



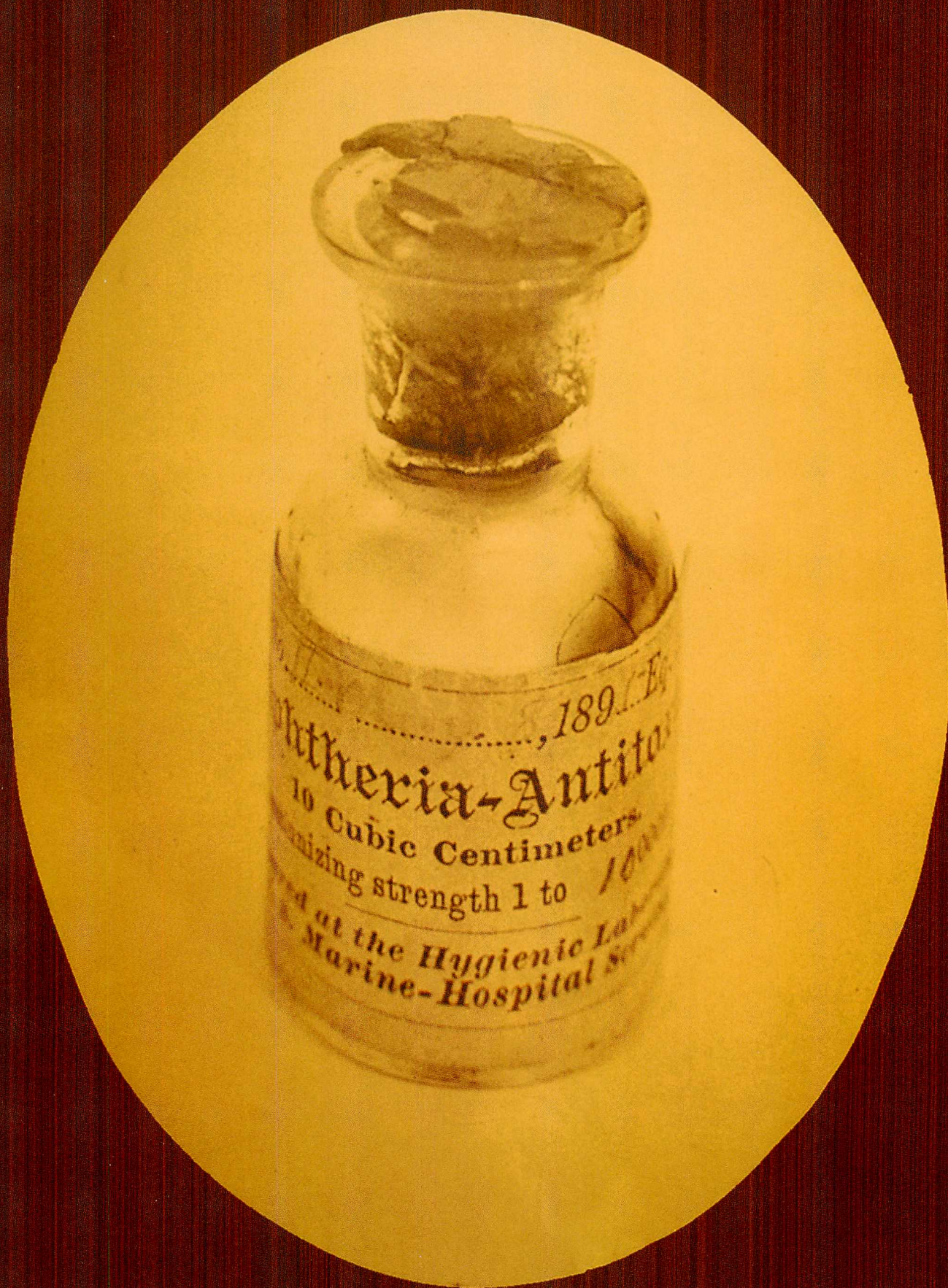
FDA *Consumer*

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

July–August 2002 • Vol. 36 No. 4

Battle of the Bugs: Fighting Antibiotic Resistance

Streptococcus pneumoniae



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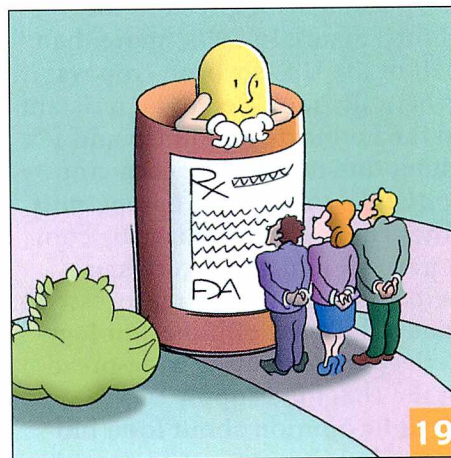
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◀ Inside Front Cover Photo:

This 1895 bottle of diphtheria antitoxin is being preserved at the National Museum of American History. It was produced by the Hygienic Laboratory, later the National Institutes of Health. For more on the history of biologics regulation, see page 8.

OBSERVATIONS



July 1, 2002 marks the 100th anniversary of the passage of the 1902 Biologics Control Act, which gave the federal government authority to regulate biological products and ensure their safety for the American public.

The act not only serves as the underpinning for the FDA's regulation of biological products today, but also marked a historic turning point in the way America protects the health of its citizens.

The FDA's Center for Biologics Evaluation and Research is responsible for the regulation of "biologics," medical products such as vaccines, blood and blood derivatives, allergic patch tests, HIV and hepatitis

tests, gene therapy products, cells and tissues for transplantation, and some treatments for cancers. For more on the FDA's oversight of biologics and its role in the development and review of the first vaccines against infectious diseases such as polio, see our story titled "100 Years of Biologics Regulation" on page 8.

Antibiotic resistance has been called one of the world's most pressing public health problems. Today, virtually all important bacterial infections in the United States and throughout the world are becoming resistant to antibiotics, also called antimicrobial drugs. Antibiotic resistance can occur when bacteria change in a way that reduces or eliminates the effectiveness of drugs designed to cure or prevent infections. The bacteria that survive continue to multiply, causing more harm. Our cover story titled "Battle of the Bugs: Fighting Antibiotic Resistance," on page 28, will help you learn how to use antibiotics wisely.

Botox Cosmetic injections are all the rage among aging baby boomers and others eager to erase the wrinkles of their furrowed brows. You've probably seen or read news stories touting the popular, paralyzing alternative to some plastic surgeries. Find out the latest in our article titled "Botox Cosmetic: A Look at Looking Good," on page 11.

We also unravel the twists and turns of the FDA's thorough drug review process, complete with a two-page centerfold that illustrates the main steps involved with developing a new drug. See "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective" on page 19.

And are you wearing the right shades this summer? We tell you what you need to know about protecting your eyes from the sun's rays; see page 27.

Raymond Formanek Jr.
Editor

TO THE EDITOR

Biotechnology and Foods

My concerns involve the use of biotechnology in agriculture. Biotechnology used in our food supply has become widespread in the United States. In 1999, more than half of the U.S. soybean crop was genetically modified to be resistant to the herbicide Round Up and about one-third of the corn crop contained the *Bacillus thuringiensis* (Bt) gene to resist damage by corn borers. Food manufacturers use corn and soy in many reprocessed foods; thus, use of biotechnology-derived ingredients is widespread in the U.S. food supply.

Public opinion about food biotechnology has not yet coalesced because the adoption of the technology has moved faster than the public's ability to fully understand the process and its implications.

The FDA reported that most participants in consumer focus groups assembled in March 2000 expressed great surprise that food biotechnology has become so pervasive in the U.S. food supply. The typical participant reaction was outrage that such a change could happen without them knowing about it.

I would like the public to be informed about what they are eating and be able to read labels to have a choice whether they want to buy biotech foods. As it stands, we are unaware whether our food is tainted or pure.

Back in the 1950s, DDT was deemed to be safe and we, as babies, ingested many products sprayed with this pesticide. Do we have to take more risks again? How is biotechnology going to affect our ecological balance with nature?

Please respond with your position on this very controversial subject.

Heidi Naud, Ph.D., R.D.
Mason, Ohio

A reply from the FDA's Center for Food Safety and Applied Nutrition:

The FDA does not require special labeling for foods to indicate whether or not a food or food ingredient is a bioengineered product, just as it does not require labeling to indicate which breeding technique was used in developing a food plant. Rather, any significant differences in the food itself have to be disclosed in labeling. The agency's 1992 policy statement on bioengineered foods asserts that labeling requirements that apply to foods in general also apply to foods produced using biotechnol-

TO THE EDITOR

ogy. However, if genetic modifications materially change the composition of a food product, these changes must be reflected in the food's labeling. For example, if a bioengineered food is significantly different from its traditional counterpart such that the common or usual name no longer adequately describes the new food, the name must be changed to describe the difference. Also, the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that the label of the food must reveal all "material facts" about the food. This means that the label must make clear any other differences between a bioengineered food and its conventional counterpart, including any significant differences in nutritional properties, the presence of an allergen that consumers would not expect in the food, or any other issues that would affect how the food is used or the consequences of its use.

Historically, the agency has interpreted the requirement for labels to reveal "material facts" to mean information about the attributes of the food itself, not how it was produced. The FDA has required special labeling when the absence of such information may: 1) pose special health risks, such as a warning statement on protein products used in very low calorie diets; 2) mislead the consumer in light of other statements made on the label, such as the requirement for quantitative nutrient information when certain nutrient content claims are made about a product; or 3) in cases where a consumer may assume that a food, because of its similarity to another food, has the same nutritional content, looks and smells the same, or has functional characteristics of the food it resembles when in fact it does not (for example, stating that reduced fat margarine is not suitable for frying).

The FDA has received comments suggesting that foods developed through modern biotechnology should bear a label informing consumers that the food was produced using bioengineering. While we have given careful consideration to these comments, we do not have data or other information that would lead us to conclude that bioengineered foods are materially different from conventional foods as defined by the FD&C Act. Hence, we believe that we have neither a scientific nor a legal basis to require disclosure in the labeling. Food processors can voluntarily label either the presence or absence of bioengineered food in food products. The FDA announced the availability of draft guidance for this voluntary labeling in the *Federal Register* of January 18, 2001.

The FDA is confident that the bioengineered plant foods on the U.S. market today are as safe as their conventionally bred counterparts. This conclusion was echoed by a report published in 2000 by the National Resource Council of the National Academy of Sciences that stated, "The committee is not aware of any evidence that foods on the market are unsafe to eat as a

result of genetic modification."

Since the FDA's 1994 evaluation of the Flavr Savr tomato, the first genetically engineered plant food to reach the U.S. market, the FDA has reviewed the data on more than 50 other products, ranging from herbicide-resistant soybeans to a canola plant with modified oil content.

Although the FDA believes that it has been consulted regarding the safety of the bioengineered foods currently in the U.S. food supply, it has proposed that manufacturers be required to consult with the agency about new bioengineered foods before they are marketed. This will further assure that all such products are known to the FDA and that we have had input regarding any need for special labeling or a premarket safety review.

Find more information on the FDA's Web site at www.cfsan.fda.gov/~lrd/biotechm.html.

Regarding concerns for the ecological consequences of bioengineered crop plants: All such plants are required to be field tested by the U.S. Department of Agriculture (USDA), and the USDA is required to consider the environmental impact of permitting the use of new crop plants. ■

UPDATES

New Use Approved for Vioxx



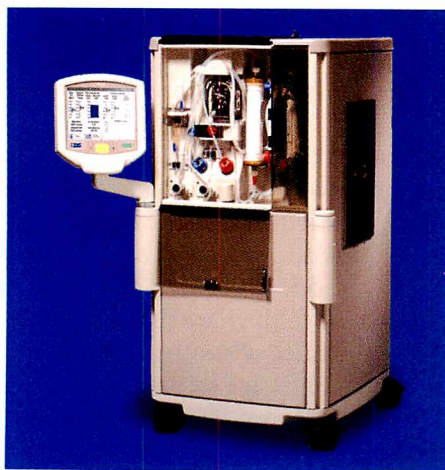
The FDA has approved the use of Vioxx (rofecoxib) for rheumatoid arthritis. Vioxx previously had been approved for osteoarthritis and pain.

The agency also approved new label text and

precautions that are based on the results of a one-year study. The study demonstrated that Vioxx was associated with a lower incidence of serious upper gastrointestinal (GI) adverse events, including major bleeding, perforation, and obstruction. However, the study also found that Vioxx was associated with a higher rate of heart attacks and other adverse cardiovascular events, compared with other medications approved for the same uses.

Home Dialysis System

The FDA has cleared the first dialysis system that is specifically designed for home use by people with chronic or



Courtesy: Aksys Ltd.

acute kidney disease. The Personal Hemodialysis (PHD) System, made by Aksys Ltd., Lincolnshire, Ill., automates the dialysis process, allowing people with kidney failure to perform daily dialysis at home or in a clinic. In either setting, the system requires a prescription from a physician and training for the user.

Hemodialysis works by circulating blood through special filters to remove waste from the body, much like a fully functioning kidney does. The PHD System includes equipment that purifies water, prepares a chemical solution to help remove toxins, pumps blood, and delivers the dialysis solution. A computer-like touch screen prompts the operator through each step of the procedure. Between treatments, the system automatically cleans and disinfects the fluid pathways.

The PHD System is designed to be used five or six days per week, in shorter dialysis sessions than the conventional dialysis regimen of three days per week. In clinical tests, the PHD System was found to be similar to conventional hemodialysis equipment in effectiveness, accuracy, and safety.

FDA Approves Restricted Marketing of Lotronex

The FDA has approved the marketing of Lotronex (alosetron hydrochloride) with restrictions, nearly two years after its manufacturer removed it from the market. Lotronex is the only medication proven effective in treating the symptoms of irritable bowel syndrome (IBS).

GlaxoSmithKline (GSK) of Research Triangle Park, N.C., voluntarily withdrew Lotronex in November 2000 after the FDA received reports of serious and life-threatening intestinal complications, including severe constipation and ischemic colitis. These conditions resulted in hospitalization, blood transfusions, surgery, and even death.

Lotronex slows the movement of stools through the bowels. It does not cure IBS and it will not help every person who takes it. For those with IBS who are helped, Lotronex reduces lower abdominal pain and discomfort, urgency to have a bowel movement, and diarrhea.

The FDA recognizes the need to carefully balance making effective therapies available with protecting the public from drug-related adverse events. As a result, the agency worked together with GSK to develop a Risk Management Plan (RMP) that allows market reintroduction of Lotronex, but only with limited access to women suffering with severe diarrhea-predominant IBS that is disabling.

This restricted marketing program ensures not only that patients and physicians are fully informed of the risks and benefits of Lotronex prior to using it, but also that only appropriate patients are prescribed the drug. The program enrolls only qualified physicians who agree to accept certain responsibilities.

The RMP brings together active participation by the doctor, the patient

and the pharmacist. It includes the following components:

- GSK will establish a prescribing program for Lotronex to enroll physicians who plan to prescribe the drug.
- GSK will enroll physicians who agree to educate patients on the risks and benefits of Lotronex treatment, and to provide patients a copy of the FDA-approved Medication Guide.
- Patients will be asked to read and sign a Patient-Physician Agreement before receiving their initial prescription for Lotronex.
- Pharmacists will be asked to fill only prescriptions that display a prescribing program sticker affixed by an enrolled physician, and to give patients a copy of the FDA-approved Medication Guide every time they dispense the drug.
- Enrolled physicians will have agreed to report serious adverse events to GSK or to the FDA.
- GSK will conduct an ongoing assessment of the RMP, including a study of the prescribing and actual use of Lotronex.

The June 7 action follows an April 23, 2002, recommendation by the FDA's Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee.

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

Additional information on Lotronex, including the revised professional and patient labels and physician and patient agreement documents, can be found on the FDA's Web site at www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm.

Blood Transfusions May Cause Lung Damage

The FDA has issued a health alert warning that people who receive blood products, particularly plasma-containing products, may be at risk for developing transfusion-related acute lung injury (TRALI). This serious pulmonary syndrome may lead to death if not recognized and treated appropriately.

TRALI can occur when white blood cell antibodies in the donor's blood react with the recipient's white blood cells, causing a change in the lung tissue that allows fluid to enter. Most donors implicated in TRALI reactions are women with more than two children or donors who have had multiple transfusions. If not treated immediately and appropriately, TRALI may cause respiratory or breathing problems that can lead to death.

The FDA's Center for Biologics Evaluation and Research (CBER) has received reports of more than 45 TRALI-related deaths since the early 1990s. The condition is a leading cause of transfusion-related death.

Symptoms of TRALI include fever, shortness of breath, and a drop in blood pressure. X-rays often show the recipient's lungs as completely white. Symptoms typically begin one to two hours after a transfusion, but may be delayed up to six hours. Health-care professionals should be alert that any respiratory distress or breathing problems during or following a blood transfusion could be caused by TRALI.

Deaths from TRALI must be reported to CBER according to FDA regulations.

The FDA encourages voluntary reporting of non-fatal TRALI reactions. Reports can be filed via the FDA's MedWatch reporting program, by phone at 1-800-FDA-1088; by fax at 1-800-FDA-0178; by e-mail at www.fda.gov/medwatch/how.htm; or by mail at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852.

Firm Signs Consent Decree Prohibiting Ephedrine Products

Biogenics Inc. of St. George, Utah, has signed a consent decree that prohibits the firm from manufacturing and distributing its ephedrine-containing AMP II Pro Drops, any other product containing ephedrine hydrochloride, any synthetic ephedrine alkaloid, or any new drug not approved by the FDA. The consent decree was signed on April 12, 2002.

The decree also gives the FDA authority to order the firm, doing business as E'OLA International, to recall and discontinue the marketing of any products that violate the law in the future.

On October 30, 2001, at the request of the FDA, U.S. Marshals

seized \$2.8 million worth of E'OLA's AMP II Pro Drops. Previous FDA inspections found that the products contain a drug, ephedrine hydrochloride, but are labeled as a dietary supplement for use in weight loss. These E'OLA products violate the law because drug ingredients are prohibited for use in dietary supplements.

