than 30,000 healthy infants were given rotavirus vaccine in the United States

and other countries. Of these infants, almost 7,000 from the United States and Finland were studied for effectiveness of the vaccine. RotaTeq prevented 74 percent of all rotavirus gastroenteritis cases and 98 percent of the severe cases. The most common side effects of the vaccine have been mild, short-lived episodes of diarrhea and vomiting.

The large study did not show an increased risk of intussusception associated with RotaTeq. Intussusception is a rare, life-threatening type of blockage or twisting of the intestine. This condition was associated with a previously licensed version of rotavirus vaccine called RotaShield, which was withdrawn from the market in 1999. Safety of the new vaccine will be closely monitored.

Before giving RotaTeq, health care



providers should determine the infant's current health status and previous vaccination history, including whether there has been a reaction to a previous dose of RotaTeq or other rotavirus vaccine.

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

**Recommendations reinstated for pneumococcal conjugate vaccine (PCV7).** Prevnar, marketed by Wyeth Vaccines of Sanford, N.C., had production problems that resulted in shortages in 2001 which changed the recommendations for the vaccine from four doses to two doses for healthy children. These shortages were resolved, and in September 2004, the ACIP recommended that health care pro-

viders resume the full four-dose vaccination schedule for young children for PCV7: one dose each at 2 months, 4 months, and 6 months of age, and one dose at 12 months to 15 months of age. According to Prevnar's label, the fourth dose should be given at least two months after the third dose. This vaccine can help prevent serious invasive pneumococcal diseases, such as meningitis, pneumonia, and blood infections, all of which can be fatal.

**Second dose of chickenpox vaccine.** The FDA licensed Varivax (varicella virus vaccine live), the first vaccine for chickenpox, in 1995. Varivax, which is manufactured by Merck & Co., is indicated for people 1 year of age and older.

In June 2006, the ACIP voted to recommend a second dose of chickenpox vaccine for children 4 years to 6 years old to further improve protection against the disease. The first dose of chickenpox vaccine is recommended at ages 12 months to 15 months. Parents should talk with physicians about the best way to catch up. The ACIP also recommended that adolescents and adults who previously received one dose receive a second dose of chickenpox-containing vaccine.

It is estimated that 15 percent to 20 percent of children who have received one dose of the vaccine are not fully protected and may develop chickenpox after coming in contact with chickenpox and shingles (varicella zoster virus). And one dose of the vaccine

## A Measles Outbreak

A 17-year-old girl from Indiana who was unvaccinated against measles went to work as a missionary in an orphanage in Bucharest, Romania, for 11 days. When she returned to Indiana on May 14, 2005, traveling on international and domestic commercial airlines, she had a cough, fever, and pink eye (conjunctivitis). The day after her return, she attended a church picnic, where many of the attendees were also unvaccinated against measles. The teenager was diagnosed with measles after family members reported that she had a rash for two days after her return to Indiana.

Measles is a highly contagious viral disease. In total, 33 church members acquired the illness. A 34th case of measles was reported in a phlebotomist who worked in an Indiana hospital where one of the measles patients had been admitted. Three of the 34 patients were hospitalized with complications. Two suffered dehydration, and a 34-year-old developed pneumonia and required six days of ventilator support.

State and local health departments in Indiana employed several strategies to control the outbreak, including voluntarily isolating patients, administering vaccine to susceptible contacts, checking the immune status of health workers, and alerting hospitals to the outbreak. High vaccination levels in the surrounding community helped avoid an epidemic.

According to the CDC, the outbreak could have been prevented if the teen had been adequately vaccinated before traveling to Romania. And the unimmunized church members who had exposure to the teen were especially vulnerable to developing the infection. The outbreak occurred in an Indiana population in which most of the children were home-schooled. Their parents

had refused to have them vaccinated because of safety concerns about the vaccine. It was the largest measles outbreak in Indiana since 1990 and the largest in the United States since 1996.

Before the measles vaccine became available in 1963, there were about 450,000 measles cases and an average of 450 measles-associated deaths reported each year in the United States. Eileen Ouellette, M.D., a pediatric neurologist who served as the immediate past president of the American Academy of Pediatrics, says she felt the devastation of measles firsthand.

Even though the incident occurred more than 60 years ago, Ouellette still remembers the ocean waves that tossed her back and forth and the whale that tried to attack her. She was 8 years old and in bed experiencing central nervous system complications associated with measles.

"In my mind, my mattress was floating on a turbulent sea and the whale wanted to devour me," Ouellette says. "It was all very real to me. My parents said that I screamed about the hallucinations for days, as my fever remained above 105 degrees." She feels lucky that she suffered no permanent damage. Measles can cause pneumonia, seizures, brain damage, and death.

Widespread use of the measles vaccine in the United States has led to greater than 99 percent reduction in measles, compared with that of the pre-vaccine era. Because of vaccines, it's now rare for American children to experience the devastating effects of many vaccine-preventable diseases. "But many diseases are still common in developing countries," Ouellette says. "We have to remember that vaccine-preventable diseases are just a plane ride away." ■



## Vaccine Safety and Effectiveness

"No vaccine is 100 percent safe or 100 percent effective," says Norman Baylor, Ph.D., director of the Office of Vaccine Research and Review in the FDA's Center for Biologics Evaluation and Research (CBER). In regard to effectiveness, there may be disease even in people who have been vaccinated. But in many cases, vaccination reduces the risk of disease complications. A disease is generally more likely to be less severe than it would have been without vaccination.

