Center for Drug Evaluation and Research

CDER 1999 Report to the Nation

Improving Public Health Through Human Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

MISSION

The Center for Drug Evaluation and Research promotes and protects public health by assuring that safe and effective drugs are available to Americans. The Food and Drug Administration Modernization Act of 1997 affirmed the center's public health protection role, clarified the FDA's mission and called for the FDA to:

1. Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner.
2. Protect the public health by ensuring that human drugs are safe and effective.
3. Participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.
4. Carry out its mission in consultation with experts in science, medicine and public health and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of human drugs.

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INTRODUCTION

Who we are

The Center for Drug Evaluation and Research is America's consumer watchdog for medicine. We are part of one of the nation's oldest consumer protection agencies—the Food and Drug Administration. The FDA is an agency of the federal government's Department of Health and Human Services. We are the largest of FDA's five centers, with nearly 1,700 employees. Approximately half of us are physicians or other kinds of scientists. Many of us have experience and education in such fields as computer science, legal affairs and regulatory matters.

What we do

Our best-known job is to evaluate new drugs for safety and effectiveness before they can be sold. Our evaluation, called a review, makes sure that the drugs we approve meet our tough standards for safety, effectiveness and quality. We also make sure that you and your doctor will have the information you need to use medicines wisely. Once drugs are on the market, we monitor them for problems.

Reviewing drugs before marketing. A drug company seeking to sell a drug in the United States must first test it. We monitor clinical research to ensure that people who volunteer for studies are protected and that the quality and integrity of scientific data are maintained. The company then sends us the evidence from these tests to prove the drug is safe and effective for its intended use. We assemble a team of physicians, statisticians, chemists, pharmacologists and other scientists to review the company's data and proposed use for the drug. If the drug is effective and we are convinced its health benefits outweigh its risks, we approve it for sale. We don't actually test the drug when we review the company's data. By setting clear standards for the evidence we need to approve a drug, we help medical researchers bring new drugs to American consumers more rapidly. We also review drugs that you can buy over-the-counter without a prescription and generic versions of over-the-counter and prescription drugs.

Watching for drug problems. Once a drug is approved for sale in the United States, our consumer protection mission doesn't stop. We monitor the use of marketed drugs for unexpected health risks. If new, unanticipated risks are detected after approval, we take steps to inform the public, change how a drug is used or even remove a drug from the market. We also monitor manufacturing changes to make sure they won't adversely affect the safety or efficacy of the medicine. We evaluate reports about suspected problems from manufacturers, health care professionals and consumers. Sometimes, manufacturers run into production problems that might endanger the health

What is a drug?

We regulate drugs used to treat, prevent or diagnose illnesses. However, drugs include more than just medicines.

For example, fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered "drugs."

You can buy some drugs in a store without a prescription, while others require a doctor's prescription. Some are available in less-expensive generic versions.

Prescription drugs

Prescription medicines must be administered under a doctor's supervision or require a doctor's authorization for purchase. There are several reasons for requiring a medicine be sold by prescription:

- **The disease or condition may be serious and require a doctor's management.**
- **The medicine itself may cause side effects that a doctor needs to monitor.**
- **The same symptoms can be caused by different diseases that only a doctor can diagnose.**
- **The different causes may require different medicines.**
- **Some medicines can be dangerous when used to treat the wrong disease.**

of patients who depend on a drug. We try to make sure that an adequate supply of drugs is always available.

Monitoring drug information and advertising. Accurate and complete information is vital to the safe use of drugs. Drug companies have historically promoted their products directly to physicians. More and more frequently now, they are advertising directly to consumers. While the Federal Trade Commission regulates advertising of over-the-counter drugs, we oversee the advertising of prescription drugs. Advertisements for a drug must contain a truthful summary of information about its effectiveness, side effects and circumstances when its use should be avoided. We are monitoring the industry's voluntary program to provide consumers useful information about prescription drugs when they pick up their prescriptions. We are watching this program closely to see that it meets its goals for quantity and quality of information.

Protecting drug quality. In addition to setting standards for safety and effectiveness testing, we also set standards for drug quality and manufacturing processes. We work closely with manufacturers to see where streamlining can cut red tape without compromising drug quality. As the pharmaceutical industry has become increasingly global, we are involved in international negotiations with other nations to harmonize standards for drug quality and the data needed to approve a new drug. This harmonization will go a long way toward reducing the number of redundant tests manufacturers do and help ensure drug quality for consumers at home and abroad.

Conducting applied research. We conduct and collaborate on focused laboratory research and testing. Research maintains and strengthens the scientific base of our regulatory policy-making and decision-making. We focus on drug quality, safety and performance; improved technologies; new approaches to drug development and review; and regulatory standards and consistency.

Why we do it

Our present and future mission remains constant: to ensure that drug products available to the public are safe and effective. Our yardstick for success will always be protecting and promoting the health of Americans.

Getting consumer input. Protecting consumers means listening to them. We routinely consult the American public when making decisions about the drugs that they use. We hold public meetings about once a week to get expert, patient and consumer input into our decisions. We also announce many of our proposals in advance. This gives members of the public, academic experts, industry, trade associations, consumer groups and professional societies the opportunity to comment and make suggestions before we make a final decision. In addition, we take part in a series of FDA-sponsored public meetings with consumer and patient groups, professional societies and pharmaceutical trade associations. These stakeholder meetings help us obtain enhanced public input into our planning and priority-setting practices.

Over-the-counter drugs

You can buy OTC drugs without a doctor's prescription.

You can successfully diagnose many common aliments and treat them yourself with readily available OTC products.

These range from acne products to cold medications.

As with prescription drugs, we closely regulate OTC drugs to ensure that they are safe, effective and properly labeled.

Generic drugs

A generic drug is a chemical copy of a brand name drug.

There are generic versions of both prescription and over-the-counter drugs. Generic drugs approved by the FDA have the same therapeutic effects as their brand name counterparts.

Brand name firms, as well as generic firms, make generic drugs.

The biggest difference between a generic drug and its brand name counterpart is usually price. A generic drug may be priced anywhere between 20 percent and 75 percent of the cost of the brand name version.

1999 HIGHLIGHTS

We are pleased to present our fourth performance report. Our work last year offered many Americans new or improved choices for protecting and maintaining their health or new ways to use existing products more safely. We began the process of engaging our stakeholders in an national effort to improve the nation's multicomponent, complex system for managing the risks and benefits associated with using medicines.

Drug Review

Children, older Americans at risk for stroke, people with rare disorders, Parkinson's disease, cancer and AIDS all benefited from significant new drugs approved in 1999. We met our obligations to the pharmaceutical industry for prompt and thorough review of drug applications supported by user fees. Our reviews of generic drugs have been prompt and predictable despite the growing complexity of drugs coming off patent. We approved 83 new drugs, including 35 new molecular entities. New molecular entities contain an active substance never before approved for marketing in any form in the United Sates. We also approved 97 new or expanded uses of already approved drugs, four over-the-counter drugs and 186 generic drugs.