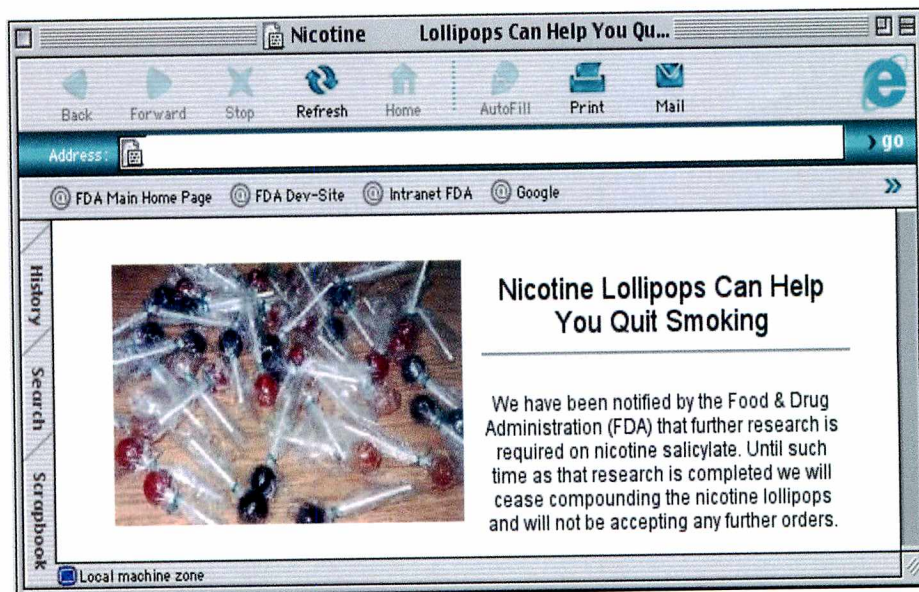
Ephedrine hydrochloride has been approved as a drug by the FDA since 1948, and therefore cannot be legally marketed as a dietary supplement. E'OLA also marketed its products as a treatment for obesity. Products marketed to treat diseases are drugs. In addition, the labeling failed to bear adequate directions for its intended use.

FDA Warns Sellers of Nicotine Lollipops, Lip Balm

Three pharmacies that sold nicotine lollipops and lip balm over the Internet have agreed to quit making and marketing the products after being warned by the FDA that they are illegal. Based on statements from the pharmacies' Internet sites, the prod-

ucts were promoted as aids to stop smoking or to treat nicotine addiction.

The FDA is concerned about the health risk of these products because they appear to be custom-made (compounded) and dispensed without a doctor's prescription, and they contain a form of nicotine that is not



used in FDA-approved smoking cessation products. In addition, their candy-like characteristics present a risk of accidental use by children.

In April, the FDA issued warning letters to the pharmacies, informing them that their nicotine lollipops and lip balm were illegal. The letters also stated that continued marketing of these drug products may result in further regulatory action, potentially including a seizure or injunction.

The products cited in the letters included compounds using nicotine salicylate, natural sweeteners, and flavorings in a sugar-free base and were available in four different dosages. The claims on the Web sites included that the products helped alleviate the "hand-to-mouth fixation" associated with smoking and were a "convenient, tasty way" to replace the cigarette habit. After investigating and carefully assessing these Web sites, the FDA determined that the pharmacies' nicotine lollipops and nicotine lip balm were intended for use as "drugs" and appeared to be il-

legal for the following reasons:

- They are compounded and dispensed without a doctor's prescription.
- They are unapproved new drugs, which need, but do not have, FDA approval.
- They are made from a drug substance, nicotine salicylate, which is not permitted for use by pharmacists in compounding drugs. The FDA-approved smoking cessation products are made from different forms of nicotine.
- They are misbranded because their labeling does not have adequate directions for the uses for which they are being offered and does not have adequate warnings against use by children.

Within the 15 days required for a response, all three pharmacies notified the FDA in writing that they had stopped making or distributing the products in question. The FDA continues to monitor Web sites for products that may endanger public health.

New Treatment for Advanced Breast Cancer



In April 2002, the FDA approved Faslodex (fulvestrant) for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women whose dis-

ease progresses following anti-estrogen therapy.

In this type of breast cancer, estrogen can stimulate the growth of tumors by entering cells at multiple sites called estrogen receptors. Faslodex inhibits this action of estrogen and appears to reduce the number of estrogen receptors in breast cancer cells.

Faslodex was found to be as effective as the drug anastrozole in two randomized, controlled clinical trials in postmenopausal women with locally advanced or metastatic breast cancer that progressed following treatment with tamoxifen. Anastrozole is another drug used to decrease estrogen production and suppress the growth of tumors that need estrogen to grow. Faslodex is administered as a monthly injection into the buttocks.

The most commonly reported side effects were nausea, headache, back pain, vomiting, constipation, diarrhea, abdominal pain, hot flushes, and pharyngitis (inflammation of the throat), regardless of whether patients were treated with Faslodex injections or anastrozole tablets. Pain at the site of the injection was reported in about 10 percent of patients treated with Faslodex.

Faslodex is indicated for postmenopausal women and should not be given to pregnant women because of the risk of harm to a fetus.

Faslodex is distributed in the United States by AstraZeneca Pharmaceuticals LP, Wilmington, Del.

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

To contact *FDA Consumer*:

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

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

New Type of Defibrillator

A new type of implantable cardioverter defibrillator (ICD) that also has the ability to deliver cardiac resynchronization therapy (CRT) was recently approved by the FDA. The device, called Contak CD CRT-D, can be used to treat symptoms of advanced heart failure in certain people who already need an ICD.

The Contak system is intended to treat people who already need an implantable defibrillator, whose heart timing is off and who, despite taking heart failure medication, have symptoms of advanced heart failure, such as fatigue, shortness of breath, and difficulty performing daily activities.

The defibrillator component of the product detects and treats life-threatening heart rhythms. The CRT component coordinates the beating of the left and right ventricles of the heart so that they work together more effectively to pump blood throughout the body.

The FDA based its approval on the results of two multicenter clinical studies conducted in the United States by the device's manufacturer, Guidant Corp. of Indianapolis. In the first study, 581 people received the Contak system; in the second study, 127 people received it. In half the people, only the defibrillator component was turned on; in the other half, both the defibrillator and the CRT components were turned on. Both groups were studied for six months.

The studies showed that the Contak system is safe and that it effectively coordinates the beating of the heart's ventricles, resulting in an improvement in some of the symptoms of heart failure. People in whom both components were turned on had a better quality of life and improved exercise capacity than those in whom just the defibrillator was turned on. The studies did not show whether or not the device ultimately affected patient survival.

The FDA is requiring Guidant to conduct a postmarketing study of 1,000 people over three years to determine the product's safety and effectiveness.

First Synthetic Secretin

The FDA has approved SecreFlo (secretin) for injection to help confirm the diagnosis of pancreatic dysfunction and the presence of a pancreatic tumor (gastrinoma) that may be cancerous. SecreFlo is a synthetic formulation of the naturally occurring porcine hormone secretin.

Patients with pancreatic dysfunction are unable to digest food properly. Thick mucus obstructs the pancreas and prevents essential enzymes from breaking down food. Left untreated, this condition can cause patients to become severely malnourished and dehydrated.

SecreFlo helps confirm the diagnosis of pancreatic dysfunction by stimulating the pancreas to secrete pancreatic juice and bicarbonate, which is used to measure the functioning of the pancreas. SecreFlo helps confirm the presence of a pancreatic tumor by stimulating the stomach to release a hormone called gastrin, which is further tested to confirm the diagnosis.

ChiRhoClin, Inc. of Silver Spring, Md., is the sponsor of SecreFlo. The product is manufactured by Chesapeake Biological Laboratories of Baltimore for RepliGen Corporation of Needham, Mass. ■

RESEARCH NOTEBOOK

First Vaccine for Cat AIDS Approved for Veterinary Use

The U.S. Department of Agriculture (USDA) has approved the first vaccine for feline immunodeficiency virus (FIV) for commercial production and veterinary use.

The patented vaccine for this disease, which is a cat form of AIDS, has been licensed for manufacture by Fort Dodge Animal Health of Overland Park, Kan., a division of Wyeth. Patents for the vaccine are held by the University of California and the University of Florida.

The vaccine, approved in March, should soon be available to veterinarians. "This vaccine offers the first effective protection for cats against this often fatal disease," says Niels Pedersen, D.V.M., Ph.D., director of the Center for Companion Animal Health at the University of California, Davis and an international authority on retroviruses and immunologic disorders of small animals. "The success of the FIV vaccine also offers hope that eventually a vaccine will be developed

that will effectively protect against AIDS in humans."

Pedersen and immunologist Janet K. Yamamoto, Ph.D., now a professor in the University of Florida's College of Veterinary Medicine, first isolated FIV in cats at UC Davis in 1986. Yamamoto has worked with researchers at Fort Dodge Animal Health for more than a decade to develop the vaccine.

FIV is transmitted from cat to cat mainly through bite wounds because the virus is present at high levels in the saliva. Like human AIDS, the virus attacks the body's immune system, making the animal susceptible to diseases and infections that usually would have little effect on an FIV-free animal.

Cats infected with FIV may remain healthy for five to 10 years before symptoms such as diarrhea, weight loss, fever, swollen lymph nodes and chronic infections appear. Although infected cats may recover from their initial illness, they become lifelong carriers of the virus. ■

100 Years of Biologics Regulation



Photos courtesy of the National Library of Medicine

Bacteriologists Ida A. Bengston (1881-1952), left, and Alice Evans (1881-1975) were the first women employed on the scientific staff of the Hygienic Laboratory, predecessor to the National Institutes of Health. Ida Bengston was particularly noted for her studies of bacterial toxins, especially the discovery of the organism *Clostridium botulinum*, which caused a paralytic disease in chickens. Alice Evans identified undulant fever as a human form of abortive fever in cattle and traced its transmission to contaminated milk. This hastened the spread of the pasteurization movement in the United States.

Around the turn of the last century, diphtheria patients were routinely treated with antitoxin derived from the blood of horses. There were no central or uniform controls in place and the antitoxin was often manufactured in local plants. In St. Louis, that combination had tragic consequences. Thirteen children died of tetanus in 1901 after being treated with diphtheria antitoxin made from

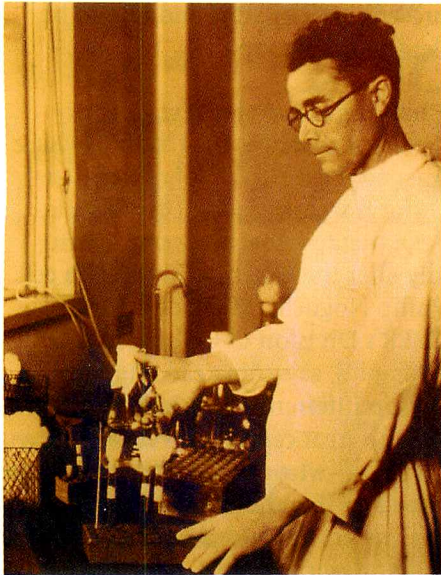
the blood of a tetanus-infected milk wagon horse named Jim.

Soon after this and a similar tragedy in Camden, N.J., involving deaths and injuries related to a tainted biological product, Congress enacted the Biologics Control Act. July 1, 2002, marks the 100th anniversary of the law, which gives the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) authority to regulate biological products

and ensure their safety.

Biologics are medical products derived from living sources. They include vaccines, blood and blood derivatives, allergenic patch tests and extracts, tests to detect HIV and hepatitis, gene therapy products, cells and tissues for transplantation, and new treatments for cancers, arthritis, and other serious diseases.

Here are some key research contributions in biologics over the last century.



Polio Vaccine

In the early 1900s, Americans were frightened of polio for good reason. Polio is a highly contagious disease that paralyzes or kills its victims, and children are especially vulnerable.

In 1908, Austrian biomedical researcher Karl Landsteiner determined that polio is caused by a virus rather than bacteria. Eight years later, thousands of New York City residents fled their homes to avoid a polio epidemic that hit the area in 1916.

Ruth Kirschstein, M.D., deputy director at the National Institutes of Health, remembers living with her parents near a park when she was 10 years old and the country was in the midst of another polio epidemic in 1936.

"They would take me to the park every day in the summer and sit down and say, 'don't talk to anybody, don't go near anybody, don't do anything because you might get polio.' That was the thing people were most scared about—having their children

end up in iron lungs. We've gotten rid of that, and it's just absolutely marvelous."

During the early 1950s, researcher Jonas Salk developed a killed virus polio vaccine. Salk tried the vaccine on volunteers, as well as himself, his wife and children. All those who received the vaccine developed antibodies to polio and no one got sick. In 1954, nationwide testing of Salk's vaccine began with mass inoculations of school children. A million children participated in the tests, making it the largest clinical test of a drug or vaccine in medical history. The Salk vaccine was found to be safe and effective. However, the tests came to a halt after more than 200 cases of polio caused by the vaccine suddenly occurred. It was determined that two batches of the vaccine produced by Cutter Labs contained live poliovirus and were responsible for the outbreak. Eleven people died as a result.

In 1955, the U.S. Surgeon General recommended that all polio vaccinations be suspended until a thorough inspection of each manufacturing facility and review of the procedure for testing vaccine safety had been completed. Manufacturing resumed after stricter standards were adopted, and more than 4 million doses of the Salk vaccine were distributed by August of that year.

In the late 1950's, Albert Sabin theorized that a weakened, live-virus polio vaccine would provide longer-lasting immunity. The Sabin vaccine, which was inexpensive and administered orally, became the primary weapon for polio prevention in the United States by the end of the 1960s. Ironically, because the vaccine contains weakened live forms of the virus that can mutate, some people develop polio after taking this vaccine.

Now, with polio on the brink of eradication throughout the world, the Salk inactivated vaccine is the only product recommended for routine childhood vaccination in the United States.

Measles Vaccine

In 1964, a global epidemic of



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Botox 'Parties'

The recent rise in the popularity of Botox has much to do with the manner in which it is frequently marketed. Some practitioners buy the toxin in bulk and arrange get-togethers for people receiving their treatments. As in business, volume discounts can be found in medicine.

Plastic surgery events known as Botox parties—also seminars, evenings and socials—are a key element of Botox marketing in much of the United States. The gatherings are thought to be a convenient means of providing Botox treatments more economically, and may help reduce the anxiety that normally goes along with getting an injection. Doctors are finding that treating people

in groups allows them to make the procedure more affordable to their patients.

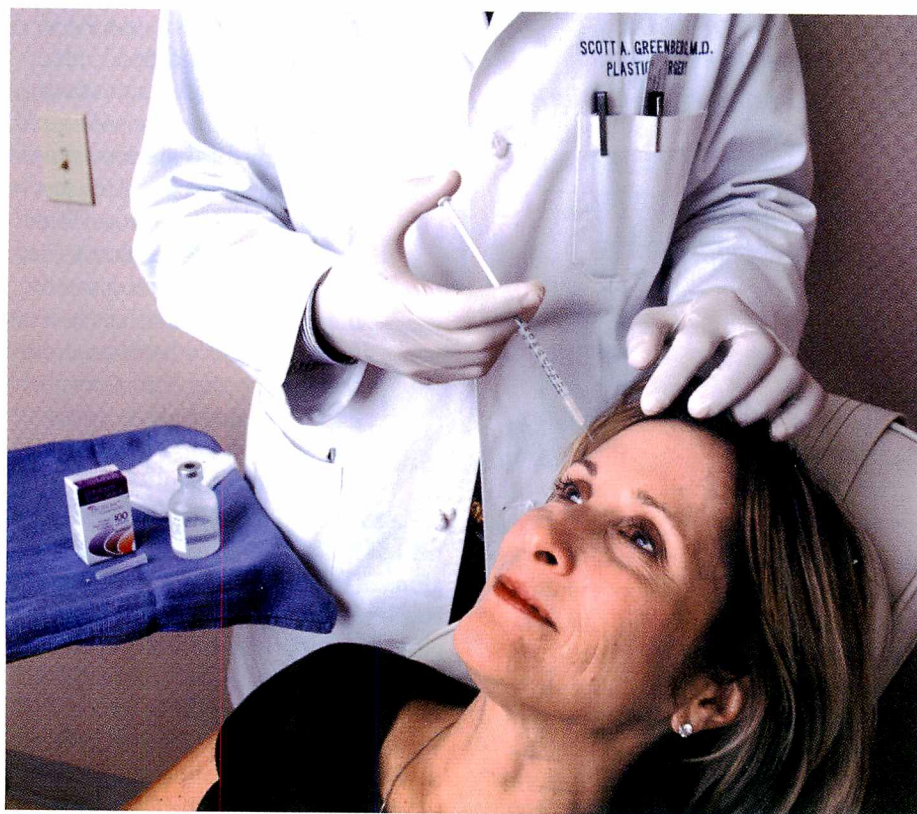
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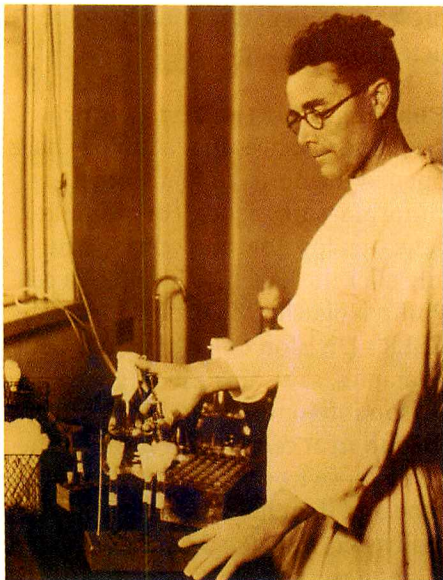


Black Star/Todd Anderson



Courtesy: Scott Greenberg, M.D.

Scott Greenberg, M.D., of Winter Park, Fla., injects Botox Cosmetic into the forehead muscles of Mary Schwallenberg, of Orlando, Fla. Top right shows Schwallenberg's forehead before treatment. The effects of Botox Cosmetic can be seen on bottom right.



Testing vaccines and serums for purity and potency. The National Institutes of Health played a leading role in the development and regulation of biologic products from 1903, when the 1902 Biologics Control Act became effective, until the transfer of these regulatory functions to the FDA in 1972.

Polio Vaccine

In the early 1900s, Americans were frightened of polio for good reason. Polio is a highly contagious disease that paralyzes or kills its victims, and children are especially vulnerable.

In 1908, Austrian biomedical researcher Karl Landsteiner determined that polio is caused by a virus rather than bacteria. Eight years later, thousands of New York City residents fled their homes to avoid a polio epidemic that hit the area in 1916.

Ruth Kirschstein, M.D., deputy director at the National Institutes of Health, remembers living with her parents near a park when she was 10 years old and the country was in the midst of another polio epidemic in 1936.

"They would take me to the park every day in the summer and sit down and say, 'don't talk to anybody, don't go near anybody, don't do anything because you might get polio.' That was the thing people were most scared about—having their children

end up in iron lungs. We've gotten rid of that, and it's just absolutely marvelous."