"With safety, it's a matter of weighing the benefits and the risks," Baylor says. "Routine vaccinations are generally safe and the risks of the vaccines are much smaller than the risks of the diseases." Side effects from vaccines, such as soreness at the injection site, are usually mild. But vaccines can cause severe allergic reactions, including time-limited difficulty breathing, wheezing, hives, and rapid heartbeat. Consumers should talk with their physicians about the risks and benefits for them.

The CBER takes a premarket and postmarket approach to vaccine safety. "Before a vaccine gets on the market, we evaluate safety in clinical trials, as well as from a manufacturing standpoint," Baylor says.

Some adverse events become detectable only after a vaccine is used in the larger, general population. The CBER and the Centers for Disease Control and Prevention jointly manage the Vaccine Adverse Event Reporting System (VAERS), a postmarketing safety surveillance program that collects information about side effects occurring after administration of licensed vaccines.

Baylor says that in the last few years, the CBER has involved the postmarketing group, the FDA's Office of Biostatistics and Epidemiology, in earlier stages so the epidemiologic experts can get a sense of the clinical data results well before the vaccine is on the market. This step helps improve postmarketing surveillance. ■

may not continue to provide protection into adulthood when chickenpox is more severe. Some vaccinated children have developed the illness, and they can transmit it to their parents.

**Availability of measles, mumps, rubella, and varicella (MMRV) vaccine.** In September 2005, the FDA licensed ProQuad, a combined live, attenuated MMRV vaccine. It is indicated for the simultaneous vaccination against measles, mumps, German measles, and chickenpox among children ages 12 months to 12 years. Manufactured by Merck & Co., the vaccine presents a more convenient way to give MMR and varicella vaccines at the same time.

**Expanded hepatitis A vaccination.** Hepatitis A is a liver disease caused by the hepatitis A virus.

Previous ACIP recommendations called for vaccinations only in states

with the highest rates of hepatitis A. The ACIP now recommends that all children in the United States receive hepatitis A vaccine. Children should get the first dose of a two-dose series at ages 1 year to 2 years.

**Expanded age range for flu vaccination.** Previously, the ACIP recommended that children ages 6 months to 23 months receive an annual flu shot. The latest ACIP recommendations expand this age range and call for children ages 6 months to 5 years to receive the flu vaccine annually. Research has shown that children ages 2 years to 5 years are nearly as likely to require visits to health care providers and emergency rooms for flu as are children 6 months to 23 months. In February 2006, the ACIP also recommended expansion of routine flu vaccination for household contacts, caregivers, and anyone else who spends a significant amount of time with children from birth to 5 years.

## For Adolescents

Adolescents ages 11 to 18 years also need to be sure that they are up-to-date with their immunizations. The checkup that takes place near age 11 years is a good time to check on what they need, says Robert Frenck, M.D., professor of pediatrics in the Division of Infectious Diseases at Children's Hospital in Cincinnati.

"At this time, parents should make sure that adolescents have had two doses of the MMR vaccine," Frenck says. "There's also a recommendation to receive a booster dose of Tdap after the eleventh birthday if it's been five years since the last Td dose. And if an adolescent has never had chickenpox and missed the chickenpox vaccine, this would be the time to get it."

Parents should discuss any concerns about booster vaccines with their children's physicians. For example, if a child had a serious reaction to a previous dose of vaccine as a young child, a booster dose in adolescence may not be recommended. Some adolescents with certain health risks may need other vaccines, such as the annual flu vaccine, hepatitis vaccine, or pneumococcal vaccine.

Three vaccines recently licensed by the FDA include adolescents in the targeted population—vaccines that protect against the human papillomavirus (HPV), whooping cough, and meningococcal disease.

**Approval of a vaccine for HPV.** In June 2006, the FDA licensed Gardasil to help prevent HPV, the most common sexually transmitted infection in the United States. The vaccine is highly effective against four types of the HPV virus, including two that cause about 70 percent of the cases of cervical cancer in the United States. Manufactured by Merck & Co., Gardasil was licensed in six months under the FDA's priority review process. This vaccine is indicated in girls and women who are ages 9 years to 26 years.

According to the ACIP, three doses of the new vaccine should be routinely given over a six-month period to girls when they are 11 years or 12 years old. But the vaccine can be given to girls as young as 9 years at the discretion of a




# Recommended Adult Immunization Schedule, by Vaccine and Age Group


United States • October 2006-September 2007

Vaccine	Age group (yrs)		
	19–49	50–64	≥ 65
Tetanus, diphtheria, pertussis (Td/Tdap)	1-doseTd booster every 10 yrs		
	Substitute 1 dose of Tdap for Td		
Human papillomavirus (HPV)	3 doses (females)		
Measles, mumps, rubella (MMR)	1 or 2 doses	1 dose	
Varicella	2 doses (0, 4–8 wks)	2 doses (0, 4–8 wks)	
Influenza	1 dose annually	1 dose annually	
Pneumococcal (polysaccharide)	1–2 doses		1 dose
Hepatitis A	2 doses (0, 6–12 mos, or 0, 6–18 mos)		
Hepatitis B	3 doses (0, 1–2, 4–6 mos)		
Meningococcal	1 or more doses		

Source: Centers for Disease Control and Prevention

These recommendations should be read with footnotes, which can be found at [www.cdc.gov/nip/recs/adult-schedule.htm](http://www.cdc.gov/nip/recs/adult-schedule.htm) on the CDC's Web site. This schedule indicates the recommended age groups and medical indications for routine administration of currently licensed vaccines for people ages 19 years and older as of Oct. 1, 2006. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturer's package inserts and complete statements from the ACIP.