Drug safety and quality

All medicines have risks. Injuries from approved medicines may rank among the top 10 causes of death in the United States. With modern, state-of-the-art tools and techniques, we are able to detect rare and unexpected risks more rapidly and take corrective action more quickly. With our colleagues in the FDA's other medical product centers, we conducted a study of the system that has evolved in this country to maximize the benefits of the use of medicines and minimize their risks. We trained our own staff on modern methods of risk management and began the process of using our influence to begin a dialogue with other components of the system.

International activities

We worked closely with our colleagues in Japan and the European Union on finding ways to make the drug development process more efficient and uniform. Our goal is to shorten drug development times, while learning the most, to make new medicines available with minimum delay. We neared completion of a common technical document that can be used to submit a marketing application in all three regions. We began the first year of a three-year implementation process for the Mutual Recognition Agreement with the European Union. This agreement will allow reciprocal reliance on inspections of pharmaceutical manufacturing plants.

Y2K drug shortage assurance

We surveyed the pharmaceutical industry on their preparedness for the Y2K transition and launched a successful information campaign to allay public fears of drug shortages.

Antibiotic resistance

We play an active role on FDA's antibiotic resistance coordinating committee to address the growing problem of antibiotic resistance and its effects on drug development and regulation. We are developing approaches to provide education and information on the appropriate use of antibiotics to health care professionals and consumers.

Communications

We continued our efforts begun in 1998 to include greater input into our planning and decision making from consumers, patients, health-care professionals, academia and industry.

We revamped our Internet site to make it more interactive and intuitive to use. We include cross-linked information on all new medicines approved since January 1998. This includes plain language information for consumers and technical information for health professions.

We executed the first phase of an information campaign to introduce the public to the new over-the-counter drug labels.

We remain a trusted and reliable source of information on drugs. We had thousands of contacts with members of the public, health professional, sate and local public health officials and the industry.

Scientific Research

We focus on advancing the scientific basis of regulatory policy by developing new scientific methods and regulatory testing paradigms and by providing scientific support for the development of regulatory policy. We have focused specifically on creating tighter linkage between nonclinical and clinical studies, enhancing the methodology for assuring product quality, building databases for improved drug development and review and providing regulatory support through laboratory testing.

We continue to seek ways to leverage our scientific resources. We collaborated with a scientific professional society and pharmaceutical trade associations to create the Product Quality Research Institute as a nonprofit corporation. The institute will bring our scientists together with those from academia and industry to identify better test methods for assessing the quality of drugs and to improve manufacturing and management processes.

Other key scientific achievements include:

- Streamlining the productivity of laboratory programs that are used as an important analytical part of the new and generic drug review process.
- Refocusing our metabolism research program to examine liver toxicity issues.
- Developing behavioral assessments and noninvasive imaging techniques to detect and predict drug induced toxicity to the nervous system.
- Investigating practical biomarkers to detect and predict drug-induced damage to blood vessels.
- Developing improved animal models and skin biomarkers for drug-enhanced tendency to develop skin cancer.
- Strengthened support for alternative transgenic mouse models that take less time to test the cancer-causing potential of drugs.
- Enhancing our computational toxicology software to improve drug safety and provide better support to the drug development and review process.

Scientific excellence

We received the 2000 FDA Scientific Achievement Award for developing and implementing a guidance on that established a mechanistic basis for correlating *in vitro* drug product dissolution and *in vivo* bioavailability. The award recognizes the importance of collaboration between research and review staff to establish policy.

Alternative methods for toxicology testing

Last year, we assumed leadership of FDA's participation on the Interagency Coordinating Committee on the Validation of Alternative Methods. The committee, with representatives from 14 federal regulatory and research agencies, works on the validation, acceptance and harmonization of toxicological test methods. This process serves our needs for responding to alternative testing initiatives and provides a mechanism to interact with developers of such tests.

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DRUG REVIEW

Mission

We promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner.

Many Americans benefited from last year's timely reviews of new prescription medicines, over-the-counter medicines and their generic equivalents. We met or exceeded nearly all goals for reviews supported by manufacturer user fees. We approved 35 new medicines that have never been marketed before in this country, 186 generic versions of existing drugs and authorized four medicines to be sold over the counter without a prescription. Highlights of new medication options for American consumers include:

- Three treatments for rare cancers.
- Three drugs for breathing disorders in infants.
- A new protease inhibitor to be used in combination therapy for HIV infection.
- The second Cox-2 inhibitor to treat arthritis.
- A new treatment for atrial fibrillation, a type of irregular heartbeat.
- Two drugs for type II diabetes that help the body make better use of insulin.
- A therapy to reduce the risk of stroke in people who have had a stroke or transient ischemic attack.
- The first in a new class of drugs that enhance standard therapy for Parkinson's disease.
- The first in a new class of medicines to prevent organ rejection after transplant.
- Twelve new drugs for orphan uses in patient populations of 200,000 or fewer.
- Four new orphan uses for already approved drugs.

1999 drug review accomplishments:

83 new drugs

35 new molecular entities

97 new uses for already approved drugs

4 over-the-counter drugs

4 new uses for an over-the-counter drug

186 generic equivalents for prescription and over-the counter drugs

43 first-ever generic approvals

16 orphan uses

New Drug Review

We took 190 actions on original new drug applications, of which 83 were approvals. The proportion of total actions that are approvals has risen steadily from under one-third in 1993 to approximately half in recent years. The lower number of actions represents a decline in the number of applications submitted to us. The higher percentage of approvals in recent years stems from our increased predictability and accountability and improved performance on the part of manufacturers.

New drug statistics:

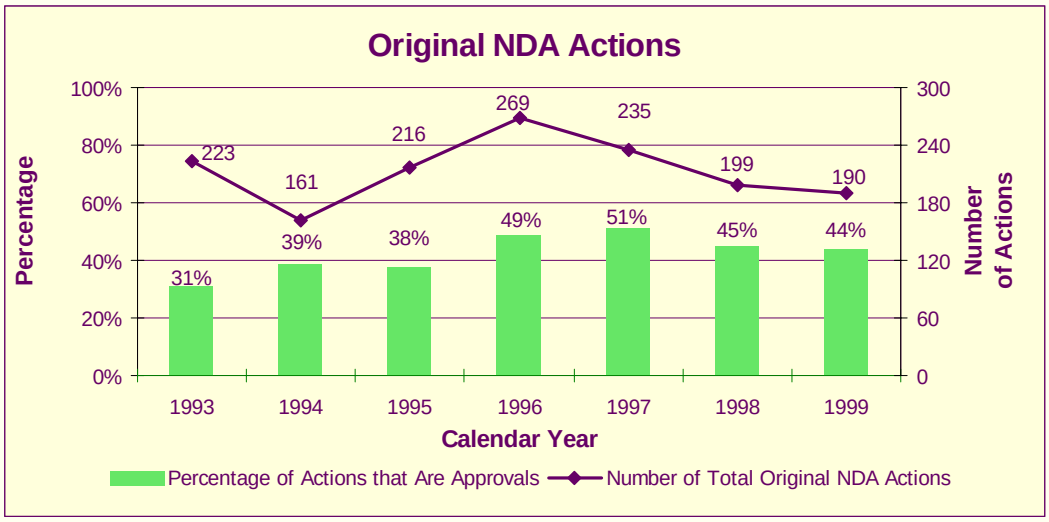
- **83 new drugs**
- **35 new molecular entities**
- **28 priority approvals**
- **Median total approval time: 12.0 months**
- **Median FDA review time: 11.8 months**