During the early 1950s, researcher Jonas Salk developed a killed virus polio vaccine. Salk tried the vaccine on volunteers, as well as himself, his wife and children. All those who received the vaccine developed antibodies to polio and no one got sick. In 1954, nationwide testing of Salk's vaccine began with mass inoculations of school children. A million children participated in the tests, making it the largest clinical test of a drug or vaccine in medical history. The Salk vaccine was found to be safe and effective. However, the tests came to a halt after more than 200 cases of polio caused by the vaccine suddenly occurred. It was determined that two batches of the vaccine produced by Cutter Labs contained live poliovirus and were responsible for the outbreak. Eleven people died as a result.

In 1955, the U.S. Surgeon General recommended that all polio vaccinations be suspended until a thorough inspection of each manufacturing facility and review of the procedure for testing vaccine safety had been completed. Manufacturing resumed after stricter standards were adopted, and more than 4 million doses of the Salk vaccine were distributed by August of that year.

In the late 1950's, Albert Sabin theorized that a weakened, live-virus polio vaccine would provide longer-lasting immunity. The Sabin vaccine, which was inexpensive and administered orally, became the primary weapon for polio prevention in the United States by the end of the 1960s. Ironically, because the vaccine contains weakened live forms of the virus that can mutate, some people develop polio after taking this vaccine.

Now, with polio on the brink of eradication throughout the world, the Salk inactivated vaccine is the only product recommended for routine childhood vaccination in the United States.

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rubella, also known as German measles, spread to the United States. About 12.5 million cases were reported that year, and 20,000 infants were born with birth defects as a result.

In 1966, former CBER directors Paul D. Parkman, M.D., and Harry M. Meyer, Jr., M.D., reported that they had developed the first effective experimental vaccine for rubella. The researchers prepared a weakened, live vaccine for human testing and inoculated 34 children. None of the children developed rubella, nor did they transmit the disease to their unvaccinated playmates. By 1988, only 225 cases of rubella were reported in the United States.

Pertussis Vaccine

Whooping cough (pertussis) vaccine had been available since 1915, but results from its use were not entirely satisfactory. There were many concerns regarding the potency of the vaccine. A CBER researcher named Dr. Margaret Pittman helped improve the vaccine in 1944. By 1949, manufacturers were able to sell whooping cough vaccine approved on potency as well as on safety and sterility.

CBER licensed the vaccine that is in use today on July 31, 1996. It is the first acellular pertussis vaccine for use in infants and children two months of age and older for the primary series of immunizations. This new vaccine contains only the parts of the pertussis bacterium thought to be important for immunity. So it protects infants against whooping cough while causing fewer side effects than the whole-cell pertussis vaccines that were previously on the market.

Blood and Plasma Products

From the 1950s through the 1970s, evidence indicated that the blood obtained from commercial blood banks carried a greater risk of hepatitis transmission. This led to more careful testing, and to increased regulation of blood to further protect the blood supply.

According to John Finlayson, Ph.D., associate director for science in CBER's Office of Blood Research and Review, "Hepatitis loomed very large.

Most of us talked about serum hepatitis and that it was a very large threat post-transfusion," says Finlayson.

"We had no tests for hepatitis A, no tests for hepatitis B, and of course, hepatitis C had not even been discovered. So that was a very big challenge, and there was also the challenge that there could be post-transfusion bacterial infections."

During World War II, there were two major concerns—providing clean blood and preserving blood plasma. But when soldiers were transfused, they had no guarantee of receiving clean blood because none of the tests used today were available.

Furthermore, because plasma was pooled for preservation, one infected donor could contaminate an entire batch. In response, an American chemist named Dr. Edwin Joseph Cohn led a team that devised a method called fractionation. This separated the individual proteins out of plasma. The resulting protein products, known as plasma derivatives, can be given in response to specific medical needs and with a high degree of confidence that they are safe.

AIDS and the Blood Supply

Safeguards over the years for blood donor screening and blood collection, processing, and testing led to increased confidence and perhaps a relative degree of complacency in the United States concerning safety of the blood supply. Thus, the scientific and health-care community, as well as government agencies and the public, were not prepared when AIDS emerged with full fury in the 1980s.

Blood transfusions became suspect, and improved screening tests for donated blood were necessary to protect the American people. CBER researchers and the blood and medical product industries responded to the challenge. The first test kit to detect HIV, the virus that causes AIDS, in donated blood was licensed in 1985. Inspections of blood banks were increased to ensure compliance with strict screening and processing procedures. Now, highly sensitive and specific nucleic acid-based tests allow the

presence of hepatitis and HIV to be detected more rapidly.

Challenges for the 21st Century

Recent advances in technology have opened the doors to many other exciting areas in science. For example, gene therapy now allows us to actually alter the genetic makeup of a cell. Philip Noguchi, M.D., director of CBER's Division of Cellular and Gene Therapies, says, "Instead of giving a person interferon—which is a protein used to treat certain cancers and other diseases—why not give the person the gene and then his own body will actually start to make the protein, and might never have to replace it again? That's one of the very intriguing theories of gene therapy."

Xenotransplantation, the transplantation of animal cells, tissues or organs into a human, offers new hope for an added source of organs. New vaccines are being developed and modified as new discoveries teach us more about the human immune system. And the genomics revolution has scarcely begun. The study of gene structures is leading to potentially effective treatments for a variety of serious diseases, including cancer, diabetes, and heart disease.

"New biological products such as vaccines and therapeutics have already improved the health of the public," says Kathryn Zoon, Ph.D., director of CBER. "The blood supply has never been safer. And, as we move through the 21st century, our strong leadership in science-based regulation, coordinated research, and the use of partnerships will continue to assure that safe and effective new biological products reach the public." ■

This article was adapted from the CBER publication "Commemorating 100 Years of Biologics Regulation." To view the document, visit CBER's Web site at www.fda.gov/cber/inside/centennial.htm.

In memory of Harry M. Meyer, Jr., M.D., director of the FDA's Bureau of Biologics, 1972-1987. Dr. Meyer and Paul D. Parkman, M.D., developed the first licensed rubella virus vaccine.

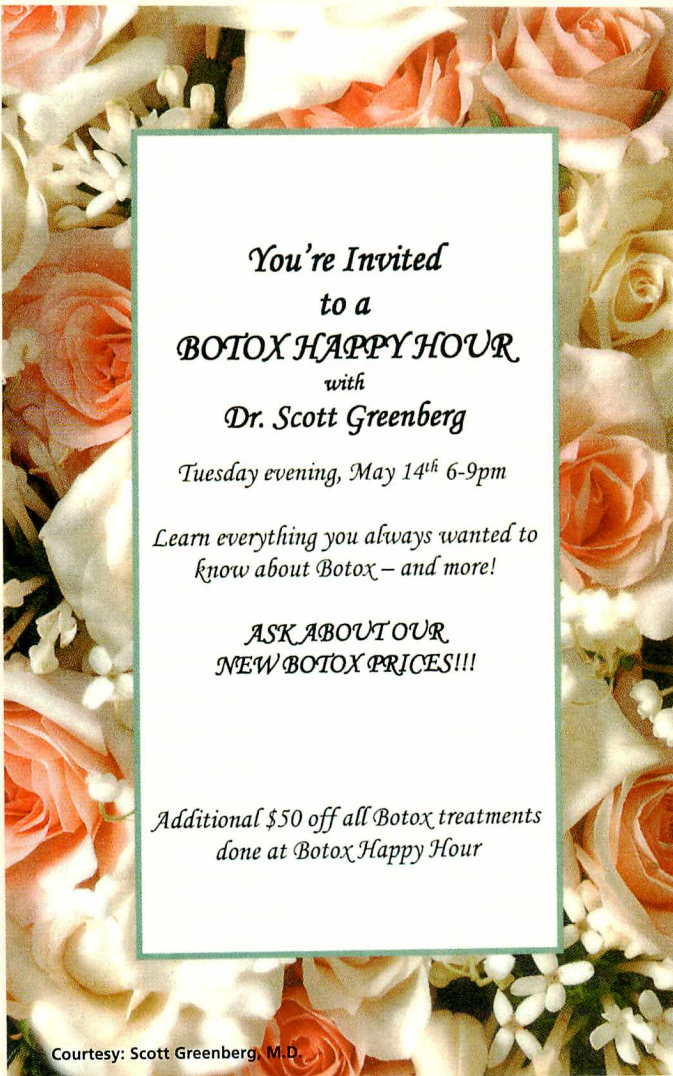
Botox Cosmetic: A Look at Looking Good

By Carol Lewis

The promise of a more youthful look was too tempting for 53-year-old Mary Schwallenberg to pass up. So, when the Food and Drug Administration approved a product that temporarily improves the appearance of frown lines between the eyebrows, the Orlando, Fla., resident took a shot at it. And it wasn't long before she became one of many people clamoring for regular treatments that often include refreshments and friendly conversation, as well as injections.

Botulinum Toxin Type A (Botox Cosmetic) is a protein complex produced by the bacterium *Clostridium botulinum*, which contains the same toxin that causes food poisoning. When used in a medical setting as an injectable form of sterile, purified botulinum toxin, small doses block the release of a chemical called acetylcholine by nerve cells that signal muscle contraction. By selectively interfering with the underlying muscles' ability to contract, existing frown lines are smoothed out and, in most cases, are nearly invisible in a week.

Botox injections are the fastest-growing cosmetic procedure in the industry, according to the American Society for Aesthetic Plastic Surgery (ASAPS). In 2001, more than 1.6 million people received injections, an increase of 46 percent over the previous year. More popular than breast enhancement surgery and a potential blockbuster, Botox is regarded by some as the ultimate fountain of youth.



You're Invited
to a
BOTOX HAPPY HOUR
with
Dr. Scott Greenberg
Tuesday evening, May 14th 6-9pm
Learn everything you always wanted to
know about Botox – and more!
ASK ABOUT OUR
NEW BOTOX PRICES!!!
Additional \$50 off all Botox treatments
done at Botox Happy Hour

Courtesy: Scott Greenberg, M.D.

Schwallenberg, a pharmaceutical sales representative who is excited about her next round of injections, says she wants to look her best for her job. "That's corporate America for you," she says. "I have a lot of energy and I just wanted to look good."

Botox was first approved in 1989 to treat two eye muscle disorders—uncontrollable blinking (blepharospasm) and misaligned eyes (strabismus). In 2000, the toxin was approved to treat a neurological movement disorder that causes

severe neck and shoulder contractions, known as cervical dystonia. As an unusual side effect of the eye disorder treatment, doctors observed that Botox softened the vertical frown (glabellar) lines between the eyebrows that tend to make people look tired, angry or displeased. But until this improvement was actually demonstrated in clinical studies, Allergan Inc., of Irvine, Calif., was prohibited from making this claim for the product.

By April 2002, the FDA was satisfied by its review of studies indicating that Botox reduced the severity of frown lines for up to 120 days. The agency then granted approval to use the drug for this condition.

The FDA regulates products, but not how they are used. Approved products are sometimes used by a licensed practitioner for uses other than those stated in the product label. Botox Cosmetic, for example, is currently being used by physicians to treat facial wrinkles other than those specified by the FDA. Consumers should be aware, however, that this "off-label" use has not been independently reviewed by

the agency, and the safety and effectiveness of Botox injections into other regions of the face and neck, alone or in combination with the frown-lines region, have not been clinically evaluated.

Ella L. Toombs, M.D., a dermatologic medical officer in the FDA's Office of Cosmetics and Colors, says, "Careful deliberation, investigation and evaluation is undertaken by the agency before any prescription product is approved." Drugs such as Botox, which are not indicated for serious or life-threatening

conditions, "are subject to a greater level of scrutiny because of the benefit-to-risk ratio." Toombs says this means that the FDA may allow someone to incur a greater risk from products that treat medical conditions, rather than from those that are approved for cosmetic purposes.

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The recent rise in the popularity of Botox has much to do with the manner in which it is frequently marketed. Some practitioners buy the toxin in bulk and arrange get-togethers for people receiving their treatments. As in business, volume discounts can be found in medicine.

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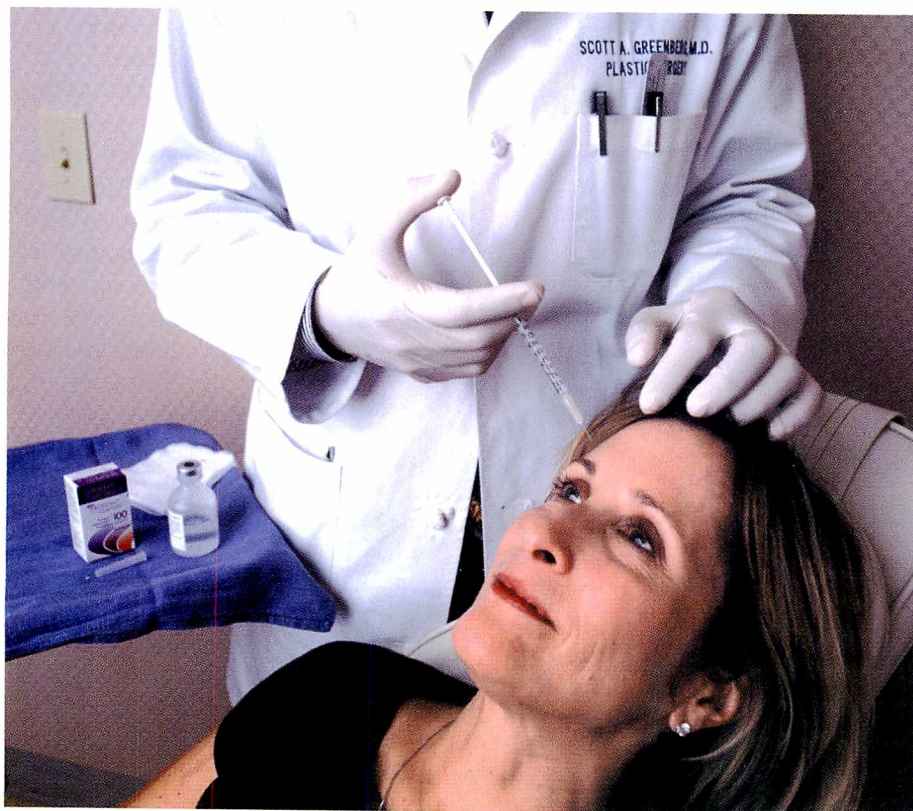
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Black Star/Todd Anderson



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Scott Greenberg, M.D., of Winter Park, Fla., injects Botox Cosmetic into the forehead muscles of Mary Schwallenberg, of Orlando, Fla. Top right shows Schwallenberg's forehead before treatment. The effects of Botox Cosmetic can be seen on bottom right.

tients as possible trivializes a medical treatment, which could deteriorate over time into a nonprofessional environment." DiSpaltro says there's more to medicine "than just dispensing drugs."

Schwallenberg, however, insists that "Dr. Greenberg was very professional. It wasn't a cattle call," she says. "And I don't think I'd go to a doctor I didn't know."

The FDA is concerned that Botox has the potential for being abused. The ASAPS recently reported that unqualified people are dispensing Botox in salons, gyms, hotel rooms, home-based offices, and other retail venues. In such cases, people run the risks of improper technique, inappropriate dosages, and unsanitary conditions. "Botox is a prescription drug that should be administered by a qualified physician in an appropriate medical setting," says Toombs.

Greenberg agrees. "Patient safety has to be of prime concern," he says. "People need to be in the right hands when complications arise." That's why Greenberg does not allow his staff to

administer Botox treatments. Even the most skilled health-care providers, he says, can have complications as well as dissatisfied customers.

Although there is no chance of contracting botulism from Botox injections, there are some risks associated with the procedure. If too much toxin is injected, for example, or if it is injected into the wrong facial area, a person can end up with droopy eyelid muscles (ptosis) that could last for weeks. This particular complication was observed in clinical trials.

Other common side effects following injection were headache, respiratory infection, flu syndrome, and nausea. Less frequent adverse reactions included pain in the face, redness at the injection site, and muscle weakness. These reactions were generally temporary, but could last several months.

While the effects of Botox Cosmetic don't last, still, people don't seem to mind repeating the procedure every four to six months in order to maintain a wrinkle-free look. Battling the signs of aging in a non-invasive way, after all,

is part of the allure of the product—that and the fact that there are no unsightly scars, and that there is very little recovery time with the procedure.

The FDA recommends that Botox Cosmetic be injected no more frequently than once every three months, and that the lowest effective dose should be used. ■

For More Information:

American Academy of Dermatology
P.O. Box 4014
Schaumburg, IL 60168-4014
1-888-462-3376
www.aad.org

American Society for Dermatologic Surgery
5550 Meadowbrook Drive, Suite 120
Rolling Meadows, IL 60008
1-800-441-2737
www.aboutskinsurgery.com

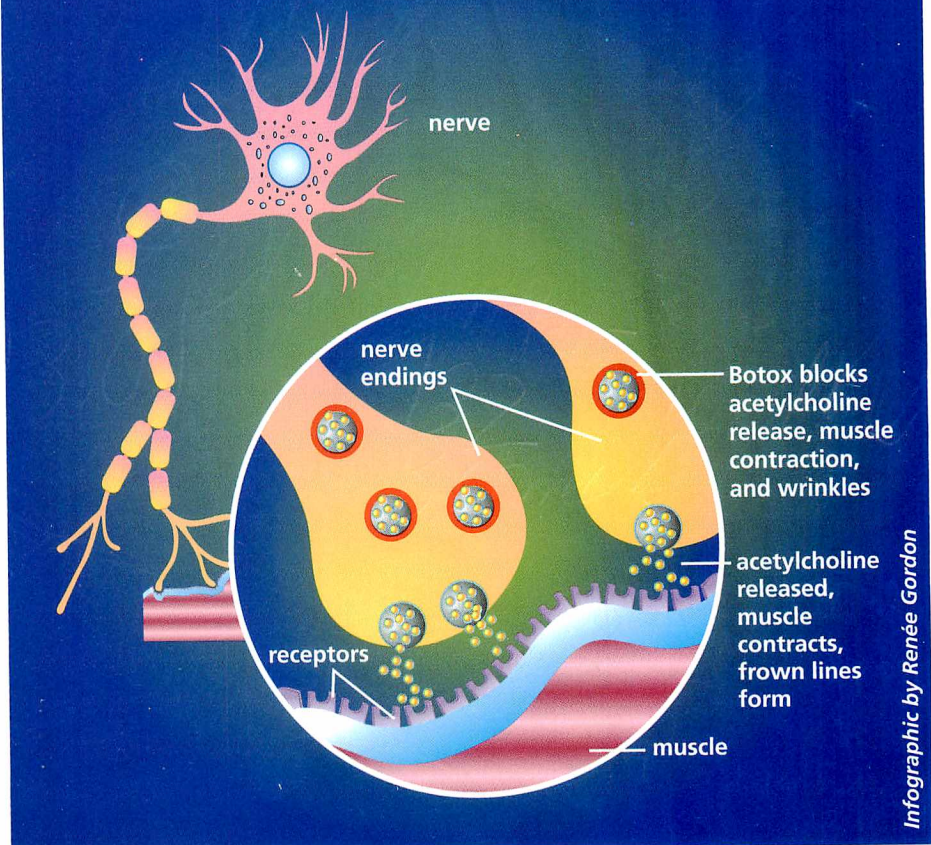
American Society for Aesthetic Plastic Surgery
11081 Winners Circle
Los Alamitos, CA 90720
1-888-272-7711
www.asaps.org

Considering Botox Cosmetic?