 For all people in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection).

 Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications).

health provider, and can be given to women up to age 26. Gardasil's label indicates that the three doses should be given according to the following schedule: The first dose should be given at an elected date, the second dose should be given two months after the first dose, and the third dose should be given six months after the first dose.

**Approval of vaccines for whooping cough.** In May 2005, the FDA licensed two new combination vaccines to prevent tetanus, diphtheria, and whooping cough. One preparation of Tdap, Boostrix, is licensed for use for people 10 years to 18 years of age. The other preparation, Adacel, is licensed for people ages 11 years to 64 years.

In June 2005, the ACIP recommended

that adolescents ages 11 years to 18 years be given a single shot of Tdap in place of the tetanus–diphtheria (Td) booster typically given to adolescents. Those who already received a Td booster should get the Tdap five years after having received the Td vaccine. If they live in an area where pertussis is epidemic, the Tdap vaccine can be given two years after having received a Td vaccine.

**Approval of vaccine for meningococcal disease.** In January 2005, the FDA licensed Menactra (MCV4) for people ages 11 years to 55 years. MCV4 is a meningococcal vaccine manufactured by Sanofi Pasteur of Swiftwater, Pa. The vaccine is not indicated for the treatment of meningococcal infections.

Meningococcal disease strikes up to

3,000 Americans, killing 300 people every year. The infection can present as meningitis or an overwhelming bloodstream infection. The disease often begins with symptoms that can be mistaken for flu or other common illnesses. But it progresses rapidly and can kill within hours. People at elevated risk include first-year college students living in dorms, military recruits, and travelers to areas with high meningococcal disease.

In May 2006, the ACIP recommended routine meningococcal vaccine for adolescents at 11 to 12 years of age. For those who have not previously received MCV4, the ACIP recommends vaccination at high school entry, for entering college students who plan to live in dorms, and for people at high risk for



## Vaccines in Pregnancy

If a woman gets German measles (rubella) in pregnancy, she could have a miscarriage or the baby could be born with serious birth defects. An increase in miscarriages has also been found among women who develop mumps during the first trimester of pregnancy.

Jon Temte, M.D., Ph.D., associate professor of family medicine at the University of Wisconsin, says it's ideal if women can check their vaccination status before pregnancy.

For example, the tetanus, diphtheria, and pertussis (Tdap) vaccine, which should not be administered during pregnancy, would be good to get in pre-pregnancy to provide protection from these diseases for the newborn.

"Women who are pregnant shouldn't get live viral vaccines," Temte says. "Even when there is no data of adverse effects, it's to protect against any possible transmission to the fetus."

A pregnant woman can and should get inactivated flu vaccine if she will be pregnant during flu season. FluMist, a live virus influenza vaccine, should not be given to pregnant women. "Pregnant women also should not get the measles, mumps, and rubella (MMR) vaccine or chickenpox (varicella) vaccine, both of which contain weakened live viruses," Temte says. Other vaccines that pregnant women shouldn't get are Gardasil for the human papillomavirus (HPV), Menactra (MCV4) for meningococcal disease, and Zostavax for shingles.

Temte says that other vaccines for pneumococcal disease, tetanus, meningitis, and hepatitis A or B would be given in pregnancy only if there was some medical reason to do so. ■

spread," Pickering says. The CDC, the FDA, and state and local health departments investigated a mumps outbreak that began in Iowa in December 2005 and involved at least 10 other states. The first cases were detected on a college campus in eastern Iowa. In 2006, cases continued to be reported from college campuses. As a result of these outbreaks, a two-dose mumps vaccine regimen has been recommended.

"Adults should talk with their physicians about their risks for vaccine-preventable diseases, and the elderly population should be especially encouraged to get the flu-vaccine and pneumococcal vaccine," Pickering says. Some adults may need revaccination with the pneumococcal vaccine, which should be discussed with their physicians. Influenza, pneumococcus, tetanus, and shingles can be especially serious diseases for adults ages 65 years and older.

Most hospitalizations and deaths from the flu occur in people ages 65 years and older. Among this group, overall flu vaccination coverage declined from 68 percent in 2004 to 63 percent in 2005, according to data published in the CDC's *Morbidity and Mortality Weekly Report* on Oct. 6, 2006. Pneumococcal vaccination coverage remained about the same—64 percent. Adults 65 years and older should get the pneumococcal polysaccharide vaccine, which protects against blood-borne pneumococcal disease. This illness can lead to serious infections of the lungs, the blood, and the covering of the brain.

All adults should receive the Td booster every 10 years throughout life to protect against these infections. Some adults should get the MMR vaccine and have all of their recommended vaccines reviewed regularly. According to the CDC, generally any people born after 1956 should get at least one dose of MMR vaccine unless they can show that they have had either the vaccine or each of the three diseases.

"Adults also are at greater risk of com-

meningococcal disease.

MCV4 is given as a single injection, and the most common reaction is a sore arm.

In September 2005, the FDA and the CDC issued an alert on MCV4 and Guillain-Barré Syndrome (GBS), a serious neurological disorder that can occur either spontaneously or after certain infections. The disorder typically involves increasing weakness in the legs and arms that can be severe and that can require hospitalization.

As of October 2006, 15 cases of GBS were reported in people ages 11 years to 19 years with onset within 6 weeks of vaccination with MCV4, according to the CDC. So far, the data suggest that there is no definitive link between the MCV4 vaccine and GBS, and there hadn't been any changes in vaccina-

tion recommendations as of December 2006. The FDA and the CDC continue to evaluate the cases. The ACIP has recommended that people with a history of GBS should not be vaccinated with MCV4.