Total original NDA approvals

The median total approval time for new drugs acted on in 1999 was 12.0 months, the same as in 1998. Approval time represents the total review time at the Agency plus industry response time to the Agency's requests for additional information. The median FDA review time—FDA time only—was slightly shorter at 11.8 months. Twelve of the NDAs were approved for "orphan" uses in patient populations of 200,000 or fewer. In 1998, nine NDAs were approved for orphan uses.

Priority reviews

Last year's new drug approvals included 28 priority drugs. We perform a six-month review on priority drugs because these drugs represent an advance in medical treatment. The median total approval time for these priority applications was 6.1 months, and the median FDA review time was also 6.1 months.



New molecular entity approvals

Thirty-five of the original new drugs we approved in 1999 were new molecular entities, and 19 of these received priority approvals. The median total approval time for NMEs was 11.6 months. NMEs contain an active substance that has never before been approved for marketing in any form in the United States. The median FDA review time was 10.0 months. Sixteen of the 30 NMEs approved in 1998 were priority reviews. Eight of the 1999 NMEs were for orphan uses compared to seven in 1998.

Priority new drug approvals:

Alitretinoin

Amprenavir (2 dosage forms)

Aspirin/extended release-dipyridamole

Bexarotene

Busulfan

Caffeine citrate

Cytarabine liposome

Dalfopristin/quinupristin

Epirubicin hydrochloride

Ganirelix acetate

Ketotifen fumarate

Levonorgestrel

Nedocromil sodium

Nitric oxide

Orlistat

Oseltamivir phosphate

Pemirolast potassium

Pioglitazone hydrochloride

Rofecoxib (2 dosage forms)

Rosiglitazone maleate

Sirolimus

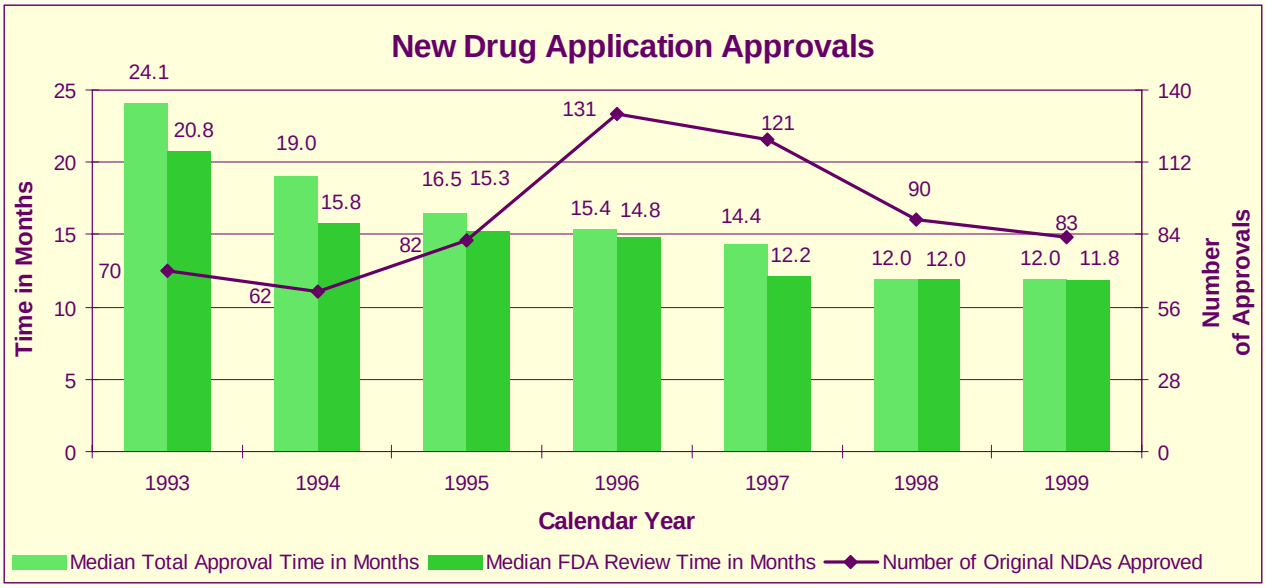
Sodium ferric gluconate

Somatropin (rDNA origin)

Technetium Tc 99m depreotide kit

Temozolomide

Zanamivir



1999 new molecular entities:

Alitretinoin (Panretin)

Aminolevulinic acid hydrochloride (Levulan Kerastick)

Amprenavir (Agenerase)

Bexarotene (Targretin)

Cilostazol (Pletal)

Dalfopristin/quinupristin (Synercid)

Dexmedetomidine hydrochloride (Precedex)

Dofetilide (Tikosyn)

Doxercalciferol (Hectorol)

Entacapone (Comtan)

Epirubicin hydrochloride (Ellence)

Exemestane (Aromasin)

Gadoversetamide (Optimark)

Ganirelix acetate (Antagon)

Notable 1999 new drug approvals

Last year's approvals benefited people with rare disorders, those with HIV infection, older Americans and people with diabetes and other disorders.

People with rare diseases

Twelve of the new drugs approved last year are for rare diseases with patient populations too small to make the development of such drugs and devices routinely profitable. We approve these drugs under the 16 year-old Orphan Drug Program which grants special privileges and marketing incentives for drugs that treat conditions affecting fewer than 200,000 Americans.

Bexarotene (Targretin) offers new hope for patients with rare forms of cancer, including those who have advanced or recurrent cutaneous T-cell lymphoma, a slow-growing form of non-Hodgkin's lymphoma, and who have not been helped by other treatments. *Epirubicin hydrochloride injection (Ellence)* treats early stage breast cancer that has spread to the lymph nodes under the arm and has been treated surgically. Epirubicin is commonly used in combination with other medications to slow or halt the progression of cancer. Adult patients who have anaplastic astrocytoma, a rare form of brain cancer, and who have relapsed after chemotherapy can now be treated with *temozolomide (Temodar)*.