- Be sure that a qualified doctor performs the procedure.
- Make sure that the doctor is trained and qualified in cosmetic skin surgery of the face.
- Ask questions and be informed about the benefits and risks involved in the procedure.
- Avoid alcohol and remain upright for several hours following the procedure.
- Choose a medical setting using sterile techniques. Necessary equipment should be available to respond to any potential problems.


Source: The American Society for Dermatologic Surgery

How Botox Works



Bottled Water: Better Than the Tap?

By Anne Christiansen Bullers



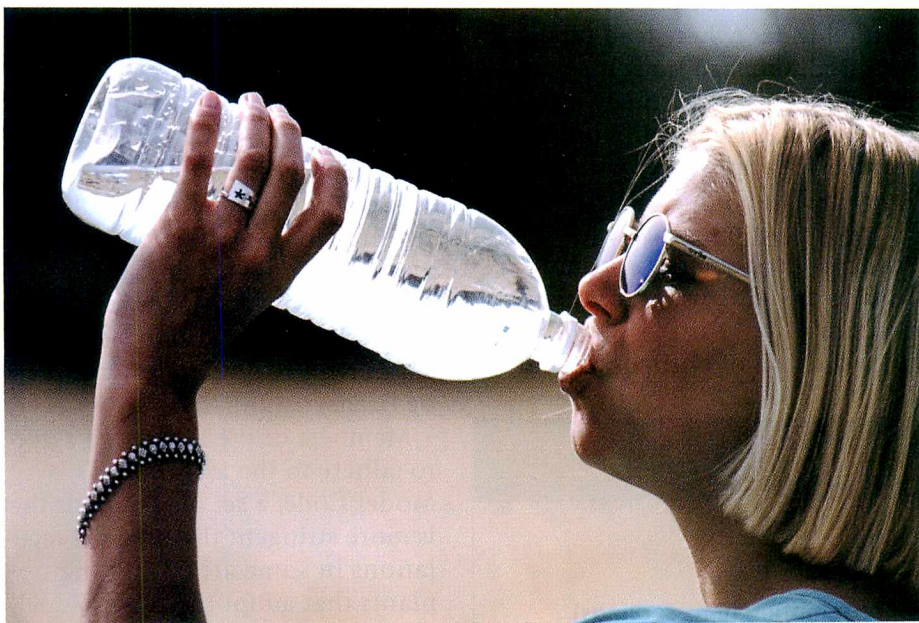
It's a rare day that Kelly Harrison, a mother of five from Tulsa, Okla., doesn't find herself chauffeuring kids to some kind of sports practice or school activity. As she checks to see that each child is seat-belted into the family's minivan, Harrison also makes sure they've got the essentials: the right sports equipment, the right clothes, and what she considers to be the right drink—bottled water.

When she was growing up, Harrison, 34, might have grabbed a soft drink or juice on her way out the door. But for her kids, Harrison insists on what she thinks is a healthier choice—water. She says her children's young bodies need water as they play in the Oklahoma sun. Bottled water also contains no caffeine, no calories and no sugar. Plus, bottled water comes in convenient bottles, easy to tote from home to wherever the busy family goes.

"I really think this is best for a lot of different reasons," says Harrison, who often tucks a bottle for herself into the basket in her minivan that contains other on-the-go mom necessities, such as a paperback book and her cell phone.

Once, most Americans got their water only from the tap. Now, like Harrison, they're often buying their water in a bottle. At work, after a workout, or just about any time, Americans are drinking bottled water in record numbers—a whopping 5 billion gallons in 2001, according to the International Bottled Water Association (IBWA), an industry trade group. That's about the same amount of water that falls from the American Falls at Niagara Falls in two hours.

At work, after a workout, or just about any time, Americans are drinking bottled water in record numbers—a whopping 5 billion gallons in 2001.



Explosive growth in the industry for more than a decade has placed bottled water in nearly every supermarket, convenience store and vending machine from coast to coast, where dozens of brands compete for consumers' dollars. In four years, industry experts anticipate that bottled water will be second only to soda pop as America's beverage of choice.

Water, of course, is essential to human health. Drinking enough water to replace whatever is lost through bodily functions is important. But surveys indicate that most of us might not be drinking enough. Is bottled water part of the answer? To decide, consumers need to arm themselves with knowledge about what they're buying before they grab the next bottle of Dasani, Evian or Perrier off the shelf. "It really pays to do your homework," says Stew Thornley, a water quality health educator with the Minnesota Department of Health.

Different Varieties

Bottled water may seem like a relatively new idea—one born during the heightened awareness of fitness and potential water pollution during the last two or three decades. However, water has been bottled and sold far from its source for thousands of years. In Europe, water from mineral springs was often thought to have curative and sometimes religious powers. Pioneers trekking west across the United States during the 19th century also typically considered drinkable (potable) water a staple to be purchased in anticipation of the long trip across the arid West.

Today, of course, there are dozens of brands of bottled water and many different kinds, including flavored or fizzy, to choose from.

Federal Regulations

The Food and Drug Administration regulates bottled water prod-

ucts that are in interstate commerce under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Under the FD&C Act, manufacturers are responsible for producing safe, wholesome and truthfully labeled food products, including bottled water products. It is a violation of the law to introduce into interstate commerce adulterated or misbranded products that violate the various provisions of the FD&C Act.

The FDA also has established regulations specifically for bottled water, including standard of identity regulations, which define different types of bottled water, and standard of quality regulations, which set maximum levels of contaminants (chemical, physical, microbial and radiological) allowed in bottled water.

From a regulatory standpoint, the FDA describes bottled water as water that is intended for human consumption and that is sealed in bottles or other containers with no added ingredients, except that it may contain a safe and suitable antimicrobial agent. Fluoride may also be added within the limits set by the FDA.

High Standards

Is the extra expense of bottled water worth it? One thing consumers can depend on is that the FDA sets regulations specifically for bottled water to ensure that the bottled water they buy is safe, according to Henry Kim, Ph.D., a supervisory chemist at the FDA's Center for Food Safety and Applied Nutrition, Office of Plant and Dairy Foods and Beverages. Kim,

whose office oversees the agency's regulatory program for bottled water, says that major changes have been made since 1974, when the Safe Drinking Water Act (SDWA) first gave regulatory oversight of public drinking water (tap water) to the U.S. Environmental Protection Agency (EPA). Each time the EPA establishes a standard for a chemical or microbial contaminant, the FDA either adopts it for bottled water or makes a finding that the standard is not necessary for bottled water in order to protect the public health.

"Generally, over the years, the FDA has adopted EPA standards for tap water as standards for bottled water," Kim says. As a result, standards for contaminants in tap water and bottled water are very similar.

However, in some instances, stan-

dards for bottled water are different than for tap water. Kim cites lead as an example. Because lead can leach from pipes as water travels from water utilities to home faucets, the EPA set an action level of 15 parts per billion (ppb) in tap water. This means that when lead levels are above 15 ppb in tap water that reaches home faucets, water utilities must treat the water to reduce the lead levels to below 15 ppb. In bottled water, where lead pipes are not used, the lead limit is set at 5 ppb. Based on FDA survey information, bottlers can readily produce bottled water products with lead levels below 5 ppb. This action was consistent with the FDA's goal of reducing consumers' exposure to lead in drinking water to the extent practicable.

Production of bottled water also

must follow the current good manufacturing practices (CGMP) regulations set up and enforced by the FDA. Water must be sampled, analyzed and found to be safe and sanitary. These regulations also require proper plant and equipment design, bottling procedures and recordkeeping.

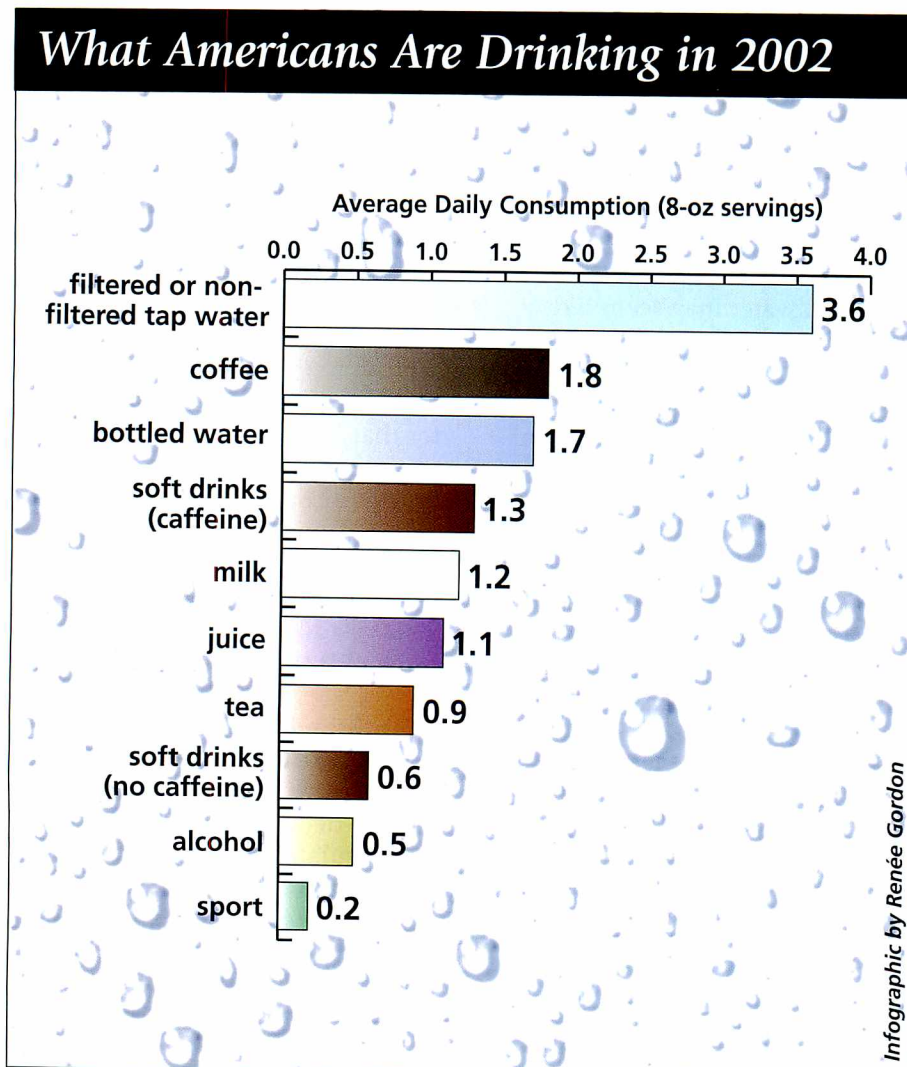
The FDA also oversees inspections of the bottling plants. Kim says, "Because the FDA's experience over the years has shown that bottled water poses no significant public health risk, we consider bottled water not to be a high risk food." Nevertheless, the FDA inspects bottled water plants under its general food safety program and also contracts with the states to perform some bottled water plant inspections. In addition, some states require bottled water firms to be licensed annually.

Members of the IBWA also agree to adhere to the association's Model Code, a set of standards that is more stringent than federal regulations in some areas. Bottling plants that adopt the IBWA Model Code agree to one unannounced annual inspection by an independent firm.

The FDA also classifies some bottled water according to its origin.

- **Artesian well water.** Water from a well that taps an aquifer—layers of porous rock, sand and earth that contain water—which is under pressure from surrounding upper layers of rock or clay. When tapped, the pressure in the aquifer, commonly called artesian pressure, pushes the water above the level of the aquifer, sometimes to the surface. Other means may be used to help bring the water to the surface.

According to the EPA, water from artesian aquifers often is more pure because the confining layers of rock and clay impede the movement of contamination. However, despite the claims of some bottlers, there is no guarantee that artesian waters are any cleaner than ground water from an unconfined aquifer, the EPA says.



Source: International Bottled Water Association

- **Mineral water.** Water from an underground source that contains at least 250 parts per million total dissolved solids. Minerals and trace elements must come from the source of the underground water. They cannot be added later.

- **Spring water.** Derived from an underground formation from which water flows naturally to the earth's surface. Spring water must be collected only at the spring or through a borehole tapping the underground formation feeding the spring. If some external force is used to collect the water through a borehole, the water must have the same composition and quality as the water that naturally flows to the surface.

- **Well water.** Water from a hole bored or drilled into the ground,

which taps into an aquifer.

Bottled water may be used as an ingredient in beverages, such as diluted juices or flavored bottled waters. However, beverages labeled as containing "sparkling water," "seltzer water," "soda water," "tonic water," or "club soda" are not included as bottled water under the FDA's regulations, because these beverages have historically been considered soft drinks.

Some bottled water also comes from municipal sources—in other words—the tap. Municipal water is usually treated before it is bottled. Examples of water treatments include:

- **Distillation.** In this process, water is turned into a vapor. Since minerals are too heavy to vaporize, they are left behind, and the vapors

To Filter or Not to Filter?

Consumers can buy purified water. They also have the option of doing it at home.

Numerous companies sell filtration systems. Some attach to the faucet and filter the water as it comes through the tap. Others are containers that filter the water in them. Among the best-known manufacturers are PUR and Brita.

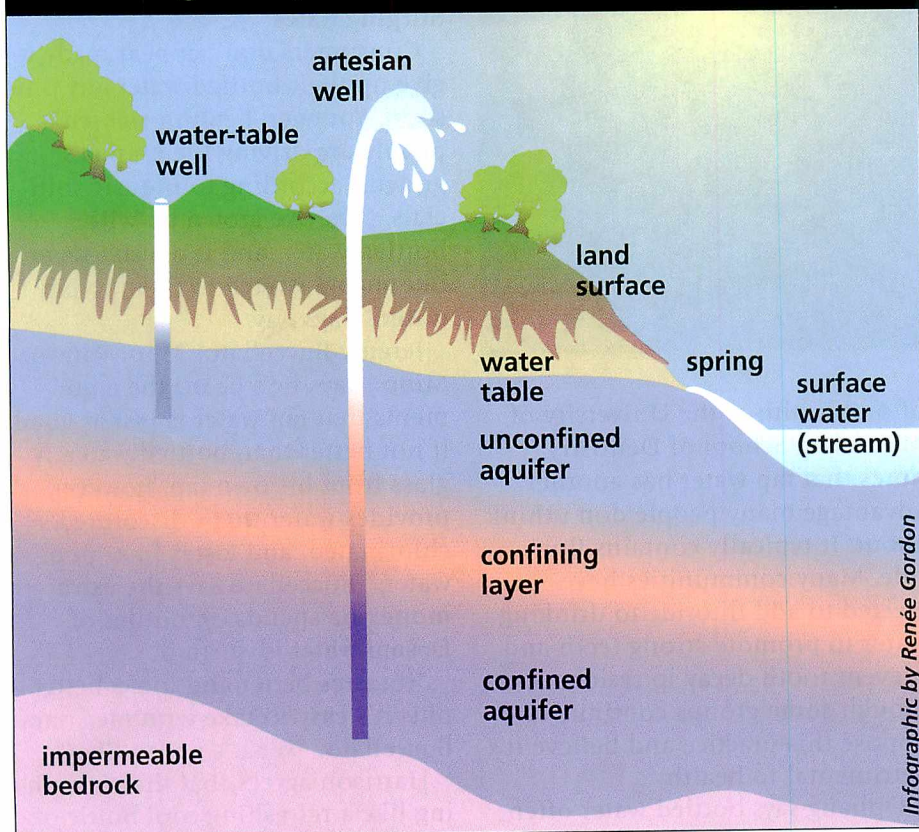
Water purified with these products typically costs less than buying bottled water. According to Brita, its high-end faucet filter system provides water for 18 cents a gallon, a considerable saving from \$1 or more typically charged for an 8- to 12-ounce bottle of water.

John B. Ferguson, communications manager/executive editor with the Water Quality Association, says that consumers can feel confident about the water quality provided by brand name home-filtration systems.

Stew Thornley of the Minnesota Department of Health agrees that home filtration systems can improve the taste or appearance of tap water at a minimal cost. However, Thornley points out that consumers need to be careful about maintaining these filters. Typically, specific instructions are included with the purchase of the product. Without proper maintenance, he says, it's possible bacteria or other contaminants can build up in the products. ■

—A.C.B.

The Origins of Bottled Water



Sources: U.S. Geological Survey; U.S. Environmental Protection Agency

Aquifers—layers of porous rock, sand and earth that contain water—supply water to wells and springs. An unconfined aquifer has an upper water surface that is at atmospheric pressure, so it is able to rise and fall. A confined aquifer, also called an artesian aquifer, has layers of impermeable material both above and below, exerting pressure. When a confined aquifer is penetrated by a well, this pressure will cause the water to rise above the top of the aquifer, sometimes to above ground level.

are condensed into water again.

- **Reverse osmosis.** Water is forced through membranes to remove minerals in the water.

- **Absolute 1 micron filtration.** Water flows through filters that remove particles larger than one micron in size, such as *Cryptosporidium*, a parasitic protozoan.

- **Ozonation.** Bottlers of all types of waters typically use ozone gas, an antimicrobial agent, to disinfect the water instead of chlorine, since chlorine can leave residual taste and odor to the water.

Bottled water that has been treated by distillation, reverse osmosis, or other suitable process and that meets the definition of "purified water" in the U.S. *Pharmacopeia* can be labeled as "purified water."

Bottled vs. Tap

Whether bottled water is better than tap water, and justifies its expense, remains under debate. Stephen Kay, vice president of the IBWA, says member bottlers are selling the quality, consistency and safety that bottled water promises, and providing a service for those whose municipal systems do not provide good quality drinking water.