### For Adults

More than 30,000 adults die each year from vaccine-preventable diseases, according to the CDC. Adults ages 19 years and older should talk with their physicians about what vaccines they might need, says Larry Pickering, M.D., senior adviser to the director of the CDC's National Center for Immunization and Respiratory Disease.

"Many young adults entering college are more susceptible to some infectious diseases because they live in dorms, which makes it easier for illness to

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*More than 30,000 adults die each year from  
vaccine-preventable diseases ...*



plications from chickenpox than young children," Pickering says. "People without a reliable history of having the disease or a vaccine should get two doses of varicella vaccine." Complications from chickenpox include swelling of the brain, pneumonia, and death.

New vaccine developments for adults include a recently licensed shingles vaccine, the availability of more flu vaccine, and the availability of a Tdap booster. If you have no idea of your vaccination record, your physician can help evaluate your vaccination status. In some cases, a blood test can indicate whether you have immunity to particular diseases, such as measles, mumps, and rubella.

**More flu vaccines available.** During an influenza vaccine shortage in the 2004–2005 flu season, the ACIP recommended that the vaccine be reserved for people in high-priority groups, including people ages 65 years and older. This year, it is estimated that 110 million to 115 million doses of flu vaccine will be available in the United States, which should be sufficient to meet the demand.

To further the availability of flu vaccine, the FDA recently licensed two more manufacturers to market flu vaccines in the United States. Fluarix, manufactured by a subsidiary of Glaxo-SmithKline (GSK) Biologicals, protects people ages 18 years and older against influenza types A and B. FluLaval, another vaccine manufactured by ID Biomedical, also a subsidiary of GSK, is for people ages 18 years and older. Both vaccines contain inactivated or killed virus, and were approved using the FDA's accelerated approval pathway, which allows the agency to approve products for serious or life-threatening diseases based on early evidence of a product's effectiveness.

Household contacts of children younger than 6 years of age, especially children younger than 6 months of age, should be vaccinated against the flu.

**Approval of a booster for tetanus, diphtheria, and whooping cough.** The FDA approved Adacel, for people ages 11 years to 64 years, in June 2005. In November 2005, the ACIP announced

its decision to recommend that adults ages 19 years to 64 years be vaccinated with the newly licensed adult Tdap booster vaccine. The ACIP recommended that adults receive a booster dose of Tdap if they haven't received a Td booster dose in five or more years. Every year, whooping cough affects about 600,000 U.S. adults ages 20 years to 64 years, and can result in weeks of coughing, cracked ribs from coughing spells, and pneumonia.

Tdap should also be given to adults who have close contact with infants younger than 12 months of age, ideally at least one month before beginning close contact. In infants, the disease can be more severe and even fatal. And Tdap should be given to health care professionals because there have been whooping cough outbreaks in hospitals.

**Approval of a vaccine for HPV.** The FDA has also approved Gardasil to help prevent HPV in adults. For additional details, see the information on HPV in the "For Adolescents" section of this article.

**Approval of a vaccine for meningococcal disease.** The FDA has licensed Menactra (MCV4) for people ages 11 years to 55 years. MCV4 is a meningococcal vaccine manufactured by Sanofi Pasteur of Swiftwater, Pa. For additional details on this vaccine and its use, refer to the "For Adolescents" section of this article.

**Approval of a vaccine for shingles (herpes zoster).** The FDA licensed Zostavax in May 2006 to reduce the risk of shingles in people ages 60 years and older. Shingles is 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 we age, the virus can reappear in the form of shingles. It's characterized by clusters of blisters that can cause severe pain that may last for weeks, months, or years.

Zostavax is a live virus vaccine that's given as a single injection under the skin, preferably in the upper arm. The most common side effects in people who received Zostavax were redness, pain and tenderness, swelling at the



Merck & Co. Inc.

**In May 2006, the FDA licensed Zostavax to reduce the risk of shingles in people ages 60 years and older.**

site of the injection, itching, and headaches.

Zostavax was studied in about 38,000 people in the United States ages 60 years and older. Researchers found that the vaccine, overall, reduced the occurrence of shingles by about 50 percent. For people ages 60 years to 69 years, it reduced occurrence by 64 percent. ■

#### **For More Information**

Vaccine information from the FDA's CBER

[www.fda.gov/cber/vaccines.htm](http://www.fda.gov/cber/vaccines.htm)

Vaccines for travelers

[www.cdc.gov/travel/vaccinat.htm](http://www.cdc.gov/travel/vaccinat.htm)

Complete schedule of recommended childhood vaccines

[www.cdc.gov/nip/recs/child-schedule.htm](http://www.cdc.gov/nip/recs/child-schedule.htm)

Complete schedule of recommended adult vaccines

[www.cdc.gov/nip/recs/adult-schedule.htm](http://www.cdc.gov/nip/recs/adult-schedule.htm)

National Immunization Program

[www.cdc.gov/nip](http://www.cdc.gov/nip)

Vaccine Adverse Event Reporting System

[www.vaers.hhs.gov/](http://www.vaers.hhs.gov/)



# Study:

## Half of People at High Risk Unaware They Need a Flu Shot

**M**any people at high risk of flu infection mistakenly believe they're in a low-risk group and, as a result, are much less likely to get a flu shot, according to a researcher from the University of North Carolina (UNC) at Chapel Hill School of Public Health.