Infants and children with rare diseases could benefit from several new drugs approved under the Orphan Drug Program. *Caffeine citrate (Cafcit)* is a short-term pediatric treatment for apnea (breathing interruptions), and *poractant alfa (Curosurf)* can be used for relief from the respiratory distress syndrome. Another new product for respiratory failure in term or near-term infants is *nitric oxide (INOmax)*.

1999 new molecular entities (continued)

Gatifloxacin (Tequin)

Ketotifen fumarate (Zaditor)

Levetiracetam (Keppra)

Mequinol/tretinoin (Solage)

Moxifloxacin hydrochloride (Avelox)

Nitric Oxide (INOmax)

Orlistat (Xenical)

Oseltamivir phosphate (Tamiflu)

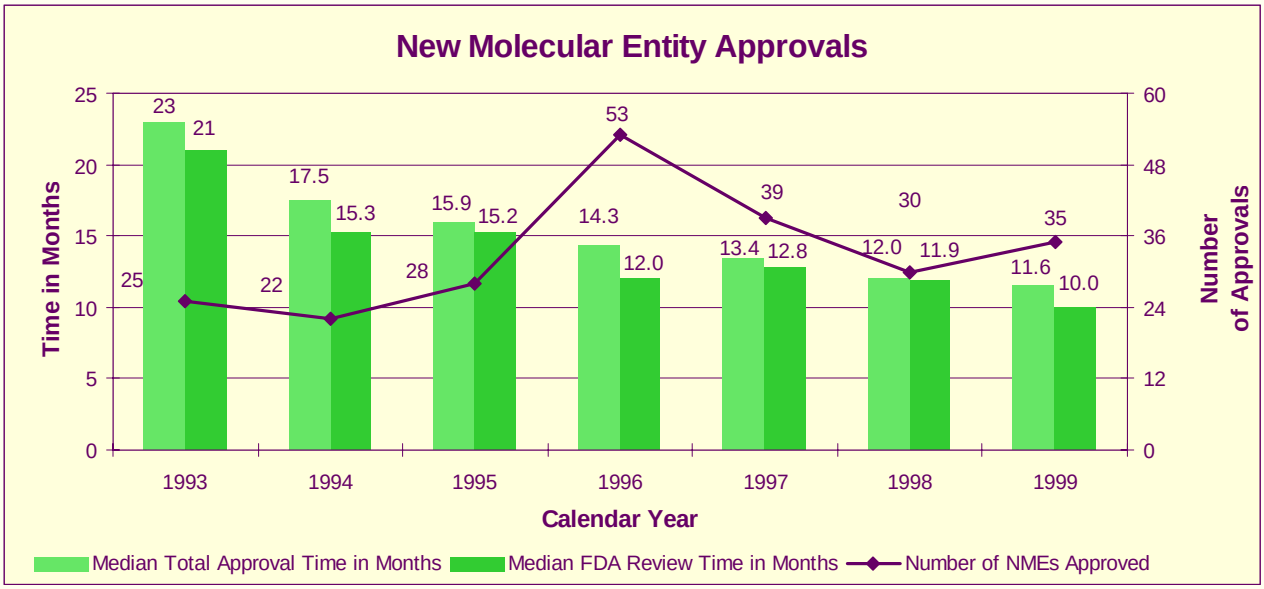
Pemirolast potassium (Alamast)

Pioglitazone hydrochloride (Actos)

Poractant (Curosurf)

Rabeprazole sodium (Aciphex)

Rapacuronium bromide (Raplon)



1999 new molecular entities (continued)

Rofecoxib (Vioxx)

Rosiglitazone maleate (Avandia)

Sirolimus (Rapamune)

Sodium ferric gluconate complex (Ferrlicet)

Technetium Tc 99m depreotide kit (NeoTect)

Temozolomide (Temodar)

Zaleplon (Sonata)

Zanamivir (Relenza)

People with Cancer

In addition to *epirubicin (Ellence)*, which was approved under the Orphan Drug Program, we approved *exemestane (Aromasin)* for advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. A potentially cancer-preventing product is *aminolevulinic acid hydrochloride (Levulan Kerastick)*, the first drug/device for the treatment of precancerous skin lesions on the face and scalp.

People with HIV and AIDS

Amprenavir (Agenerase), a new protease inhibitor received an accelerated approval for use in children as young as 4 and in adults in combination with other anti-retrovirals for HIV infection. Amprenavir is one of five protease inhibitors that attempt to prevent HIV from making new copies of itself by interfering with the HIV protease enzyme. Another new HIV product is *alitretinoin (Panretin)*, a topical gel for the treatment of skin lesions in patients with AIDS-related Kaposi's sarcoma.

Older people

Rofecoxib (Vioxx), a new drug for treatment of osteoarthritis, menstrual pain and the management of acute pain in adults, is a type of nonsteroidal anti-inflammatory drug (NSAID) known as a "Cox-2 inhibitor." NSAIDs temporarily relieve pain by blocking the body's production of prostaglandins, the chemicals believed to be associated with the pain and inflammation of injuries and immune reactions.

A combination of *aspirin and extended-release dipyridamole (Aggrenox)* reduces the risk of stroke in people who have had transient ischemia attack or completed stroke. *Dofetilide (Tikosyn)* is an anti-arrhythmic agent for the maintenance and conversion of normal sinus rhythm in patients with highly symptomatic atrial fibrillation and atrial flutter, types of irregular heartbeats. *Cilostazol (Pletal)* is for treating stable intermittent claudication, a severe pain, aching or cramping in the legs that occurs with walking. *Entacapone (Comtan)* enhances the benefits of standard treatment for

New molecular entity statistics

- **35 approvals**
- **19 priority reviews**
- **Median total approval time: 11.6 months**
- **Median total FDA review time: 10.0 months**

Median time

The median time is a value that falls in the middle of all times. It provides a truer picture of performance than average time, which can be unduly influenced by a few extremely long or short times.

Information on average, or mean, approval times and other statistics are available on our Web site at http://www.fda.gov/cder/rdmt/default.htm.

Parkinson's disease. *Zaleplon (Sonata)* is for the short-term treatment of insomnia in adults, including elderly patients.

People with Diabetes.

Patients with type II or adult-onset diabetes who are not adequately controlled by diet and exercise alone can be treated with *pioglitazone (Actos)* or *rosiglitazone (Avandia).* These medicines are members of the thiazolidinedione class of drugs that can improve the body's ability to use insulin.

Infectious diseases

Dalfopristin and quinupristin injection (Synercid) is the first antibacterial drug to treat infections caused by vancomycin-resistant *Enterococcus faecium,* which has become highly resistant to older antibiotics. This drug was also approved for complicated skin and skin structure infections. *Gatifloxacin (Tequin)* is a new type of quinolone antibiotic for treating community-acquired respiratory tract infections such as pneumonia, acute exacerbation of chronic bronchitis and acute sinusitis. *Moxifloxacin hydrochloride (Avelox)* is a once-a-day antibiotic to treat common respiratory tract infections, including bacterial exacerbations of chronic bronchitis, community-acquired pneumonia of mild to moderate severity and acute bacterial sinusitis.