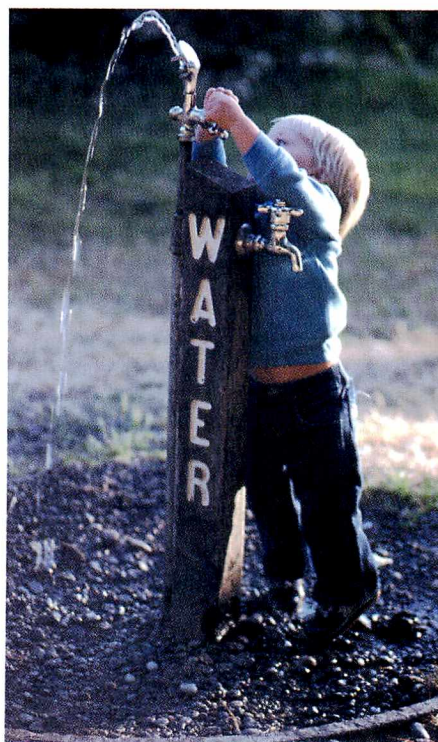
"Bottled water is produced and regulated exclusively for human consumption," Kay says. "Some people in their municipal markets have the luxury of good water. Others do not."

Thornley, of the Minnesota Department of Health, agrees that consumers can depend on bottled water's safety and quality. But he says consumers should feel the same way about the quality of their tap water. Tap water may sometimes look or taste differently, he says, but that doesn't mean it's unsafe. In fact, the most dangerous contaminants are those that consumers cannot see, smell or taste, he says. But consumers don't need to worry about their presence, he adds. Municipal water systems serving 25 people or more are subject

to the federal Safe Drinking Water Act. As such, the water constantly and thoroughly tested for harmful substances, he says. If there is a problem, consumers will be warned through the media or other outlets.

"In lieu of being told otherwise, consumers should feel confident of the safety of their water," Thornley says.

Dr. Robert Ophaug, a professor



of oral health at the University of Minnesota School of Dentistry, notes that tap water has another advantage many people don't think about: It typically contains fluoride. Many communities have elected to add fluoride to drinking water to promote strong teeth and prevent tooth decay in residents, though some groups continue to oppose this practice and believe it's detrimental to health.

Ophaug says bottled water often does not have fluoride added to it. Or, if it has been purified through reverse osmosis or distillation, the fluoride may have been removed. People who drink mostly bottled water, especially those who have children, need to be aware of this,

he says. They may need to use supplemental fluoride that is available by prescription from dentists or doctors. The supplements are usually recommended for children ages 7 to 16. Fluoride supplements cost around \$15 for a three-month supply.

"At the least, inform the children's dentist or doctor that you are relying on bottled water," Ophaug says.

The IBWA says there are more than 20 brands of bottled water with added fluoride available to consumers today. When fluoride is added to bottled water, the FDA requires that the term "fluoridated," "fluoride added," or "with added fluoride" be used on the label. Consumers interested in how much fluoride bottled water contains can usually find out by contacting individual companies directly.

Surging Sales

Consumers don't appear ready to give up their bottled water any time soon. Younger, health-oriented people are driving the market's growth, according to industry officials. "They've grown up with bottled water, and it doesn't seem like such a stretch to them to buy water," says Kay.

Jeremy Buccellato, 31, of Ramsey, Minn., says he's heard the arguments that tap water is just as good if not better than bottled water. A glass from his own tap, however, provides water that's discolored, chlorinated, and tastes like "pool water." Buccellato says the extra money he spends on bottles of Dasani water is worth it.

"It tastes better and looks better, plus it's easy to take with me," says Buccellato. "What's not to like?"

Harrison agrees that there's nothing like a refreshing cool bottle of water to beat the heat during an Oklahoma summer.

"It's a product that fits our needs and our lifestyle," she says. ■

Anne Christiansen Bullers is a freelance writer in Prairie Village, Kan.

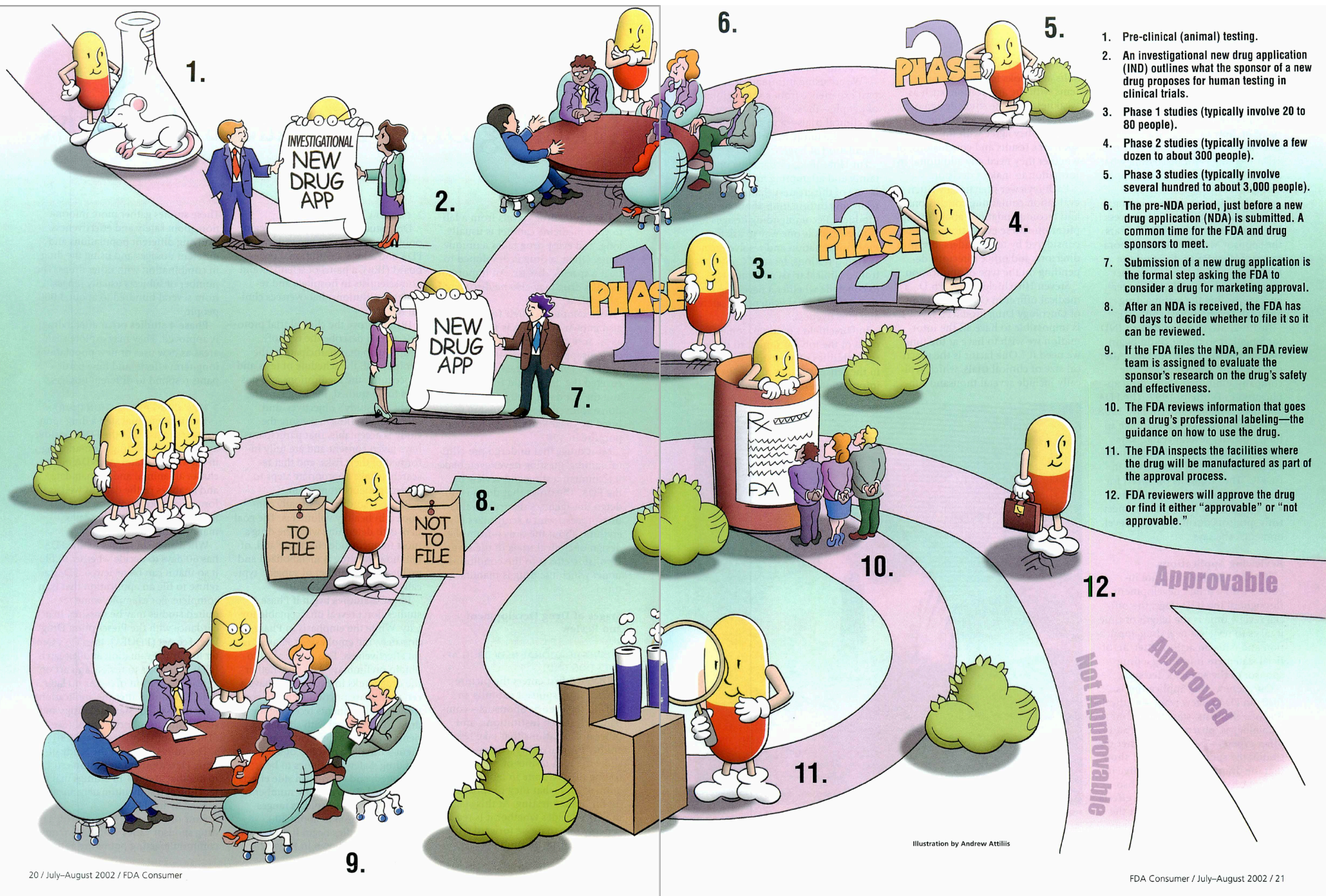


Illustration by Andrew Attilis

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

By Michelle Meadows

The path a drug travels from a lab to your medicine cabinet is usually long, and every drug takes a unique route. Often, a drug is developed to treat a specific disease. An important use of a drug may also be discovered by accident.

For example, Retrovir (zidovudine, also known as AZT) was first studied as an anti-cancer drug in the 1960s with disappointing results. It wasn't until the 1980s that researchers discovered the drug could treat AIDS, and the Food and Drug Administration approved the drug, manufactured by GlaxoSmithKline, for that purpose in 1987.

Most drugs that undergo pre-clinical (animal) testing never even make it to human testing and review by the FDA. The drugs that do must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug—from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.

Stages of Drug Development and Review

1. INVESTIGATIONAL NEW DRUG APPLICATION (IND)

The FDA first enters the picture when a drug sponsor submits an IND to the agency. Sponsors—companies, research institutions, and other organizations that take responsibility for marketing a drug—must show the FDA results of pre-clinical testing they've done in laboratory animals and what they propose to do for human testing. At this stage, the FDA decides whether it is reasonably safe to move forward with testing the drug on humans.

2. CLINICAL TRIALS

Drug studies in humans can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB), a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research.

IRBs approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details. IRBs make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm.

Phase 1 studies are usually conducted in healthy volunteers. The goal here is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80.

Phase 2 studies begin if Phase 1 studies don't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300.

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2.

These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people.

Phase 4 studies occur after a drug is approved. They may explore such areas as new uses or new populations, long-term effects, and how participants respond to different dosages.

3. NEW DRUG APPLICATION (NDA)

This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. FDA can refuse to file an application that is incomplete. For example, some required studies may be missing. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA's Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs no later than 10 months after the applications were received for standard drugs and six months for priority drugs. (See "The Role of User Fees," page 23.)

The Tufts Center for the Study of Drug Development in Boston estimates that about 1 in 5 drugs that enter clinical testing ultimately are approved by the FDA.

How often the FDA meets with a drug sponsor varies, but the two most common meeting points are at the

end of Phase 2 clinical trials and pre-NDA—right before a new drug application is submitted.

At the end of Phase 2, the FDA and sponsors try to come to an agreement on how the large-scale studies in Phase 3 should be done. The pre-NDA meeting is for discussing what the FDA expects to see in the application.

There is also continuous interaction throughout the review process. For example, over roughly six years, the sponsor Merck Research Laboratories of West Point, Pa., and the FDA had a half-dozen face-to-face meetings and about 28 teleconferences regarding the asthma drug Singulair (montelukast sodium).

In 1992, Merck submitted an IND for Singulair so that it could begin conducting studies in humans. After clinical trials were complete, the company submitted a new drug application in February 1997. The FDA approved Singulair in February 1998.

"It's the clinical trials that take so long—usually several years," says Sandra Kweder, M.D., deputy director for the Office of New Drugs in CDER. "The emphasis on speed for FDA mostly relates to review time and timelines of being able to meet with sponsors during a drug's development," she says.

Reviewing Applications

Though FDA reviewers are involved with a drug's development throughout the IND stage, the official review time is the length of time it takes to review a new drug application and issue an action letter, an official statement informing a drug sponsor of the agency's decision.

Once a new drug application is filed, an FDA review team—medical doctors, chemists, statisticians, microbiologists, pharmacologists and other experts—evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. No drug is absolutely safe; all drugs have side effects. "Safe" in this sense means that the benefits of the drug appear to outweigh the risks.

The review team analyzes study results and looks for possible problems with the application, such as weaknesses of the study design or analyses. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision.

Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. These evaluations are then considered by team leaders, division directors, and office directors, depending on the type of application.

Steven Hirschfeld, M.D., Ph.D., a medical officer in CDER's Division of Oncology Drug Products, says, "It is impossible to have all the information we wish to have at the time we need it." One factor is the practical size of clinical trials, which typically include several thousand sub-

jects at the most.

"We are using information about past experience from a select group of people—those enrolled in particular clinical trials—and attempting to predict the future experience of the population at large."

For Hirschfeld, recognizing uncertainty and attempting to minimize it is one of the greatest challenges in reviewing information about health products. Recommending designs for clinical trials is one way to ask for more information and resolve unanswered questions, he says. Controlled clinical trials allow the FDA to conclude whether a new drug has shown substantial evidence of safety and effectiveness.

In Hirschfeld's opinion, some aspects of the job are similar to the responsibilities of air traffic controllers in the sense that they also analyze information that's available to them



Ruggeri Photo.com

As a medical officer in the FDA's Division of Oncology Drug Products, Steven Hirschfeld, M.D., Ph.D., helps evaluate whether studies show that a drug is safe and effective for its proposed use.

and make recommendations that can be acted on.

"People bringing planes in have to balance weather, other planes in the sky, ground traffic, and arrival and departure schedules, all without placing people at greater risk," he says. They

can rearrange flight schedules and use different runways to lower the risk of problems, and the FDA can limit a drug's use or take other steps to lower the risk of problems, he says. "We all have responsibilities to protect or guide those who are vul-

nerable, and we use the best analytic tools at our disposal."

Reviewers receive training that fosters consistency in drug reviews, and good review practices remain a high priority for the agency. In October 2001, CDER held a two-day retreat where clinical reviewers discussed review priorities, including improved communication between different drug review divisions in CDER regarding drugs being reviewed for more than one indication.

Sometimes the FDA calls on advisory committees made up of outside experts who help the agency decide on drug applications. Whether an advisory committee is needed depends on many things.

"Some considerations would be if it's a drug that has significant questions, if it's the first in its class, or the first for a given indication," says Mark Goldberger, M.D., director of CDER's office that evaluates drugs to treat infectious diseases and immunosuppressive agents. "Generally, FDA takes the advice of advisory committees, but not always," he says. "Their role is just that—to advise."

Accelerated Approval

Traditional approval requires that clinical benefit be shown before approval can be granted. Accelerated approval is given to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments. This allows an NDA to be approved before measures of effectiveness that would usually be required for approval are available.

Instead, less traditional measures called "surrogate endpoints" are used to evaluate effectiveness. These are laboratory findings or signs that may not be a direct measurement of how a patient feels, functions, or survives, but are considered likely to predict benefit. For example, a surrogate endpoint could be the lowering of HIV blood levels for short periods of time with anti-retroviral drugs.

Gleevec (imatinib mesylate), an oral treatment for patients with a life-threatening form of cancer called chronic myeloid leukemia (CML), received accelerated approval. The drug

The Role of User Fees

Since the Prescription Drug User Fee Act (PDUFA) was passed in 1992, more than 700 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections. PDUFA has allowed the FDA to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process.

Under PDUFA, drug companies agree to pay fees that boost FDA resources, and the FDA agrees to time limits for its review of new drug applications. Along with supporting increased staff, drug user fees help the FDA upgrade resources in information technology. The agency has moved toward an electronic submission and review environment, now accepting more electronic applications and filing review documents electronically.

The goals set by PDUFA apply to the review of original new human drug and biological applications, resubmissions of original applications, and supplements to approved applications. The second phase of PDUFA, known as PDUFA II, was reauthorized in 1997 and will expire on Sept. 30, 2002. PDUFA III, which extends to 2007, was reauthorized in June 2002.

The FDA continues to meet or exceed PDUFA's review goals, which have become more demanding each year. FDA's Center for Drug Evaluation and Research (CDER) approved 66 new drugs last year, 24 of which were new molecular entities (NMEs) with ingredients never marketed before in the United States. Ten were priority products, believed to represent an advance over available therapies. The FDA's Center for Biologics Evaluation and Research (CBER) reviewed 16 complex biological license applications (BLA) last year. Two of the BLAs reviewed were classified as priority products. Biologics are medical products derived from living sources, such as vaccines and blood products.

In addition to setting timeframes for review of applications, PDUFA sets goals to improve communication between the FDA and drug sponsors. PDUFA outlines how fast the FDA must respond to requests from sponsors and how often meetings should occur. Throughout a drug's development, the FDA advises sponsors on how to study certain classes of drugs, how to submit data, what kind of data is needed, and how clinical trials should be designed. ■

—M.M.

was also approved under the FDA's orphan drug program, which gives financial incentives to sponsors for manufacturing drugs that treat rare diseases. Gleevec blocks enzymes that play a role in cancer growth. The approval was based on results of three large Phase 2 studies, which showed the drug could substantially reduce the level of cancerous cells in the bone marrow and blood.

The sponsor, Novartis Pharmaceuticals Corp. of East Hanover, N.J., submitted the IND in April 1998. The FDA received the NDA in February 2001, and the drug was approved two and a half months later in May 2001. Novartis has made commitments to conduct Phase 4 studies that investigate Gleevec's clinical benefit, such as increased progression-free survival in the treatment of CML.

Most drugs to treat HIV have been approved under accelerated approval provisions, with the company required to continue its studies after the drug is on the market to confirm that its effects on virus levels are maintained and that it ultimately benefits the patient. Under accelerated approval rules, if studies don't confirm the initial results, the FDA can withdraw the approval.

Because premarket review can't catch all potential problems with a drug, the FDA continues to track approved drugs for adverse events through a postmarketing surveillance program.

Bumps in the Road

If the FDA decides that the benefits of a drug outweigh the risks, the drug will receive approval and can be marketed in the United States. But if there are problems with an NDA, the FDA may decide that a drug is "approvable" or "not approvable."

A designation of approvable means that the drug can probably be approved, provided that some issues are resolved first. This might involve the sponsor and the FDA coming to a final agreement on what should go on the drug's label, for example. It could also involve more difficult issues, such as the adequacy of infor-

mation on how people respond to various dosages of the drug.

A designation of "not approvable" describes deficiencies significant enough that it is not clear that approval can be obtained in the future, at least not without substantial additional data.

Common problems include unexpected safety issues that crop up or failure to demonstrate a drug's effectiveness. A sponsor may need to conduct additional studies—perhaps studies of more people, different types of people, or for a longer period of time.

Manufacturing issues are also among the reasons that approval may be delayed or denied. Drugs must be manufactured in accordance with standards called good manufacturing practices, and the FDA inspects manufacturing facilities before a drug can be approved. If a facility isn't ready for inspection, approval can be delayed. Any manufacturing deficiencies found would need to be corrected before approval.

"Sometimes a company may make a certain amount of a drug for clinical trials. Then when they go to scale up, they may lose a supplier or end up with quality control issues that result in a product of different chemistry," says the FDA's Kweder. "Sponsors have to show us that the product that's going to be marketed is the same product that they tested."

John Jenkins, M.D., director of CDER's Office of New Drugs, says, "It's often a combination of problems that prevent approval." Close communication with the FDA early on in a drug's development reduces the chance that an application will have to go through more than one cycle of review, he says. "But it's no guarantee."

The FDA outlines the justification for its decision in an action letter to the drug sponsor. When the action is either approvable or not approvable, CDER gives the sponsor a chance to meet with agency officials to discuss the deficiencies. At that point, the sponsor can choose to ask for a hearing or correct any deficiencies and submit new information. ■

The Quality of Clinical Data

The FDA relies on data that sponsors submit to decide whether a drug should be approved. To protect the rights and welfare of people in clinical trials, and to verify the quality and integrity of data submitted, the Food and Drug Administration's Division of Scientific Investigations (DSI) conducts inspections of clinical investigators' study sites. DSI also reviews the records of institutional review boards to be sure they are fulfilling their role in patient protection.