A study, conducted during the flu vaccine shortage of 2004–2005, found that underestimating risk was common, particularly among people younger than 65 years old, says Noel T. Brewer, Ph.D., an assistant professor of health behavior and health education at UNC. Only 26 percent of younger adults at high risk were vaccinated that flu season, despite recommendations from the Centers for Disease Control and Prevention (CDC) urging high-risk groups to get a flu shot.

The results also indicate what messages will encourage those most likely to get the flu to be vaccinated, Brewer says. "We need to be clearer about who is in the high risk groups. If we can frame health messages around easily identifiable risk categories, then others—including family and friends of high risk individuals—can help per-

suade those at high risk to get their flu shot," says Brewer. "This simple message could very well save lives."

The study, funded by the CDC, appears in the Dec. 1, 2006, issue of *Clinical Infectious Diseases*.

Brewer notes that the 2004–2005 shortage apparently discouraged about 24 percent of high-risk people from being vaccinated. But the majority of study participants—73 percent—said the shortage did not affect their behavior.

The study, led by Brewer and William K. Hallman, Ph.D., professor of human ecology at Rutgers University, surveyed a random sample of 300 adults in September 2004 and March 2005. The researchers examined the number of people at high risk of getting the virus, as defined by the CDC, and assessed how many got vaccinations.

High-risk groups include older adults, ages 65 and older, and people from 18 years to 64 years old who had chronic health conditions. A third high-priority group comprised people who had regular contact with high-risk adults or children. Reasons for not getting vaccinated were also examined.

Of the 300 people surveyed, half who met the CDC's criteria for being top priority for vaccination said they believed their risk was low, and as a result they were not vaccinated. Also, though more than 60 percent of older people were vaccinated, according to Brewer, only 26 percent of younger adults at high risk and 36 percent of people who had regular contact with either of the other two groups were vaccinated.

"Underestimating one's risk was common, particularly among people under age 65," Brewer says. "Most older people understood their high risk, but two thirds of respondents in the other high risk categories mistakenly thought they were at low risk. Only a couple people overestimated their risk of infection."

The study also examined whether the news of a vaccine shortage during that flu season changed behaviors. Twenty-four percent said the shortage discouraged them from being vaccinated, while only 3 percent said the shortage encouraged them to get a flu shot. Nearly 3 out of 4 participants said the shortage had no effect on their behavior.

"This study helps us understand what messages will resonate with people, and encourage those most likely to get the flu to be vaccinated," Brewer says. About 36,000 people in the United States die each year from flu-related illnesses, so vaccinating the people who would be in the most danger if they got sick is a critical public health priority, he added. ■

### For More Information

<http://www.cdc.gov/flu/keyfacts.htm>

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*'We need to be clearer about who is in the high risk groups.'*



# HHS, FDA Announce New Tools for the Nutrition Facts Label

New learning tools are part of a commitment by HHS and the FDA to help reduce obesity and the number of overweight people in America.

The U.S. Department of Health and Human Services (HHS) and the Food and Drug Administration's Center for Food Safety and Applied Nutrition (CFSAN) have unveiled two new learning tools to help consumers use the Nutrition Facts label to choose nutritious foods and to achieve healthy weight management.

The tools are *Make Your Calories Count*, a Web-based learning program, and a new *Nutrition Facts Label* brochure.

"The risk of many diseases and health conditions may be reduced through preventive actions and a culture of wellness deters or diminishes debilitating and costly health events. Individual health care is built on a foundation of responsibility for personal wellness," said HHS Assistant Secretary for Health John Agwunobi, M.D., in announcing the nutrition aids. "We at HHS are pleased to introduce both the new Web-based program and the brochure, which contribute to the nutrition focus of the department's prevention priority."

The Web program is part of the FDA's response to the recommendations contained in a 2004 report issued by the agency's Obesity Working Group. The program is based on recommendations in the federal government's 2005 *Dietary Guidelines for Americans*. The *Dietary Guidelines* contain science-based advice designed to help Americans choose diets that meet nutrient requirements without exceeding calo-

rie needs, promote health, support active lives, and reduce the risk of chronic disease.

"This learning program provides a quick and simple way to educate consumers on how to use the nutrition facts label," said FDA Commissioner Andrew C. von Eschenbach, M.D. "By making it easier for consumers to understand the Nutrition Facts label, the FDA is helping them make quick and informed food choices that contribute to lifelong healthy eating habits."

*Make Your Calories Count* is an interactive online learning program that is also available in a downloadable format. It is designed to help consumers understand and use the Nutrition Facts label to plan a healthy diet while managing calorie intake.

The program guide features an animated character, called Labelman, who expertly leads the viewer through a series of exercises on the food label. The program includes exercises to help consumers explore the relationship between serving sizes and calories while they learn how to limit certain nutrients and get enough of others. For simplicity, the program presents two nutrients that should be limited—saturated fat and sodium—and fiber and calcium, two nutrients that should be consumed in adequate amounts.

Consumers can use the Nutrition Facts label to take control of their caloric intake and weight and to make



healthy food choices, if they know how. This program will show consumers how, in part, by explaining what serving sizes, percentages, and daily values mean and how to use them. The program is available for online use and in a downloadable format at [www.cfsan.fda.gov/labelman](http://www.cfsan.fda.gov/labelman). A new downloadable *Nutrition Facts Label* brochure for use by consumers is also available. The brochure can be used by health professionals to teach people how to make healthier food choices. The brochure includes information that will help consumers understand the relationship between calories and serving size, which may help them use the label to manage their intake of calories. Visit [www.cfsan.fda.gov/~dms/lab-gen.html](http://www.cfsan.fda.gov/~dms/lab-gen.html) to download. ■



# The FDA Takes Action Against Unapproved Drugs

By Michelle Meadows

**M**ost prescription drugs marketed in the United States have been reviewed and approved by the Food and Drug Administration as required by law. Thousands of unapproved prescription drugs, however, are still being prescribed and sold. The FDA, as part of its drug safety efforts, is bolstering its efforts against unapproved drugs in the United States.