Two anti-viral therapies treat people infected with the virus that causes influenza. These are *zanamivir (Relenza),* an inhaled drug for adults and adolescents who are 12 or older, and *oseltamivir phosphate (Tamiflu),* a capsule indicated for onset of influenza A and B.

Other significant approvals

Dexmedetomidine hydrochloride (Precedex) is a sedative for people in intensive care settings who have undergone major surgery. *Doxecalciferol (Hectoral)* helps manage secondary hyperparathyroidism in patients undergoing chronic renal dialysis. *Gadoversetamide (OptiMARK)* is a magnetic resonance imaging agent to help diagnose lesions, including tumors, of the brain, spine and liver. *Ganirelix acetate (Antagon)* reduces *in vitro* fertilization treatment times from four weeks to about 10 days and simplifies treatment regimens. *Ketotifen fumarate (Zaditor)* is an ophthalmic solution for the temporary relief of itchy eyes due to allergic conjunctivitis. *Levetiracetam (Keppra)* is a new epilepsy drug that helps control partial onset seizures in adults. *Orlistat (Xenical)* is a lipase inhibitor to treat obesity.

Rabeprazole sodium (Aciphex) is a once-a-day proton pump inhibitor to heal duodenal ulcers and erosive gastroesophageal reflux disease. *Pemirolast potassium (Alamast)* is an ophthalmic solution to prevent itchy eyes caused by allegic conjunctivitis. *Rapacuronium bromide (Raplon)* is an adjunct to general anesthesia to facilitate tracheal intubation and provide skeletal muscle relaxation. *Sirolimus (Rapamune)* is the first in a new class of immunosuppressant agents that prevent organ rejection in people with transplants. *Sodium ferric gluconate (Ferrlecit)* treats iron deficiencyin end-stage renal disease for patients in hemodialysis who are receiving erythropoietin therapy. The *technetium Tc 99m depreotide kit (NeoTect)* is for imaging suspected malignant tumors in the lung.

Orphan new drug approvals

***Alitretinoin (Panretin),* a topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma**

***Bexarotene (Targretin)* for treating cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy**

***Busulfan (Busulfex)* as a preparative therapy in the treatment of malignancies with bone marrow transplantation**

***Caffeine citrate (Cafcit)* for apnea of prematurity**

***Cytarabine (Depocyt)* for neoplastic meningitis**

***Epirubicin hydrochloride (Ellence)* as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer**

***Exemestane (Aromasin)* for treating advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy**

Orphan new drug approvals (continued)

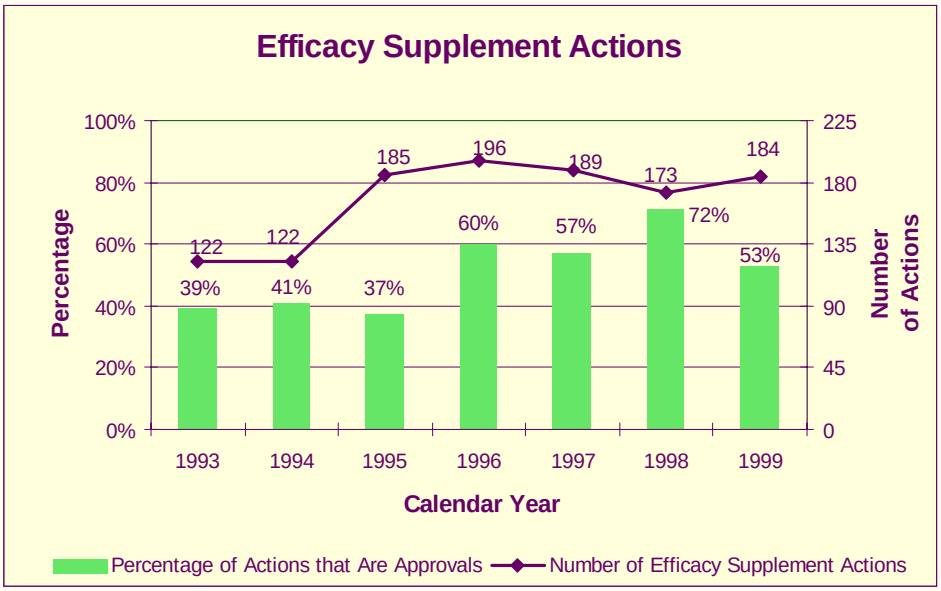
***Lidocaine patch (Lidoderm)* for relief of allodynia (painful hypersensitivity) and chronic pain in post-herpetic neuralgia**

***Nitric oxide (INOmax)* for the treatment of persistent pulmonary hypertension in the newborn**

***Poractant alfa (Curosurf)* for the treatment of respiratory distress syndrome in premature infants**

***Somatropin (Nutropin depot)* for the long-term treatment of growth failure**

***Temozolomide (Temodar)* for the treatment of recurrent malignant glioma**



New or Expanded Use Review

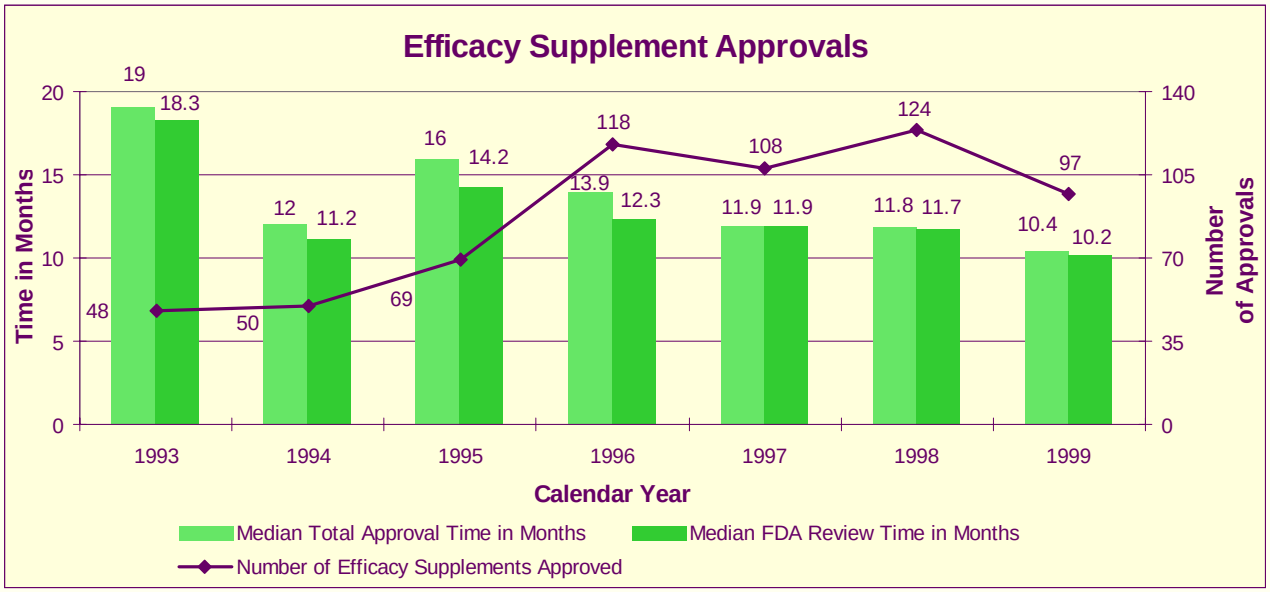
Applications for a new or expanded use, often representing important new treatment options, are formally called "efficacy supplements" to the original new drug application.