"FDA investigators compare information that clinical investigators provided to sponsors on case report forms with information in source documents such as medical records and lab results," says Carolyn Hommel, a consumer safety officer in DSI.

DSI seeks to determine such things as whether the study was conducted according to the investigational plan, whether all adverse events were recorded, and whether the subjects met the inclusion/exclusion criteria outlined in the study protocol.

At the conclusion of each inspection, FDA investigators prepare a report summarizing any deficiencies. In cases where they observe numerous or serious deviations, such as falsification of data, DSI classifies the inspection as "official action indicated" and sends a warning letter or Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to the clinical investigator, specifying the deviations that were found.

The NIDPOE begins an administrative process to determine whether the clinical investigator should remain eligible to receive investigational products and conduct clinical studies.

CDER conducts about 300-400 clinical investigator inspections annually. About 3 percent are classified in this "official action indicated" category. ■

—M.M.

'Six-Pack Abs' Electronically?



You've probably seen the ads on television that promise "six-pack abs" without a workout. Can you really tone your muscles using an electrical muscle stimulator while lounging around the pool like the models on TV?

In May, the Federal Trade Commission (FTC) filed complaints against three manufacturers of these devices, alleging that they have made false claims in their advertising, seen in heavily aired infomercials on national cable television, shorter television commercials, and ads in the print media.

The unfounded claims cited by the FTC include the promise of

"six pack" or "washboard" abs without exercise, claims that the devices will give users a trimmer waist or cause fat loss, and that use of the device is equivalent to (or better than) regular abdominal exercises, such as sit-ups or crunches. The FTC complaints also allege that the advertising claimed falsely that the stimulators are safe for all to use, and did not disclose adequately the possible health hazards for some people.

Here's more information about the devices, what they can and can't do, and how they are regulated by the Food and Drug Administration's Center for Devices and Radiological Health.

Q. Why does the FDA regulate electrical muscle stimulators?

A. Electrical muscle stimulators are considered medical devices under the Federal Food, Drug, and Cosmetic Act. Under this law and the agency's regulations, the FDA is responsible for regulating the sale of all electrical muscle stimulators in the United States. Therefore, firms must comply with appropriate FDA premarket regulatory requirements before they can legally sell their stimulators. Most electrical muscle stimulators (EMS devices) that have been reviewed by the FDA are intended for use in physical therapy and rehabilitation under the direction of a health-care professional. If a company wants to sell EMS devices directly to consumers, the company needs to show the FDA that the device can be used safely and effectively in that setting.

Q. These electrical muscle stimulators are advertised not only to tone, firm, and strengthen abdominal muscles, but also to provide weight loss, girth reduction, and "rock hard" abs. Do they really work?

A. While an EMS device may be able to temporarily strengthen, tone or firm a muscle, no EMS devices have been cleared at this time for weight loss, girth reduction, or for obtaining "rock hard" abs.

Q. Is the FDA concerned about the unregulated marketing of these devices?

A. Yes. The FDA has received reports of shocks, burns, bruising, skin irritation, and pain associated with the use of some of these devices. There have been a few recent reports of interference with implanted devices such as pacemakers and defibrillators. Some injuries required hospital treatment. It is very important that these devices be properly designed, manufactured, and labeled with clear and complete instructions for use and that all users follow the instructions carefully. The FDA is also concerned because many of these devices have cables and leads. If those cables and leads do not comply with electrical safety standards, there is the possibility that users and other household members could be electrocuted. The FDA is currently investigating firms that are illegally marketing EMS devices.

Q. What does FDA regulation accomplish?

A. Before they may legally sell their devices, firms that market EMS devices must be able to demonstrate that these products are as safe and as effective as similar devices that are legally marketed. Devices may be marketed only for uses that are established for the device or for uses that the firm can support with data. At this time, the FDA is not aware of scientific information to support many of the promotional claims being made for numerous devices being widely promoted on television, infomercials, newspapers, and magazines.

Q. Why should I select an electrical muscle stimulator that is legally marketed according to FDA regulations?

A. Electrical muscle stimulators that have not met FDA requirements are illegal, and the FDA has not determined whether or not they are properly designed, manufactured, and labeled to provide reasonable assurance that they are safe and effective.

Q. Does that mean that it's unsafe to use an electrical muscle stimulator that has not met FDA requirements?

A. Using a product that has not met FDA requirements isn't necessarily unsafe or dangerous. But it could be. The FDA has received reports of injuries and interference with other critically important medical devices associated with the use of unregulated products. Unregulated devices also may have safety problems associated with cables and leads that can lead to accidental shock and electrocution of users and other household members, including children.

Q. If I use an electrical muscle stimulator that has met FDA regulatory requirements, will it give me the same kind of effect that lots of sit-ups, stomach crunches and other abdominal exercises will?

A. Using these devices alone will not give you "six-pack" abs. Applying electrical current to muscles may cause them to contract. Stimulating muscles repeatedly with electricity may eventually result in muscles that are strengthened and toned to some extent but will not, based on currently available data, create a major change in your appearance without the addition of weight loss and regular exercise.

Q. But hasn't the FDA cleared electrical muscle stimulators to treat medical conditions?

A. Yes. The FDA has cleared many electrical muscle stimulators for prescription use in treating medical conditions. Doctors may use electrical muscle stimulators for patients who require muscle re-education, relaxation of muscle spasms, increased range of motion, prevention of muscle atrophy, and for treating other medical conditions that usually result from a stroke, a serious injury, or major surgery. Again, the effect of using these devices is primarily to help a patient recover from impaired muscle function due to a medical condition, not to increase muscle size enough to affect appearance.

Q. Are there any over-the-counter EMS devices that have met the FDA's regulatory requirements?

A. Yes. At this time, Slendertone Flex, marketed by BMR NeuroTech Inc. of Phoenix, has been cleared by the FDA for toning, strengthening and firming abdominal muscles.

Q. How do I report a problem with an EMS device?

A. Medical device malfunctions can be reported directly to the manufacturer. You also can report problems to MedWatch, the FDA's voluntary reporting program. You may submit reports to MedWatch in one of four ways:

- online at www.fda.gov/medwatch/how.htm
- by telephone at 1-800-332-1088
- by fax at 1-800-332-1078
- by mail to MedWatch, Food and Drug Administration, HF-2, 5600 Fishers Lane, Rockville, MD 20857. ■

What to Look for in a Pair of Sunglasses

By Michelle Meadows

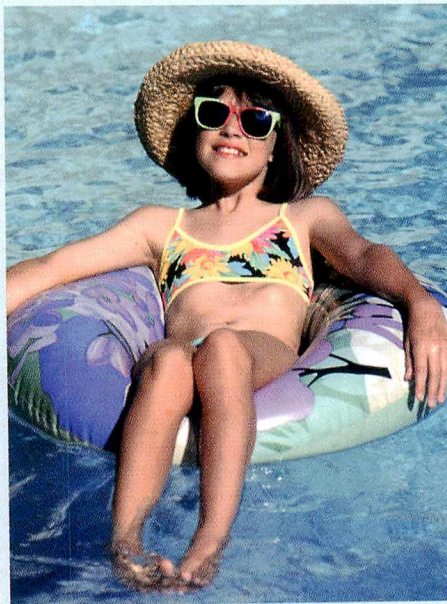
As you slather on sunscreen to protect your skin this summer, don't forget sunglasses to protect your eyes. The same harmful rays that damage skin can also increase your risk of developing eye problems, such as cataracts—a clouding of the eye's lens that develops over years.

In the short-term, people who spend long hours on the beach or in the snow without adequate eye protection can develop photokeratitis, reversible sunburn of the cornea. This painful condition can result in temporary loss of vision. When sunlight reflects off of snow, sand and water, it further increases exposure to ultraviolet (UV) radiation. These invisible high-energy rays lie just beyond the violet end of the visible light spectrum.

Everyone is at risk for eye damage from the sun year-round. The risk is greatest from about 10 a.m. to 4 p.m. Fishermen, farmers, beach-goers, and others who spend time in the sun for extended periods are at highest risk.

UV radiation in sunlight is commonly divided into UVA and UVB, and your sunglasses should block both forms. Don't assume that you get more UV protection with pricier sunglasses or glasses with a darker tint. Look for a label that specifically states that the glasses offer 99 percent to 100 percent UV protection. You could also ask an eye-care professional to test your sunglasses if you're not sure of their level of UV protection.

Sunglasses should be dark enough to reduce glare, but not dark enough to distort colors and affect the recognition of traffic signals. Tint is mainly a matter of personal preference. For best color perception, Prevent Blindness America, a volunteer eye health and safety organization dedicated to fighting blindness and saving sight, recommends lenses that are neutral



gray, amber, brown or green. People who wear contact lenses that offer UV protection should still wear sunglasses.

Children also should wear sunglasses. They shouldn't be toy sunglasses, but real sunglasses that indicate the UV-protection level just as with adults. Polycarbonate lenses are generally recommended for children because they are the most shatter-resistant.

Sheryl Berman, M.D., a medical officer in the FDA's Division of Ophthalmic and Ear, Nose, and Throat Devices, says that wearing sunglasses reduces the risk of eye damage due to sun exposure, but doesn't completely eliminate it.

"Even when we talk about 100 percent UV protection, light still enters from the sides of sunglasses and can be reflected into the eye," she says. Some people choose sunglasses that wrap all the way around the temples. A hat with a three-inch brim can help block sunlight that comes in from overhead.

The FDA's Center for Devices and Radiological Health regulates nonprescription sunglasses as over-the-

counter medical devices. Sunglasses are normally exempt from the FDA's premarket notification procedures. But sunglasses manufacturers who claim their products are of substantial importance in preventing health problems would be required to submit proof to the FDA. The only medical claim manufacturers are allowed to make on sunglasses is that they may reduce eye strain or eye fatigue due to glare.

Even though sunglasses are exempt from premarket notification, they remain subject to several regulations. Sunglasses regulated by the FDA must comply with impact-resistant requirements, for example. This doesn't mean that the glasses are shatterproof, but that they can withstand moderate impact. Sunglasses are not intended to function as protective eyewear in high-impact sports.

Manufacturers of sunglasses also must follow the FDA's labeling regulations. The FDA has issued warning letters to manufacturers about unsubstantiated performance claims, such as those relating to UV-absorbing sunglasses.

For more information about how the FDA regulates sunglasses, you can access a sunglasses guidance document at www.fda.gov/cdrh/ode/90.html. ■

UVA and UVB

- **UVA:** UVA is ultraviolet radiation with wavelengths from 320-400 nanometers. It passes through the Earth's ozone layer and can cause early aging of the skin.

- **UVB:** UVB is ultraviolet radiation with wavelengths of 280-320 nanometers. The ozone layer absorbs most of the sun's UVB, but even a small amount can do substantial damage. UVB causes skin cancer and may contribute to cataracts. ■

Source: Centers for Disease Control and Prevention

Battle of the Bugs: Fighting Antibiotic Resistance

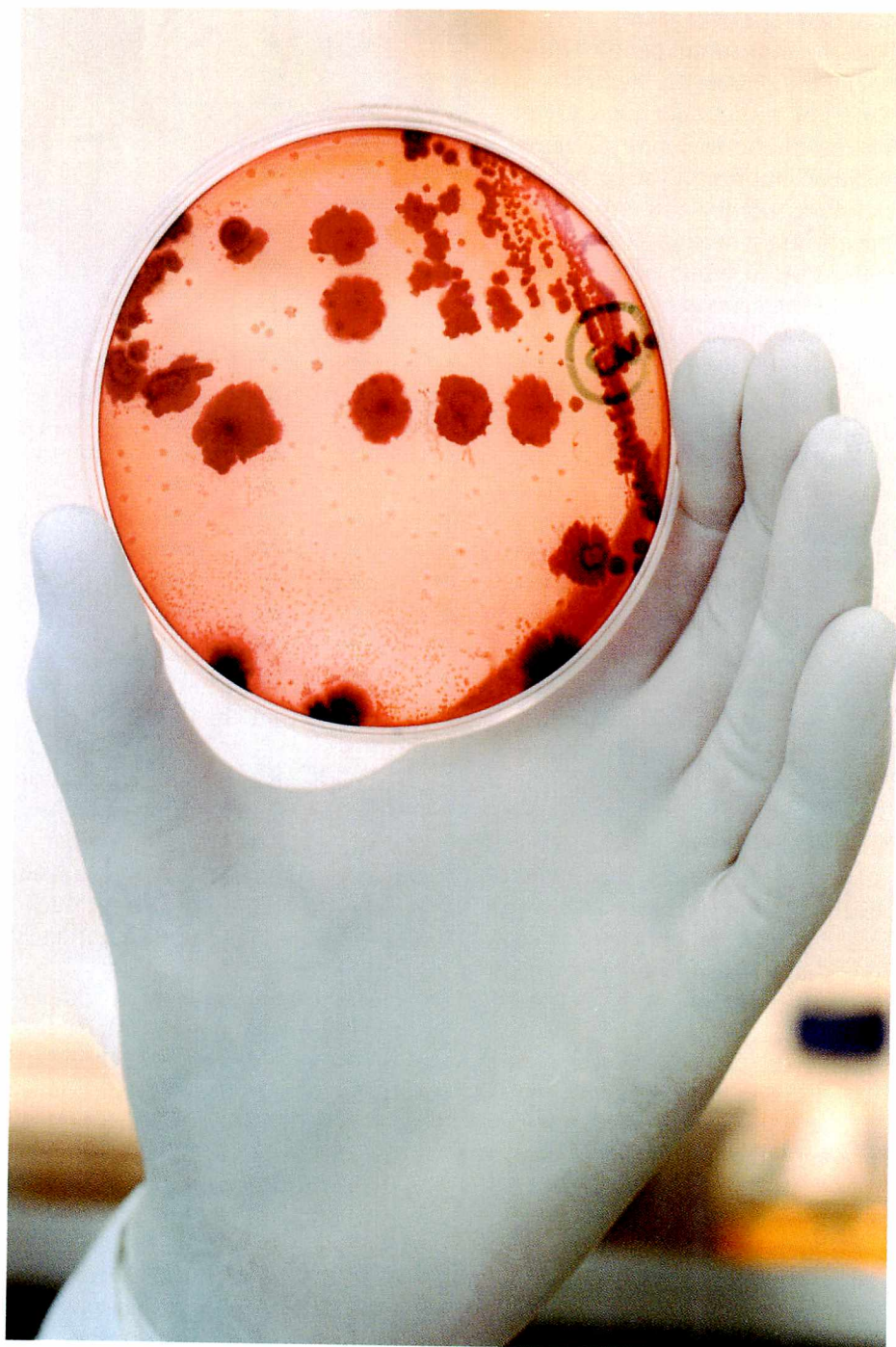
By Linda Bren

Ever since antibiotics became widely available about 50 years ago, they have been hailed as miracle drugs—magic bullets able to destroy disease-causing bacteria.

But with each passing decade, bacteria that resist not only single, but multiple, antibiotics—making some diseases particularly hard to control—have become increasingly widespread. In fact, according to the Centers for Disease Control and Prevention (CDC), virtually all significant bacterial infections in the world are becoming resistant to the antibiotic treatment of choice.

For some of us, bacterial resistance could mean more visits to the doctor, a lengthier illness, and possibly more toxic drugs. For others, it could mean death. The CDC estimates that each year, nearly 2 million people in the United States acquire an infection while in a hospital, resulting in 90,000 deaths. More than 70 percent of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them.

Antibiotic resistance, also known as antimicrobial resistance, is not a new phenomenon. Just a few years after the first antibiotic, penicillin, became widely used in the late 1940s, penicillin-resistant infections emerged that were caused by the bacterium *Staphylococcus aureus* (*S. aureus*). These “staph” infections range from urinary tract infections to bacterial pneumonia. Methicillin, one of the strongest in the arsenal of drugs to treat staph infections, is



Courtesy: Aventis

no longer effective against some strains of *S. aureus*. Vancomycin, which is the most lethal drug against these resistant pathogens, may be in danger of losing its effectiveness.

Although resistant bacteria have been around a long time, the scenario today is different from even just 10 years ago, says Stuart Levy, M.D., president of the Alliance for the Prudent Use of Antibiotics. "The number of bacteria resistant to many different antibiotics has in-

creased, in many cases, tenfold or more. Even new drugs that have been approved are confronting resistance, fortunately in small amounts, but we have to be careful how they're used. If used for extended periods of time, they too risk becoming ineffective early on."

How Resistance Occurs

Bacteria, which are organisms so small that they are not visible to the naked eye, live all around us—in drinking water, food, soil, plants,

animals, and in humans. Most bacteria do not harm us, and some are even useful because they can help us digest food. But many bacteria are capable of causing severe infections.

The ability of antibiotics to stop an infection depends on killing or halting the growth of harmful bacteria. But some bacteria resist the effects of drugs and multiply and spread.

Some bacteria have developed resistance to antibiotics naturally, long before the development of commercial antibiotics. After testing bacteria found in an arctic glacier and estimated to be over 2,000 years old, scientists found several of them to be resistant against some antibiotics, most likely indicating naturally occurring resistance.

If they are not naturally resistant, bacteria can become resistant to drugs in a number of ways (see graphic, left). They may develop resistance to certain drugs spontaneously through mutation. Mutations are changes that occur in the genetic material, or DNA, of the bacteria. These changes allow the bacteria to fight or inactivate the antibiotic.

Bacteria also can acquire resistant genes through exchanging genes with other bacteria. "Think of it as bacterial sex," says David White, Ph.D., a microbiologist in the Food and Drug Administration's Center for Veterinary Medicine. "It's a simple form of mating that allows bacteria to transfer genetic material." The bacteria reproduce rapidly, allowing resistant traits to quickly spread to future generations of bacteria. "The bacteria don't care what other bacteria they're giving their genes to," says White. This means that resistance can spread from one species of bacteria to other species, enabling them to develop multiple resistance to different classes of antibiotics.