An example of an unapproved prescription drug.

"Although we estimate that less than 2 percent of prescribed drugs are unapproved, we believe that some unapproved products raise safety concerns that warrant regulatory action," says Deborah Autor, director of the Office of Compliance in the FDA's Center for Drug Evaluation and Research (CDER).

There are several reasons why an unapproved drug may be available. One example is when only one company may have approval to market a drug, but other companies are illegally marketing their versions of the drug without having gone through the FDA's approval process. Another scenario is that a combination of ingredients is approved by the FDA, but a company is marketing a single ingredient without approval.

Some older products continue to be marketed illegally for historical reasons. "Many drugs were marketed before Congress made changes to the law requiring drugs to undergo FDA review," Autor says. There are unapproved drugs whose makers claim the drugs are "grandfathered" under older standards and therefore don't require approval under the current regulatory framework. "But the truly 'grandfathered' drugs represent only a few, at most, of all the unapproved drugs being marketed," Autor says. "Most unapproved drugs do require FDA approval."

Some drugs have been sold for so many years that physicians and pharmacists may not know they are unapproved. They even may be unaware that unapproved drugs are advertised in medical journals and listed in the

FDA



Physicians' Desk Reference (PDR) and other reference books. These practices give the false impression that the drugs were reviewed and approved by the FDA.

"Consumers who discover that they are taking an unapproved drug shouldn't stop treatment without talking to their doctor first," Autor says. The FDA advises consumers and health professionals to carefully consider the medical condition being treated, the patient's previous response to the drug, and the availability of approved alternatives as part of discussing the benefits and risks of any unapproved treatment.

The major categories in which unapproved drugs exist include certain cough and cold preparations with antihistamines, some narcotics, and some types of sedatives. Examples include

- unapproved prescription cough and cold preparations with antihistamines, such as Pheniramine maleate and Dexbrompheniramine maleate
- unapproved prescription single-ingredient narcotics such as Codeine phosphate and Oxycodone HCL 5mg
- unapproved prescription sedatives such as Phenobarbital and Chloral hydrate.

### Enforcement

In June 2006, the FDA issued a guidance called Marketed Unapproved Drugs—Compliance Policy Guide, which describes plans for enforcement in this area.

"The FDA is telling manufacturers to either obtain approval for an unapproved drug or remove it from the market," Autor says. "Even if the drug has been marketed for many years with no known safety problems, companies will still need to comply. The absence of evidence of a safety problem does not mean a product is truly safe."

A patient or physician may believe a drug is safe based on individual experience, but the FDA relies on carefully designed clinical trials that weigh the risks and benefits of taking a drug compared with taking a placebo or another accepted therapy. FDA approval means not only that the product has been reviewed for safety and effectiveness, but that the agency has reviewed man-

## Injunction of Dental Products Manufacturer

In October 2006, the FDA announced the entry of a consent decree of permanent injunction barring C.R. Canfield Co. Inc. and Gary R. Pearsons, Canfield's owner and president, from manufacturing and distributing unapproved drugs and drugs that do not satisfy current Good Manufacturing Practice (cGMP) requirements.

The products include D.S. Dressing (20% Eugenol), D.S. Mini-Dressing (20% Eugenol), D.S. Syringe (20% Eugenol), and D.S. Ointment (20% Eugenol). Canfield promoted these products for the treatment of "dry socket," a condition in which the socket does not heal properly after the extraction of a tooth. The products were available nationwide through dental practices.

Despite repeated FDA inspections and warnings, Canfield has not corrected its cGMP violations. These include releasing products for distribution without proper testing and failing to conduct studies to determine appropriate product expiration dates. The FDA is advising dental professionals and consumers to stop using and discard any product from this manufacturer. Consumers who have used this firm's products and have concerns or questions should contact their dental practitioner. ■

ufacturing quality and product labeling to ensure that it adequately conveys the drug's risks and benefits. FDA approval also means that a drug's safety and effectiveness is still monitored after marketing.

Before pursuing regulatory action against unapproved drugs, the FDA plans to consider the effects on the public health, including whether the product is medically necessary. The agency recognizes that some unapproved therapies offer benefits. An example is Phenobarbital, a drug used to control seizures. In some cases, FDA action requiring drug approvals will be gradual to avoid shortages of medically necessary products.

The guidance explains that the FDA will continue to focus enforcement actions on unapproved drugs that carry potential safety risks, lack evidence of effectiveness, and constitute health fraud. For example, the FDA has ordered all manufacturers of unapproved carbinoxamine-containing products to stop making them because of safety concerns regarding their use in children younger than 2 years. Carbinoxamine is a sedating antihistamine. Manufacturers will need to obtain FDA approval to continue marketing these products.

The FDA has received 21 reports of death associated with carbinoxamine-

containing drugs in children younger than 2 years. While it is not clear that the carbinoxamine caused these deaths, the FDA is concerned about the risks. Some of the unapproved products are being promoted for infants and young children, an age group in which carbinoxamine has never been studied. And young children are more susceptible to drug-related adverse events.