Last year we took action on 184 applications for new or expanded uses of already approved drugs. We approved 97, including nine that were given priority reviews of six months or less. Four of the approvals were for orphan uses in patient populations of 200,000 or fewer.

The median total approval time was 10.4 months, and median FDA review time was 10.2 months.

Efficacy supplement statistics:

- **97 approvals**
- **9 priority approvals**
- **Median total approval time: 10.4 months**
- **Median FDA review time: 10.2 months**



Priority efficacy supplement approvals

Amifostine

Celecoxib

Didanosine (3)

Docetaxel

Doxorubicin hydrochloride

Roloxifene hydrochloride

Paclitaxel

Notable 1998 new or expanded use approvals

Celecoxib (Celebrex), a nonsteroidal anti-inflammatory drug first approved in 1998 to treat arthritis, is the first drug treatment (together with endoscopic surveillance or surgery) for familial adenomatous polyposis, a genetic disorder. The new indication is for the reduction in the number of adenomatous colorectal polyps, which greatly increase the risk of developing colon and rectal cancer in young patients. This indication was given an accelerated approval as a product that promised therapeutic benefit for a life-threatening condition that has no other acceptable treatment.

Docetaxel (Taxotere), which was originally designed for treating patients with advanced breast cancer, and now is approved for use in non-small cell lung cancer that does not respond to chemotherapy.

Paroxetine hydrochloride (Paxil) is the first drug to receive FDA approval to treat social phobia

Sertraline hydrochloride (Zoloft) is the first drug for posttraumatic stress disorder, which has long been recognized as an important clinical problem.

Somatropin (Nutropin Depot), a genetically engineered drug, was approved for long-term treatment of growth failure.

Electronic submissions

One of the advantages of the FDA review system is the availability of complete data for reviewers. A bulky component of the application consists of case report forms and case report tabulations. We have been accepting the archive copy of these in electronic format since November 1997. In January 1999, we published guidances that provide for the receipt and archiving of a new drug application entirely in electronic format without an accompanying paper archival copy.

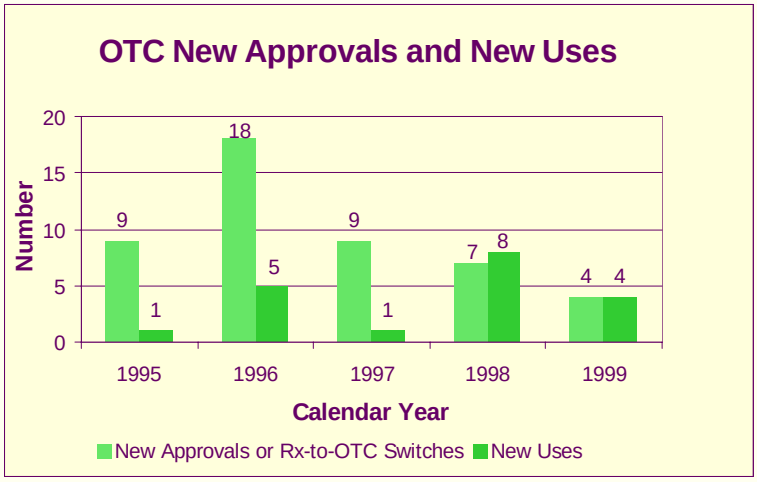
We expanded our electronic document room to manage the receipt and handling of full electronic new drug applications. We conducted workshops to assist industry in preparing their electronic submissions and trained our reviewers in using electronic submissions. The majority of original new drug applications now include electronic components. In addition, we expanded our internal electronic document management system so that we can electronically archive all of our documents for investigational new drug applications and new drug applications.

Pregnancy labeling

We have reviewed the current system of labeling drugs for use by pregnant women and developed an improved, more comprehensive and clinically meaningful approach. We consulted multiple government agencies, medical experts, consumer groups and the pharmaceutical industry in developing two draft guidances for industry and a preliminary discussion paper.

Pediatrics

We are authorized to grant six months of marketing exclusivity to manufacturers who conduct and file pediatric studies in response to our written request. We have reviewed more than 175 proposed study requests from industry and issued more than 140 written requests asking for more than 200 studies.



Over-the-counter drug statistics:

- **4 new drug approvals**
- **4 new use approvals**
- **11 rules or notices**

Over-the-Counter Drug Review

In 1999, we approved four new drugs and four new uses for over-the-counter marketing.

New OTC medicines and new uses

- *Cimetidine (Tagamet HB Suspension)* and *famotidine (Pepcid AC Gelcaps)* are new forms of OTC heartburn treatments.
- The combination *naproxen and pseudoephedrine (Aleve Cold and Sinus)* is a pain reliever, fever reducer, and cold and cough treatment.
- *Terbinafine (Lamisil Cream)* is a topical anti-fungal to treat ringworm and conditions like athlete's foot.
- The *nicotine patch (Habitrol)* was switched to OTC status.
- The combination *acetaminophen, aspirin and caffeine (Excedrin Migraine)* is a new use for an existing OTC drug.

Improved Labels for OTC Medicines

Consumers will soon find it easier to use over-the-counter medicines as a result of a final rule we published in 1999 that will provide new, easy-to-understand labels on nonprescription drugs. The regulation calls for a standardized format that will improve the labels on drugs Americans use most—nonprescription, or over-the-counter drugs. By clearly showing a drug's ingredients, dose and warnings, the new labels will make it easier for consumers to understand information about a drug's benefits and risks as well as its proper use.

Titled "Drug Facts," the new label will make it easier for consumers to identify active ingredients, which will be listed at the top, followed by uses, warnings, directions and inactive ingredients. The rule also sets minimum type sizes and other graphic features for the standardized format, including options for modifying the format for various package sizes and shapes.

OTC drug facts

As Americans continue to participate more actively in their health care decisions, many medications purchased are OTC drugs.

Currently, there are more than 100,000 OTC products on the market. However, fewer than 1,000 active ingredients are used in all OTC products.

The expanding availability of OTC drugs reclassified from prescription status offers consumers greater choices.

More than 600 OTC products use ingredients and dosages available only by prescription 20 years ago.