Combating Resistance

In 1999, 10 federal agencies and departments, led by the Department of Health and Human Services, formed a task force to tackle the

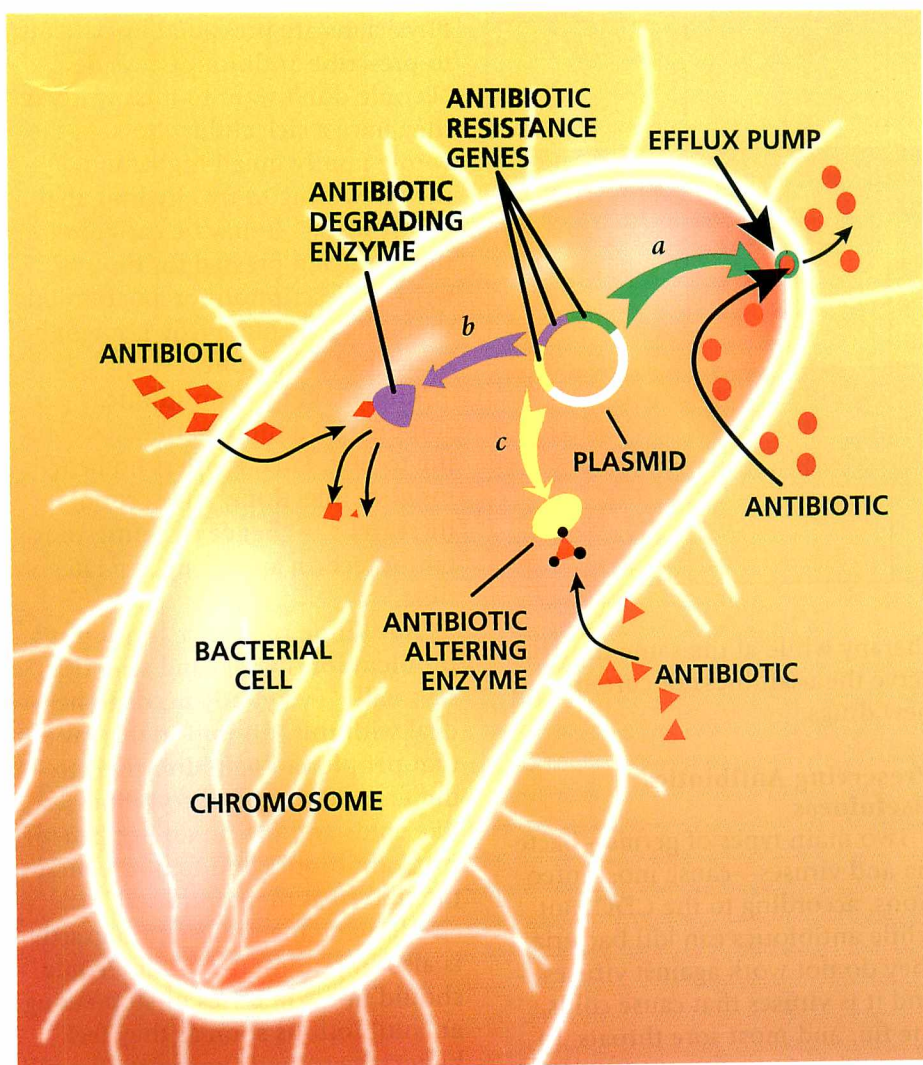


Illustration by Tomo Narashima

Antibiotic-resistant bacteria owe their drug insensitivity to resistance genes. For example, such genes might code for "efflux" pumps that eject antibiotics from cells (a). Or the genes might give rise to enzymes that degrade the antibiotics (b) or that chemically alter—and inactivate—the drugs (c). Resistance genes can reside on the bacterial chromosome or, more typically, on small rings of DNA called plasmids.

Levy, S. B. "The Challenge of Antibiotic Resistance." *Scientific American*, March 1998.

Left: Bacteria cultures are used in the lab for developing new antibiotics.

Upper Respiratory Infections and Antibiotics

Most upper respiratory infections are usually caused by viruses—germs that are not killed by antibiotics. Talk with your doctor about ways to feel better when you are sick. Ask what you should look for at home that might mean you are developing another infection for which antibiotics might be appropriate.

Illness	Usually caused by virus	Usually caused by bacteria	Antibiotic usually needed?
Cold	✓		No
Flu	✓		No
Chest Cold (in otherwise healthy children and adults)	✓		No
Sore Throats (except strep)	✓		No
Bronchitis (in otherwise healthy children and adults)	✓		No
Runny Nose (with green or yellow mucus)	✓		No
Fluid in the Middle Ear (otitis media with effusion)	✓		No

Source: Centers for Disease Control and Prevention

problem of antimicrobial resistance. Co-chaired by the CDC, the FDA, and the National Institutes of Health, the task force developed a plan of action. The success of this plan—issued in 2001 and known as the Public Health Action Plan to Combat Antimicrobial Resistance—will depend on the cooperation of many entities, such as state and local health agencies, universities, professional societies, pharmaceutical companies, health-care professionals, agricultural producers, and the public.

All of these groups must work together if the antibiotic resistance problem is to be remedied, says Mark Goldberger, M.D., director of the FDA's office responsible for reviewing antibiotic drugs. "This is a very serious problem. We need to do two things: facilitate the development of new antimicrobial

therapy while at the same time preserve the usefulness of current and new drugs."

Preserving Antibiotics' Usefulness

Two main types of germs—bacteria and viruses—cause most infections, according to the CDC. But while antibiotics can kill bacteria, they do not work against viruses—and it is viruses that cause colds, the flu, and most sore throats. In fact, only 15 percent of sore throats are caused by the bacterium *Streptococcus*, which results in strep throat. In addition, it is viruses that cause most sinus infections, coughs, and bronchitis. And fluid in the middle ear, a common occurrence in children, does not usually warrant treatment with antibiotics unless there are other symptoms. (See "Fluid in the Middle Ear," page 31.)

Nevertheless, "Every year, tens of millions of prescriptions for antibiotics are written to treat viral illnesses for which these antibiotics offer no benefits," says David Bell, M.D., the CDC's antimicrobial resistance coordinator. According to the CDC, antibiotic prescribing in outpatient settings could be reduced by more than 30 percent without adversely affecting patient health.

Reasons cited by doctors for overprescribing antibiotics include diagnostic uncertainty, time pressure on physicians, and patient demand. Physicians are pressured by patients to prescribe antibiotics, says Bell. "People don't want to miss work, or they have a sick child who kept the whole family up all night, and they're willing to try anything that might work." It may be easier for the physician pressed for time to write a prescription for an antibiotic than it is to explain why it might be better not to use one.

But by taking an antibiotic, a person may be doubly harmed, according to Bell. First, it offers no benefit for viral infections, and second, it increases the chance of a drug-resistant infection appearing at a later time.

"Antibiotic resistance is not just a problem for doctors and scientists," says Bell. "Everybody needs to help deal with this. An important way that people can help directly is to understand that common illnesses like colds and the flu do not benefit from antibiotics and to not request them to treat these illnesses."

Following the prescription exactly is also important, says Bell. People should not skip doses or stop taking an antibiotic as soon as they feel better; they should complete the full course of the medication. Otherwise, the drug may not kill all the infectious bacteria, allowing the remaining bacteria to possibly become resistant.

While some antibiotics must be taken for 10 days or more, others are FDA-approved for a shorter course of treatment. Some can be taken for as few as three days. "I would prefer



A variety of household products contain antibacterial agents.

the short course to the long course," says Levy. "Reservoirs of antibiotic resistance are not being stimulated as much. The shorter the course, theoretically, the less chance you'll have resistance emerging, and it gives susceptible strains a better chance to come back."

Another concern to some health experts is the escalating use of antibacterial soaps, detergents, lotions, and other household items. "There has never been evidence that they have a public health benefit," says

Levy. "Good soap and water is sufficient in most cases." Antibacterial products should be reserved for the hospital setting, for sick people coming home from the hospital, and for those with compromised immune systems, says Levy.

To decrease both demand and overprescribing, the FDA and the CDC have launched antibiotic resistance campaigns aimed at health-care professionals and the public. A nationwide ad campaign developed by the FDA's Center for Drug

Fluid in the Middle Ear

Fluid in the middle ear, also called otitis media with effusion, is a common condition in children. Fluid often accumulates in the ear, just like in the nose, when a child has a cold. In the absence of other symptoms, fluid in the middle ear usually doesn't bother children, and it almost always goes away on its own without treatment, says Janice Soreth, M.D., director of the FDA's Division of Anti-Infective Drug Products. "It usually does not need to be treated with antibiotics unless it is accompanied by additional signs or symptoms or it lasts a couple of months."

If your doctor does not prescribe an antibiotic for your child, do not insist on one. Taking an antibiotic when it is not necessary can be harmful. It increases the risk of getting an infection later that antibiotics cannot kill.

Instead, "observe your child," says Soreth. "If symptoms change, call your doctor to seek further help." Symptoms to watch for include fever, irritability, decreased appetite, trouble sleeping, tugging on the ear, or complaints of pain. "If symptoms occur, it doesn't mean the doctor misdiagnosed the condition," says Soreth. "What started out as a viral condition may have morphed into a bacterial infection several days later. If this happens, an antibiotic may be appropriate." ■

—L.B.

What You Can Do to Help Curb Antibiotic Resistance

- Don't demand an antibiotic when your health-care provider determines one isn't appropriate. Ask about ways to help relieve your symptoms.
- Never take an antibiotic for a viral infection such as a cold, a cough, or the flu.
- Take medicine exactly as your health-care provider prescribes. If he or she prescribes an antibiotic, take it until it is gone, even if you're feeling better.
- Don't take leftover antibiotics or antibiotics prescribed for someone else. These antibiotics may not be appropriate for your current symptoms. Taking the wrong medicine could delay getting correct treatment and allow bacteria to multiply.

Adapted from the Centers for Disease Control and Prevention.

Evaluation and Research emphasizes to health-care professionals the prudent use of antibiotics, and offers them an educational brochure to distribute to patients.

The FDA has also drafted a proposed labeling rule that would require specific language on antibiotic labels to encourage doctors to prescribe them only when truly necessary.

Stimulating Drug Development

The FDA is working to encourage the development of new antibiotics and new classes of antibiotics and other antimicrobials. "We would like to make it attractive for the development of new antibiotics, but we'd like people to use them less and only in the presence of bacterial infection," says Goldberger. This presents a challenge, he says. "Decreased use may result in sales going down, and drug companies may feel there are better places to put their resources."

Through such incentives as exclusivity rights, the FDA hopes to stimulate new antimicrobial drug development. Exclusivity protects a manufacturer's drug from generic drug competition for a specific length of time.

The FDA has a variety of existing regulatory tools to help developers of antimicrobial drugs. One of these is an accelerated approval process for drugs that treat severely debilitating or life-threatening diseases and for drugs that show meaningful benefit over existing prescription drugs to cure a disease.

The FDA is also investigating other approaches for speeding the antimicrobial approval process. One approach is to reduce the size of the clinical trial program. "We need to streamline the review process without compromising safety and effectiveness," says Goldberger. "One of the things that we are trying to look at now is how we can substitute quality for quantity in clinical studies." It has been difficult to test drugs for resistance in people, says Goldberger. "Although these resistant organisms are a problem, they are still not so common that it is very easy to accumulate patients."

From Farm to Fork

Although the inappropriate use of antibiotics in people is a major contributor to antibiotic resistance, it is not the only contributor. Another is the use of these drugs in agriculture. Antibiotics are used in agriculture when they are sprayed onto fruit trees and other food plants as a pes-

ticide for disease control. In addition, antibiotics are used to treat and prevent diseases in food-producing animals and to improve their growth rate.

Scientists have found a link between antibiotic use in agriculture and antibiotic resistance in bacteria carried by humans. "There is a small, but very important, subset of resistant infections in humans that are caused by pathogens that animals carry inherently," says Linda Tollefson, D.V.M., M.P.H., deputy director of the FDA's Center for Veterinary Medicine (CVM). "These pathogens don't make the animal sick, but the animals are treated with antimicrobials for other diseases or to promote growth. These bacteria in the animal may then become resistant to the drug and cause resistant foodborne infections in humans who consume products derived from the animals."

The resistant bacteria, which remain on the animal through the slaughtering and packaging process, make their way into home kitchens. The cooking process kills off many of the bacteria, but undercooked meat will still harbor some. In addition, if raw meat, poultry or fish comes in contact with other foods, bacteria can spread to these foods through cross-contamination.

Most people suffer only mild to moderate illness from these bacteria, but each year, thousands get severely ill and even die. People who do get sick may be treated with the same or a similar drug that is used in the animals and, because of the transfer of resistant bacteria, the drug may not be effective.

The human health impact of antibiotic use in food animals has long been debated. A 1999 National Academy of Sciences report concluded that there is "a link between the use of antibiotics in food animals, the development of bacterial resistance to these drugs, and human disease—although the incidence of such disease is very low."

However, a more recent report released by the Alliance for the Prudent Use of Antibiotics and

published in the June 2002 issue of *Clinical Infectious Diseases* recommended eliminating the use of antibiotics for growth promotion in food-producing animals and limiting farm use of drugs that are critically important to humans. "There is a critical need for more timely action to ensure that antibiotics remain effective," says Levy. "Once the resistance in a bacterial population reaches a certain level, reversal becomes extremely difficult."

The Animal Health Institute (AHI), a national trade association representing manufacturers of animal health products, is also concerned about the possibility of antibiotics used in food animals causing resistant bacteria to develop. But stopping the use of antibiotics in animals is not the solution, says Ron Phillips, AHI spokesperson.

"The number one reason that antibiotic use in animals is important is to keep animals healthy; by keeping animals healthy, we increase food safety," says Phillips. "For farmers, it's an important production tool that contributes to the relatively low cost of our food supply."

The AHI recommends several actions to better manage human resistance. "The first thing we need to do is to be able to appropriately measure it so we can manage it," says Phillips. The AHI supports more and better surveillance of both human and animal resistance, and promoting to farmers and veterinarians better practice of "judicious use" principles regarding antibiotics.

"The FDA has done some good work in helping to promote those principles and ought to continue," says Phillips. But he urges the FDA to work even more closely with the livestock production and animal health communities in promoting judicious use principles. In addition, the AHI calls for "good, sound risk assessments that will yield us the kind of information necessary

to make good management decisions."

Animal Drug Regulation

To reduce antibiotic resistance in humans caused by the use of antibiotic drugs in animals, the FDA is evaluating the animal drug pre-approval process, increasing surveillance, and expanding research.

CVM regulates drugs used in food-producing animals. One of CVM's major challenges is improving the



way the FDA regulates antibiotics in livestock and poultry, says Stephen Sundlof, D.V.M., Ph.D., director of CVM. "Our main goal is to ensure that human antimicrobial therapies are not compromised or lost due to the use of antimicrobial drugs in animals. But we also have another important goal—to provide for the safe use of antimicrobial drugs in food-producing animals, because these drugs are valuable tools in livestock production and they provide one way of making sure that the food supply is safe."

To balance these two goals, CVM has presented suggested approaches for drug regulation in food animals. These approaches are included in CVM's 1998 publication known as the "Framework Document."

Based on feedback from public forums and advisory committee meetings, CVM is drafting guidance for drug sponsors to help them implement the suggested approaches in the Framework Document. A public meeting will follow the publication of this guidance, which is expected this summer, and the FDA will invite comments on any proposed new or amended rules before they are made final. CVM's approaches, designed to discover whether specific drugs might promote antibiotic resistance, include a more rigorous safety assessment for resistance prior to drug approval and categorizing antibiotic drugs based on their importance to human medicine.

"We decided that not all antibiotics are created equal," says Sundlof. "There are some antimicrobial drugs used in human medicine that are drugs of last resort for treating a life-threatening disease." Animal drugs similar to those used to treat a serious or life-threatening human disease that has no other effective alternative treatment would be subject to the strictest criteria for approval for animal use.

CVM's post-drug-approval approaches include monitoring the development of antimicrobial resistance and collecting data on drugs used in food animal production.

Surveillance

Strengthening the approval process for antibiotics in food animals is only one piece of CVM's multifaceted approach to the resistance problem. Another important element is surveillance.

Researchers have already estab-

lished a link between antibiotic use in food animals and human disease. But information regarding where antibiotic resistance emerges, the extent of the threat, and the trends of resistance over time was limited before the creation in 1996 of the largest monitoring system for resistance in the United States—the National Antimicrobial Resistance Monitoring System (NARMS).

Through NARMS, scientists monitor both human and animal bacterial resistance to a panel of antimicrobials selected for their importance in human and animal medicine. As part of this joint effort by the CDC, the FDA, and the U.S. Department of Agriculture (USDA), NARMS scientists collect specific intestinal bacteria samples from people with diarrheal illness and test these samples for antimicrobial resistance at the CDC's laboratory in Atlanta. The NARMS program was recently expanded to include samples provided by 28

state and local public health laboratories across the country. The program continues to expand and adapt by adding new collection sites and different species of bacteria and antimicrobial drugs for evaluation.

Animal specimens for NARMS are collected from federally inspected slaughter and processing facilities as well as from healthy and ill animals on farms. These samples are then tested for antimicrobial resistance at the USDA's lab in Athens, Ga. In 2001, retail meat samples were added to NARMS, and testing began at the CVM's lab in Laurel, Md. Testing of additional retail meat samples, as well as animal feed ingredients, is being conducted in 2002.

Data provided through NARMS can help support new treatment guidelines, determine the effects of drug usage practices and intervention strategies, and shape national policy regarding the use of anti-

microbials in animals.

The high volume of international travel and food imports has intensified the risk of infectious agents and resistant pathogens crossing national borders. In a cooperative agreement with scientists in Mexico, the FDA is sharing its experience with NARMS to help establish a similar monitoring system in Mexico. This system will yield information that may one day be part of an international database, allowing comparison of trends among countries, enhanced food safety activities, improved detection of epidemics, and earlier responses to emerging pathogens on an international scale.

Research

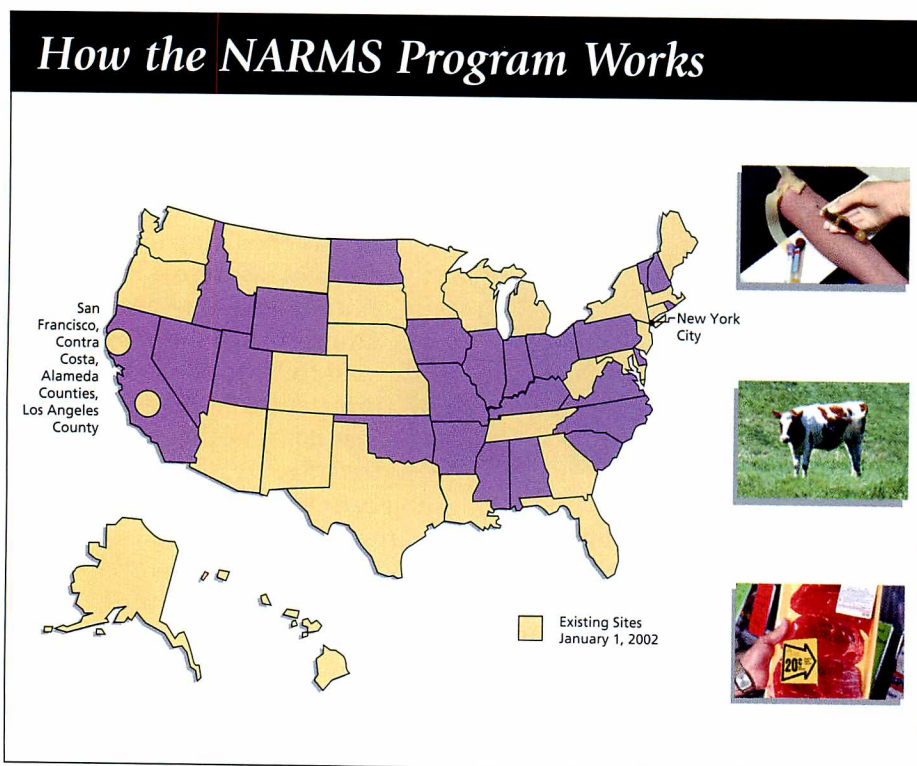
Scientists and health professionals are generally in agreement that a way to decrease antibiotic resistance is through more cautious use of antibiotic drugs and through monitoring outbreaks of drug-resistant infections.