Some of these unapproved products are labeled for treatment of cough and cold symptoms, an indication for which carbinoxamine has not been found safe by the FDA. The two carbinoxamine-containing products approved by the FDA are indicated for treating allergic reactions or their symptoms, and are manufactured by Atlanta-based Mikart Inc. The products contain carbinoxamine maleate as the active ingredient without any additional active ingredients.

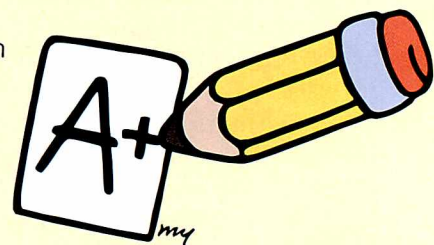
Visit [www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) to find out whether a drug may be unapproved. If the drug is not listed there, contact your drug's manufacturer and ask whether the drug is approved. ■



# Take the FDA Consumer Quiz

How many U.S. adults die each year from vaccine-preventable diseases? What is an adjuvant treatment for cancer? Roughly what percentage of prescribed drugs is unapproved? What is a bacteriophage? 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 January–February 2007 issue of FDA Consumer (and at the bottom of this page).

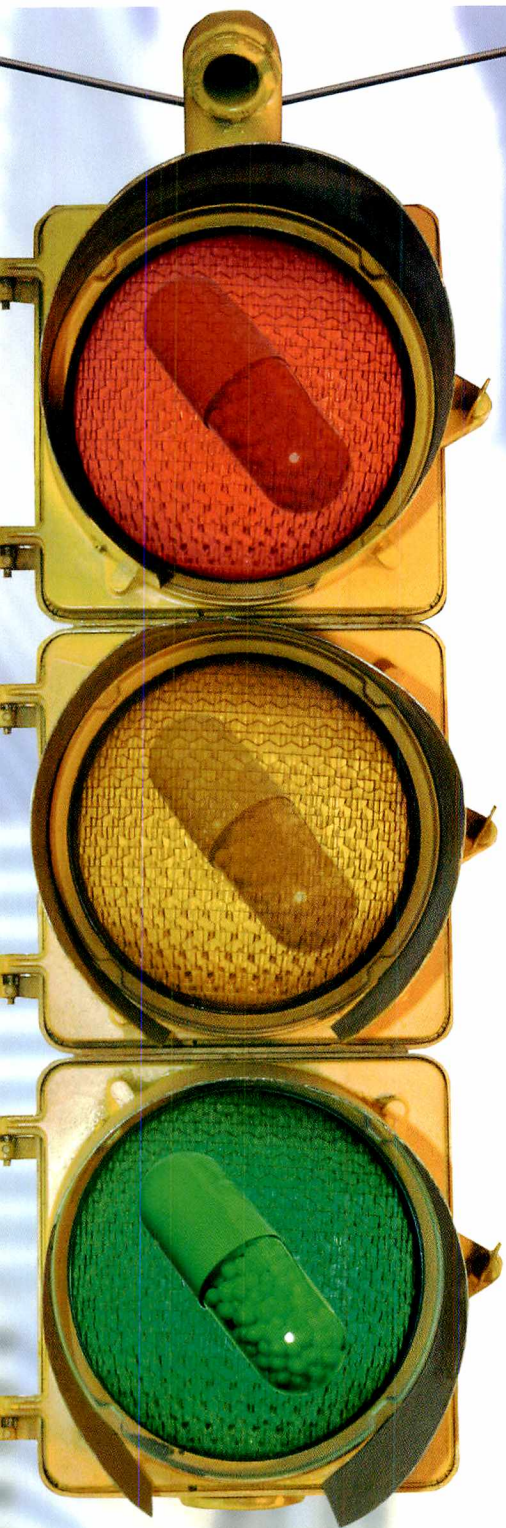


1. **During clinical trials of cancer drugs, a new drug is usually compared to what?**
  - a. an inactive substance (placebo)
  - b. a placebo and at least one other drug
  - c. a drug or a combination of drugs that are commonly accepted and used to treat the same type of cancer
  - d. every other drug approved to treat the same type of cancer
2. **What is adjuvant treatment for cancer?**
  - a. therapy given in place of chemotherapy
  - b. therapy given in place of radiation
  - c. therapy given in place of surgery to remove a tumor
  - d. "talk therapy" in a support group to help people cope with cancer
  - e. therapy given after the main treatment to lower the chance of a cancer returning
3. **When we speak of an FDA-approved cancer drug, what does "safe" mean?**
  - a. There are no serious side effects at least 75 percent of the time it's used.
  - b. The benefits of the drug outweigh the risks for its intended use in the population the drug is intended to treat.
  - c. There is no possible risk of death when taking the drug.
  - d. More than 50 percent of patients in clinical trials said they were willing to take the drug despite its risks.
  - e. When taken properly, the drug causes only mild side effects.
4. **What is a bacteriophage?**
  - a. the stage of growth when a bacterium is non-infective
  - b. a killer bacterium
  - c. a mixture of bacteria used in cancer treatments
  - d. any virus that infects bacteria
  - e. any bacterium that infects viruses
5. **How many adults die each year from vaccine-preventable diseases?**
  - a. 5,000
  - b. 12,000
  - c. 22,000
  - d. more than 30,000
6. **To market a new food additive, a manufacturer must:**
  - a. petition the FDA for its approval
  - b. submit safety information on the additive to the FDA concurrent with marketing the ingredient
  - c. submit an application to the FDA similar to that used in the drug approval process
  - d. report the new ingredient to the FDA before marketing it
  - e. ensure the safety of the ingredient in its own tests, but no information is required to be submitted to the FDA
7. **Which of the following vaccines was recently licensed by the FDA and includes adolescents in the target population?**
  - a. RotaTeq to protect against rotavirus
  - b. Zostavax to protect against shingles
  - c. Gardasil to protect against the human papillomavirus
  - d. MMR vaccine to protect against measles, mumps, and rubella
8. **Roughly what percentage of prescribed drugs is unapproved?**
  - a. less than 2 percent
  - b. 10 percent
  - c. 20 percent
  - d. more than 40 percent
9. **Which of the following statements about unapproved drugs is false?**
  - a. Most unapproved drugs require FDA approval.
  - b. A few unapproved drugs were "grandfathered" under older standards.
  - c. An unapproved drug with no known safety problems isn't required to undergo FDA review.
  - d. Some unapproved drugs are advertised in medical journals.