OTC drug monographs

One of our goals is to publish monographs that establish acceptable ingredients, doses, formulations and consumer labeling for OTC drugs. Products that conform to a final monograph may be marketed without further FDA clearance.

Generic Drug Review

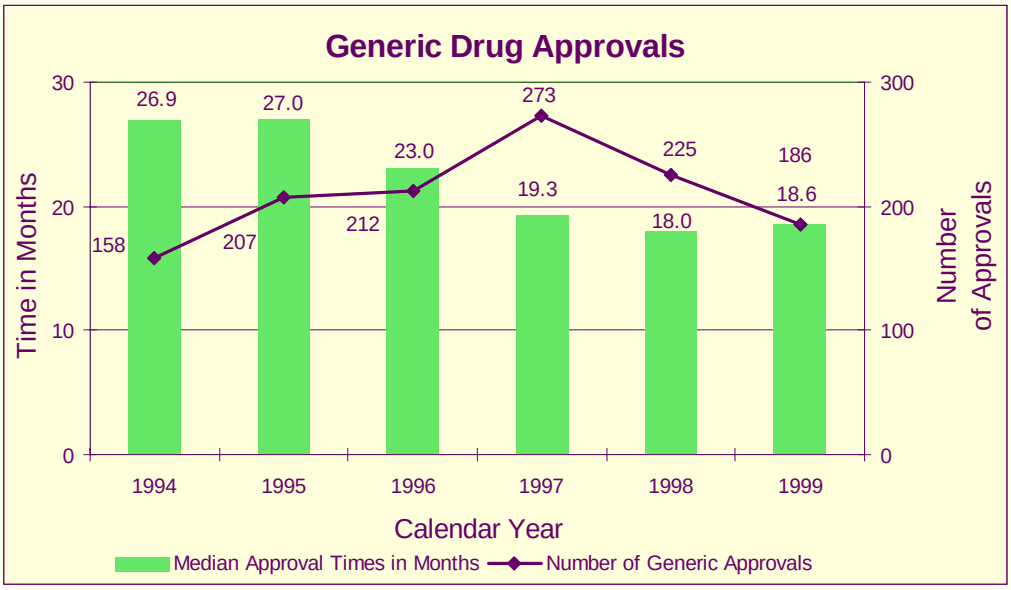
1999 generic drug statistics

- **186 generic drug approvals**
- **Median approval time: 18.6 months**

We received 196 submissions and approved 186 generic products in 1999, including 43 that represent the first time a generic drug was available for the brand name product. The median approval time for generic drugs stabilized last year at 18.6 months, about half a month longer than required in 1998.

Initiatives to streamline the generic drug review process have paid off in an overall downward trend in approval times since 1994. The 18.6-month median approval time last year compares to 18.0 in 1998 and 19.3 in 1997.

We have also seen a drop in the number of review cycles needed to approve abbreviated applications for generic drugs. In 1999, the average application required 2.5 cycles to reach approval compared to 2.6 cycles in 1998. These were down from 2.9 in 1997 and 3.6 in 1996.



Notable 1999 generic drug approvals

Examples of first time approvals include:

- *Nicotine gum*, for use as a smoking deterrent.
- *Propofol injectable emulsion*, used as a sedative for maintenance of anesthesia during surgery.

We also issued 56 tentative approvals last year compared to 40 in 1998. The only difference between a full approval and a tentative approval is that the final approval of these applications is delayed due to existing patent or exclusivity on the innovator's drug product. Examples of tentative approvals include:

- *Lovastatin tablets*, a cholesterol lowering agent.
- *Fluoxetine hydrochloride capsules* used for depression.

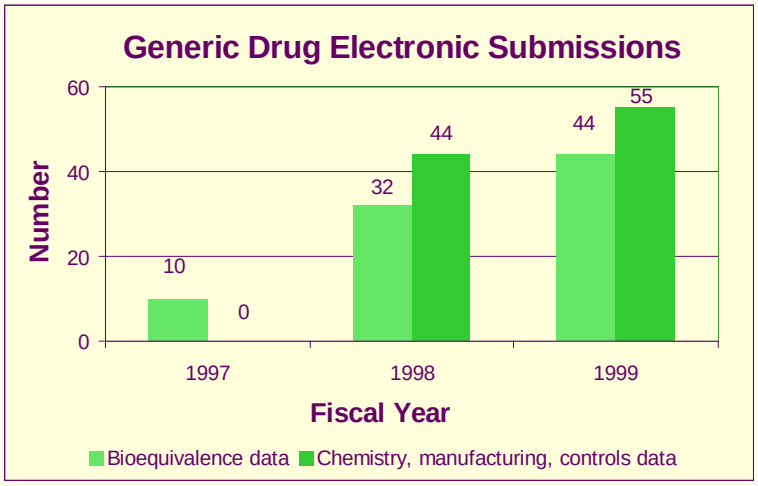
Quicker approvals without user fees

We don't receive user fees to review applications for marketing generic equivalents of prescription or over-the-counter drugs.

New Counting System

Note: Drug approval data in this report are based on a new counting system that allows certain variations in a drug product to be included in a single application. This year's report reflects our final conversion to the new system, and numbers in this report cannot be directly compared to those in previous reports.

The approval of generic versions of these products and other generic approvals in 1999 could save the American people and the federal government hundreds of millions of dollars.



Generic drug electronic submission initiative

Last year, for original submissions, we received 44 electronic submissions for bioequivalence data and 55 electronic submissions for chemistry, manufacturing and controls data. For comparison, we received 32 bioequivalence electronic submissions and 44 CMC in 1998 and ten bioequivalence and none with CMC data prior to 1998. In continued support of the electronic submissions initiative, we:

- Enhanced our information technology infrastructure to support the electronic review process.
- Promoted electronic submissions directly to industry and trade groups.
- Held training sessions for industry.
- Published a Guidance for Industry: *Preparing Data for Electronic Submissions in ANDAs.*

"In 1994, purchasers saved a total of $8 billion to $10 billion on prescriptions at retail pharmacies by substituting generic drugs for their brand-name counterparts."

***—How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry,* Congressional Budget Office, July 1998**

How we approve generic drugs

The abbreviated mechanism for approving generic copies of drug products was established by the Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Act.

Generics are not required to repeat the extensive clinical trials used in the development of the original, brand-name drug. Instead, they must show they are bioequivalent to the pioneer drug and fall into acceptable parameters for bioavailability, or the extent and rate at which the body absorbs the drug.

Scientists measure the time it takes a generic drug to reach the bloodstream. This gives them the rate of absorption or bioavailability of the generic drug, which they then compare to that of the pioneer drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream and in the same time as the pioneer drug. Brand-name drugs are subject to the same bioequivalency tests as generics when their manufacturers reformulate them.