But research is also critical to help understand the various mechanisms that pathogens use to evade drugs. Understanding these mechanisms is important for the design of effective new drugs.

The FDA's National Center for Toxicological Research (NCTR) is studying the mechanisms of resistance to antibiotic agents among bacteria from the human gastrointestinal tract, which can cause serious infections.

In addition, the NCTR has studied the amount of antibiotic residues that people consume in food from food-producing animals and the effects of these residues on human intestinal bacteria. This information led to a new approach for assessing the safety of antibiotic drug residues in people, which may be adopted by the FDA to help review drugs for food animals.

For more information on antibiotic resistance, see the FDA's Web site at www.fda.gov/oc/opacom/hottopics/anti_resist.html, and the CDC's Web site at www.cdc.gov/antibioticresistance. ■



Source: Centers for Disease Control and Prevention

The federal government monitors antibiotic resistance by collecting and testing certain kinds of bacteria from people with diarrheal illness. More than 25 state and local public health labs are part of this program, known as the National Antimicrobial Resistance Monitoring System (NARMS). Because antibiotic-resistant bacteria can be transmitted to humans through the food supply, samples also are collected and tested from slaughter and processing facilities, from healthy and ill animals on farms, and from retail meats.

New OTC Drug Facts Label

Whenever you use an over-the-counter (OTC) medicine, reading the drug label is important for taking care of yourself and your family. The label tells you what a medicine is supposed to do, who should or shouldn't take it, and how to use it. OTC medicine labels have always contained usage and safety information for consumers, but now the information will be more uniform and easier to read and understand.

Most OTC drug manufacturers were required to begin using the new, standardized label on the products beginning on May 16, 2002. The OTC regulation was finalized in March 1999, and manufacturers were given until the May 2002 effective date to change product labels. Manufacturers may still distribute products bearing older labels until their product inventories are exhausted.

The OTC labeling rule applies to more than 100,000 OTC drug products. Most OTC medicines manufactured after May 2002 will carry the new Drug Facts label. But certain OTC products, such as sunscreens, aren't required to use the format until 2005. Many manufacturers voluntarily used the new OTC label before the effective date, and the Food and Drug Administration estimates that a large number of medicines with the new labeling are already on store shelves.

Before simplifying the OTC label, the FDA conducted extensive research on how consumers use OTC drug labels. One major problem has been the readability of OTC drug labels, especially for older Americans, who purchase almost 30 percent of the nonprescription drugs sold in the United States. The FDA also found that consumers thought words like "indications," "precautions" and "contraindications" were too technical and confusing.

Previously, information about product directions, warnings and approved uses has appeared in different

places on the label depending on the OTC product and brand. Finding information about inactive ingredients has also been a challenge for those who may be allergic to an ingredient in a drug product.

Patterned after the Nutrition Facts food label, the new Drug Facts label uses simple language and an easy-to-read format to help people compare and select OTC medicines and follow dosage instructions. The following information must appear in this order:

- The product's active ingredients, including the amount in each dosage unit.
- The purpose of the medication.
- The uses (indications) for the drug.
- Specific warnings, including when the product should not be used under any circumstances, and when it is appropriate to consult with a doctor or pharmacist. The warnings section also describes side effects that could occur

and substances or activities to avoid.

- Dosage instructions addressing when, how, and how often to take the medication.
- The product's inactive ingredients, which is important information for those with specific allergies.

Along with the standardized format, the new drug label uses plain-speaking terms to describe the facts about each OTC drug. For example, "uses" replaces "indications," while other technical words like "precautions" and "contraindications" have been eliminated. The new label also requires a type size large enough to be easily read and specific layout details—bullets, spacing between lines and clearly marked sections—to improve readability.

If you read an OTC medicine label and still have questions about the product, talk to your doctor, pharmacist, or other health-care professional. ■

Drug Facts

Active ingredient (in each tablet)

Chlorpheniramine maleate 2 mg

Purpose

Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings

Ask a doctor before use if you have

■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product

■ You may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Other information store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Dietary Supplements and Animals

By Linda Grassie

Dietary supplements for pets and other animals have been marketed for many years; some are sold legally and others are not.

Dietary supplements for animals, such as most vitamin and mineral products, are considered animal feeds. Ensuring that animal feeds are safe and properly labeled—a requirement of the Federal Food, Drug, and Cosmetic Act—is part of the responsibilities of the FDA's Center for Veterinary Medicine (CVM).

Foods for animals do not require FDA approval before they are marketed, but they must be made with ingredients that meet at least one of the two following requirements:

- be approved food additives, or
- be substances that are "generally recognized as safe" (GRAS) for their intended use.

However, on a case-by-case basis, CVM has exercised enforcement discretion for substances that do not raise any safety concerns, often because the company has submitted the information needed to list the ingredient in the AAFCO *Official Publication*. The Association of American Feed Control Officials (AAFCO) includes officials from all the states, the U.S. federal government, Canada, and Costa Rica. These officials are responsible for enforcing the laws regulating the production, labeling, distribution, or sale of animal feeds. CVM often works with AAFCO in regulating animal feeds.

Some foods and other products containing dietary supplements for animals, such as St. John's wort, do not meet any of the requirements. And some "dietary supplement" products are being marketed to treat or prevent disease—for example, chondroitin sulfate to treat arthritis. This moves a product from the supplement category into the drug category. CVM officials, who also regulate animal drugs, are concerned



John Troha

that these products have not been shown to be safe and effective. And, some owners may be using these products instead of getting appropriate veterinary treatment for their animals.

Quite a few animal supplement products are being sold as a result of the Dietary Supplement Health and Education Act (DSHEA), passed by Congress in 1994, and these products generally contain ingredients similar to those in human dietary supplements. The FDA believes that DSHEA does not apply to animals, and that many of the products being sold are in violation of the Federal Food, Drug, and Cosmetic Act. The FDA published an explanatory notice to this effect in the *Federal Register* in 1996.

CVM officials are concerned about these products because there are no scientific data showing that they are safe or even contain the ingredients listed on the label. These concerns focus on three main areas:

- **Human food safety**—Supplements that are used in food animals must be shown to be safe for people who consume products from the animals.

Without these data, there is no assurance that an animal-derived food is safe.

- **Animal safety**—Supplements must be shown to be safe for the animals. CVM and AAFCO have not received data showing that these products have actually been tested on animals to show that a particular level is appropriate or safe for the animals.

- **Manufacturing quality**—Supplements must be shown to be manufactured to a consistent standard (for example, shown to contain a given amount of the ingredient).

CVM cautions people to check with their veterinarians before giving their pets or other animals any supplements, whether alone or in a food product. "Many people do not appreciate that dogs and cats are not small furry people," says CVM's pet food specialist William Burkholder, D.V.M., Ph.D. "They often think that a supplement that they may take themselves is good for their pet, but that may not be the case." ■

Linda Grassie is a public information specialist in the FDA's Center for Veterinary Medicine.

By John Henkel

Weighing In on Body Mass

The latest government figures show that about 60 percent of U.S. adults are either overweight or obese. Health professionals find this number unsettling because research has shown that excess weight and obesity place people at increased risk for many serious disorders, including high blood pressure, high cholesterol, diabetes, stroke, and some types of cancer.

One indicator of overweight individuals is body mass index (BMI), a number that can signal cause for concern when it reads 25 or more. But what is BMI? How is it determined? What does the number tell you about your health? The answers and much more can be found at the Nutrition and Physical Activity site run by the federal Centers for Disease Control and Prevention (www.cdc.gov/nccdphp/dnpa/bmi). The site has a handy calculator for easily figuring your BMI (for the math-inclined, the BMI formula is your weight divided by your height squared, or wt/ht^2). The site also explains how to interpret BMI for children, an important consideration in light of research quoted on the site showing that about 13 percent of U.S. children and adolescents are "seriously overweight."

The Web site points out that though BMI can be a strong predictor of serious disorders, the exact role BMI plays varies by individual. Other information must be factored in by a health-care professional to determine if a high BMI is associated with risk of disease or death in each person.

For more on the subject, see "Overweight, Obesity Threaten U.S. Health Gains" in the March–April 2002 *FDA Consumer* (www.fda.gov/fdac/features/2002/202_fat.html), and "Losing Weight: More than Counting Calories" in the January–February 2002 issue (www.fda.gov/fdac/features/2002/102_fat.html).

The Place to Go for Science Info

Finding specific science information from the many research- and technology-oriented agencies in the federal government can be a science in itself. But now there is an easy shortcut.

FirstGov for Science (www.science.gov), offers a gateway to a massive amount of federal science material geared to what the site calls "science-attentive citizens," a group that includes consumers, science professionals, students, educators, and entrepreneurs.

Fourteen federal agencies and de-

partments created the site by compiling science information with the widest appeal. The site has two features:

- a browsable directory of individual Web sites on science topics such as agriculture, computers, the environment, health, and science education
- a catalog of databases of technical reports, journal articles, conference proceedings, and other published material on science.

FirstGov for Science is one of several "cross-agency portals" hosted by *FirstGov* (www.firstgov.gov), a site that offers easy access to federal and state information and services.

Here Are the Facts on Cell Phones

The FDA has joined with the Federal Communications Commission to create *Cell Phone Facts*, a special Web site loaded with helpful background for users of the millions of wireless phones in operation across the United States.

At www.fda.gov/cellphones, the site allows browsing by category of interest such as base stations, standards, and safety concerns. Many users will find this feature adequate for basic information about cell phones. But for those who want to delve more deeply into cell phone operation, the site has an extensive list of questions

and answers that discuss hands-free sets, head shields, cell-phone research, and other wireless-related subjects.

The new Web site summarizes the government's safety standards for cell phones and describes the role of both the FDA and the FCC in regulating the safety of the radio frequency (RF) energy that is transmitted from cell phones. It also defines:

- how RF energy is used and measured
- how current safety standards were established
- the role of local and state governments
- where to obtain additional information from other sources.

Got Questions About Foods?

What's the best way to clean a kitchen counter? Does freezing affect nutrients in foods? How do you know if fish is fresh? What's the safest way to prepare eggs?

If you have questions like these, you can get answers to them and many other food-related queries at the "Consumer Advice" Web site maintained by the FDA's Center for

Food Safety and Applied Nutrition. At www.cfsan.fda.gov/~lrd/advice.html, you can learn more about using slow cookers, eating raw oysters, using food thermometers, defrosting foods, safely preparing school lunches, and taking dietary supplements. The site also has information about non-food subjects such as cosmetics and women's health. And a links section points you to other federal agency Web sites with valuable consumer information. ■

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



Florida Couple Admits Using Phony Treatment to Attract Clients

By Carol Lewis

A Florida couple who admitted using an illegal magnetic device to "treat" thousands of people suffering from the pain of arthritis and other conditions must repay the government nearly three times the amount they received in fraudulent reimbursements.

Richard Markoll and his wife, Ernestine Binder Markoll, of Boca Raton, Fla., pleaded guilty to a felony charge of conspiracy to violate the Federal Food, Drug and Cosmetic Act (FD&C Act). Richard Markoll also pleaded guilty to a felony violation of the FD&C Act. His wife pleaded guilty to a misdemeanor violation of the Act. In addition, Richard Markoll pleaded guilty to mail fraud on behalf of his corporation, Magnetic Therapy Scovill Street Inc.

The Markolls treated over 2,000 people with the Electro-Magnetic Induction Treatment System (EMIT device). They billed Medicare and other private insurance companies \$1.5 million for the "treatments" through clinics called Magnetic Therapy Center of Waterbury, Conn., Bio-Magnetic Therapy Center of Danbury, Conn., and Bio-Magnetic Therapy Center of Melville, Long Island. All the people treated at the clinics were covered by the Medicare program.

The EMIT device, which Richard Markoll invented to treat arthritis and other physical conditions, consisted of either a small tabletop unit or a larger bed-type unit. The device directed low-frequency magnetic pulses through coils of electric wire to create a pulsed electromagnetic field. An affected joint, such as a knee, elbow, back, or shoulder area, was placed inside an attached circular unit for a selected period of treatment time.

Richard Markoll first sought approval of the EMIT device from the Food and Drug Administration in 1980. The agency denied his request, citing that it was not determined to be safe and effective. All subsequent requests also were denied for the same reasons.

Under the FD&C Act, it is illegal to commercially use a medical device for treatment of specific illnesses if it has not been approved by the FDA. Nevertheless, between 1990 and 1994, the Markolls operated their clinics as though the device had been approved by billing Medicare and private insurance companies for reimbursement. Concurrently, they told patients at their clinics that they were conducting clinical trials on the device to determine its safety and effectiveness in order for it to be approved by the FDA.

Patients were subjected to 18 half-hour treatments with

the EMIT device, blood tests, X-rays, and an evaluation by a physician at the beginning, middle, end, and one month following the end of the course of treatment. However, no state-licensed medical doctor worked at any of the clinics full time. The few licensed physicians hired to work part time were not considered to be responsible for supervising all of the services being performed. According to FDA investigators, Richard Markoll, who holds a medical degree but is not licensed to practice medicine in any state, or his unlicensed employees performed all services related to the "treatments."

The Markolls admitted submitting claims for the treatments to Medicare and other private insurance companies, which generally do not reimburse for medical services that are investigational or are performed with medical devices not approved by the FDA. To get around this roadblock, the Markolls used the Medicare provider numbers of two licensed physicians—with their permission—to falsely bill Medicare by using the billing codes for legitimate medical services. The husband-and-wife team falsely certified that the medical services were performed or supervised by the billing physician.

Following a December 1993 letter from the FDA concerning the company's application to market the device, which cited the agency's concerns about reliability and safety, Markoll informed the FDA that he would immediately terminate patient enrollment in studies. But the studies continued until the FDA intervened.

In addition to the company's \$4 million payment due within 18 months of the August 14, 2001, sentencing date, Richard Markoll was placed on three years probation and ordered to pay a \$4,000 fine and a special assessment fee of \$100. His wife was placed on probation for two years and ordered to pay a \$1,000 fine and a special assessment fee of \$25. Magnetic Treatment Center, the professional corporation of a Huntington, N.Y. internist, also agreed to reimburse \$600,000 to the government to settle claims that his provider number was improperly used by both his company and the clinics operated by the Markolls.

Special agents from the FDA's Office of Criminal Investigations worked on this case with agents from the Office of Inspector General, Defense Criminal Investigative Service, the U.S. Postal Service, and the FBI's Health Care Fraud Task Force. ■

We Can't Forget the Value of Vaccines

By Paul D. Parkman, M.D.



I worry about people who mistrust vaccines and do not have their children immunized. With the exception of safe drinking water, vaccines have been the most successful medical interventions of the 20th century.

When I was in medical school in the 1950s, I learned about the mild, rash illness rubella (German measles). An Australian eye doctor, Norman

McAllister Gregg, knighted for his discovery, had shown that rubella caused serious birth defects in babies born to mothers infected early in pregnancy. I also learned that rubella vaccine development had been stymied because the virus had not been grown in cell culture.

As a young pediatrician-in-training, I was often called to the delivery room to give newly born infants their first medical exam. One day, I saw a baby that was stillborn. It seemed normal except for a rash—spots caused by bleeding into the skin. I went to talk with the baby's mother. She wanted to see her baby, and I was uncertain about what to do. But I retrieved the stillborn baby and rolled the bassinet with its sad cargo down the hall to her. Years later, I realized that her infant's death was likely the consequence of her having acquired rubella months earlier. Many thousands of babies with similar rashes, often accompanied by severe congenital deformities, died during the last major rubella epidemic in 1964. During this time, women very much feared the disease. And with good reason.

By 1961, as a young military doctor at the Walter Reed Army Medical Center, I had the chance to try to find this elusive virus. I was lucky enough to do so with two colleagues, Drs. Malcolm Artenstein and Edward Buescher. One of the many laboratory techniques we tried worked! From that day in May of 1961, the development of rubella vaccine became possible.

Spurred by the fear that another severe epidemic might occur within a few years, live virus vaccines were developed quickly, and several had been approved by 1969. Now, for decades, these products have been extensively used for immunizing infants, children, and certain adult populations in special need of protection.

As a result, the predicted epidemic of the 1970s never occurred. Nor has there been one since. In fact, instead of the many thousands of infants born with birth defects every year due to rubella, there have been fewer than 10 cases, often only one to three.

This is wonderful! So why do I worry? Because if we do not keep a high level of immunization, rubella and the other diseases we have controlled in the United States will regain a foothold and again become a threat. These illnesses still exist, particularly in the developing world, and could easily return to infect the unimmunized. Past examples that show this include the resurgence of whooping cough in the United Kingdom and Japan when parents failed to have their children vaccinated.

The world has changed since mid-20th century. Mothers no longer fear their children will be sickened by paralytic polio or measles, or that they will catch rubella. The real concerns of another age seem to have been replaced by theoretical concerns that vaccines themselves will be responsible for ill effects.

These concerns are common among young mothers. A friend's daughter, usually eminently sensible, decided not to have her children immunized because of these fears. I wrote to my friend (and through him, to her) appealing that she should heed the advice of scientists independent of those she suspects—the federal government, commercial vaccine producers, and medicine generally—who have concluded that the benefits of vaccinations far outweigh their risks. I found it chilling that I was ineffective in changing her mind.

As I look back on my career, I have come to think that perhaps I was involved in the easy part. It will be for others to take on the difficult task of maintaining the protections that we struggled to achieve. We must prevent the spread of this vaccine nihilism, for if it were to prevail, our successes could be lost. ■

Paul D. Parkman, M.D., served as director of the FDA's Center for Biologics Evaluation and Research from 1987 to 1990. He is a consultant for Parkman Associates in Kensington, Md.



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