## Answers:

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





# STOP

**Stop and remember that all medicines have risks**

# LEARN

**Learn how to use your medicine to increase the benefits**

# GO

**Go to**  
**[www.fda.gov/usemedicinesafely](http://www.fda.gov/usemedicinesafely)**

The consumer education materials on our website can help you work with your health professionals to:

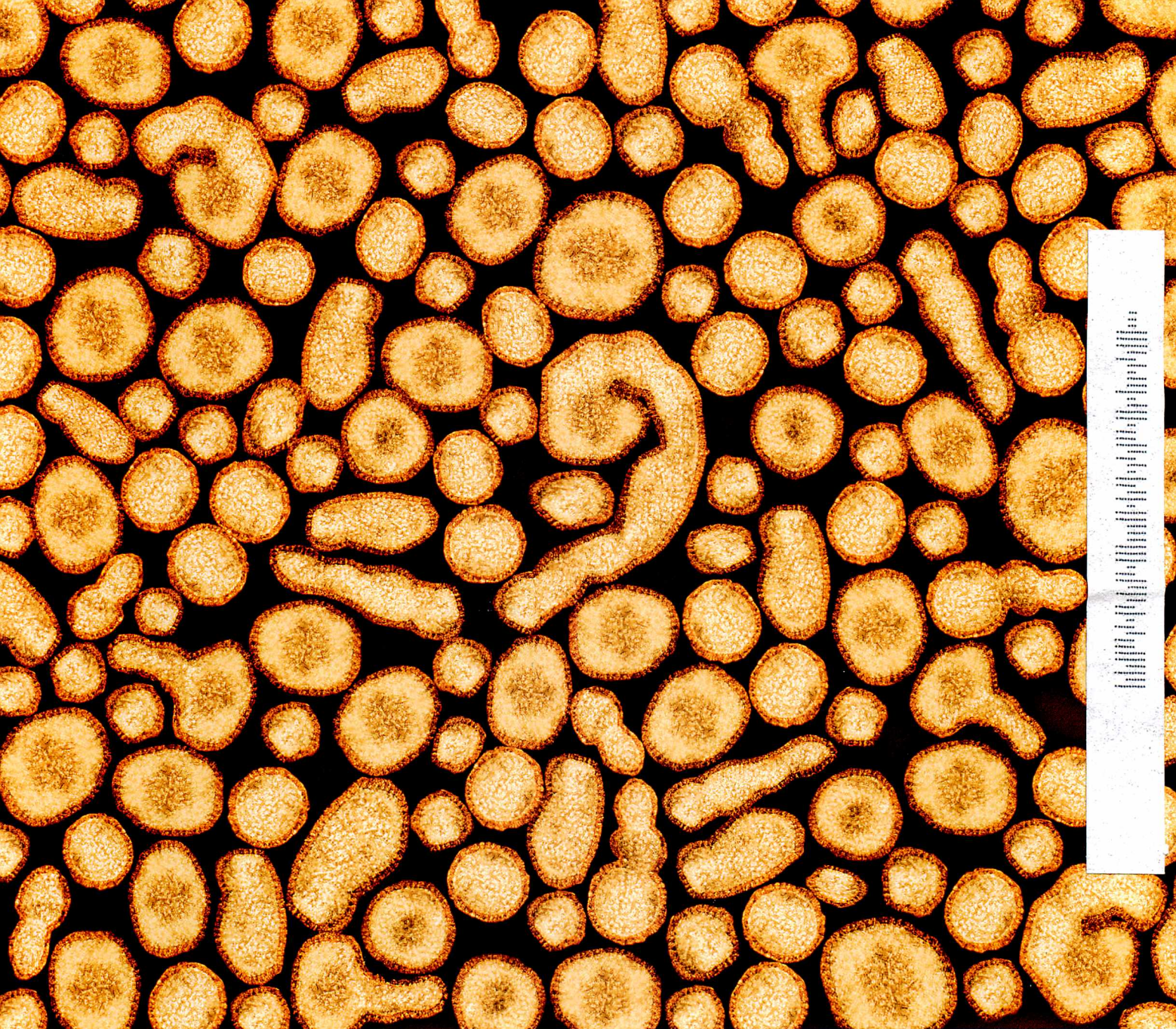
- choose medicine that's best for you
- **buy medicine from sources you can trust**
- use medicine in ways that increase its safety and effectiveness



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Dennis Kunkel/Phototake

A photograph taken through a microscope of type A influenza virus. According to the Centers for Disease Control and Prevention, the vaccine for the 2006–2007 influenza season is composed mostly of this type virus.

## DEPARTMENT OF HEALTH & HUMAN SERVICES

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