Manufacturing Supplement Review

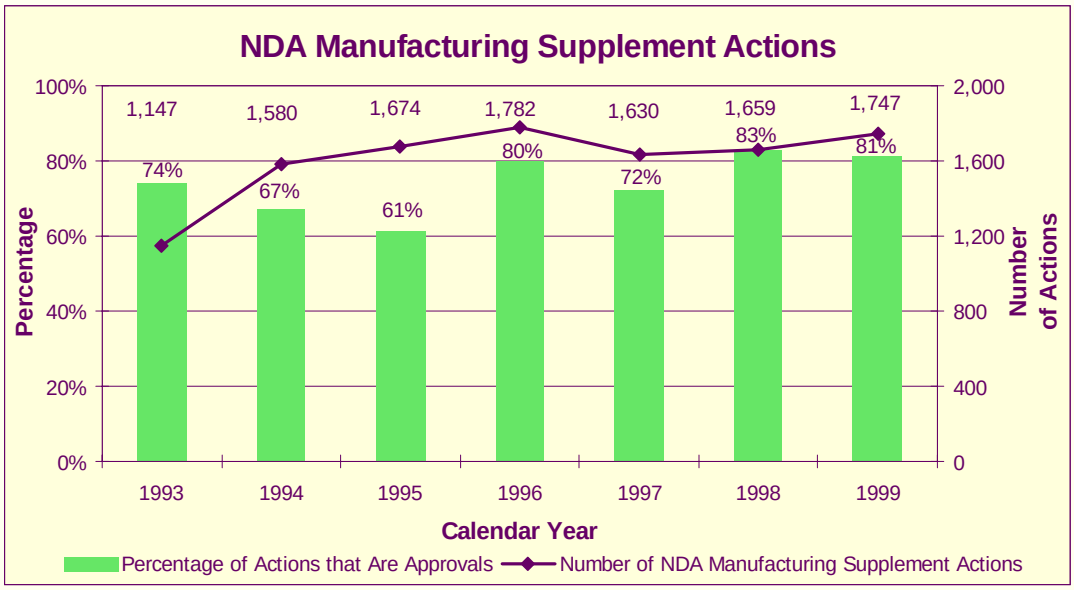
We review many types of changes in the manufacturing of drugs and their packaging, including location, machinery, processes and suppliers of raw materials. We do this so that American consumers can trust in the high quality of FDA-approved medicines. Manufacturers notify us in advance of certain manufacturing changes. These are known as "manufacturing supplements" to new drug or generic drug applications. In many cases, they represent the industry's efforts to modernize plants and equipment or to make manufacturing more efficient.

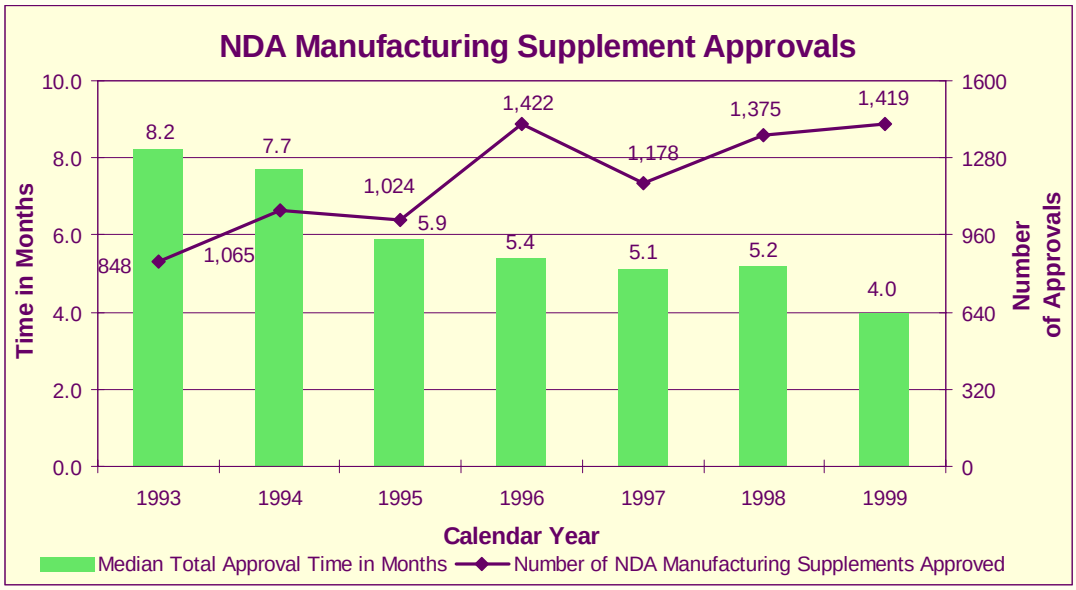
NDA manufacturing supplement statistics

- **1,419 approvals**
- **Median total review time: 5.2 months**

Manufacturing Supplements to New Drug Applications

In 1999, we took action on 1,747 manufacturing supplements, of which 1,419 were approvals.

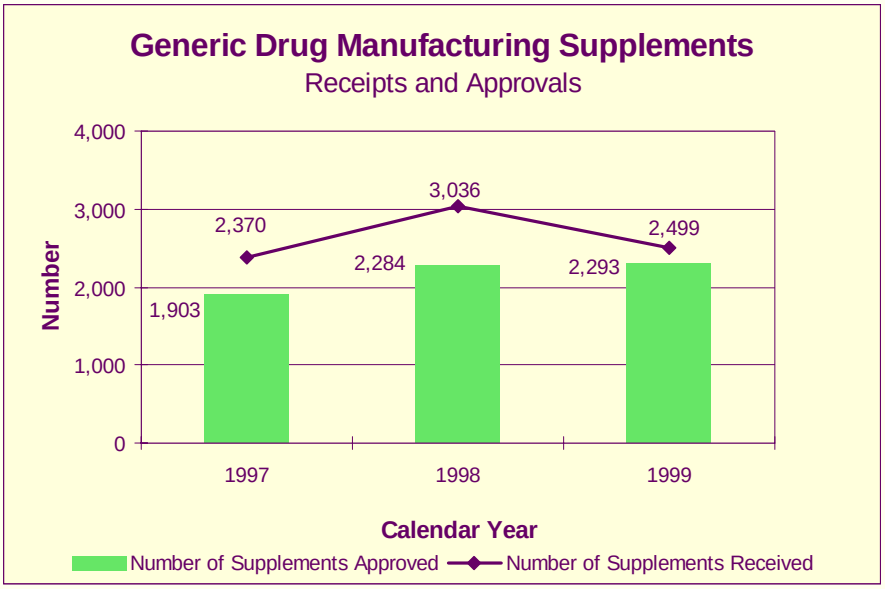




We began tracking manufacturing supplements to new drug applications and their review times as part of the performance goals agreed to for the original Prescription Drug User Fee Act.

Generic drug manufacturing supplement statistics

- **2,293 approvals**
- **3,036 receipts**



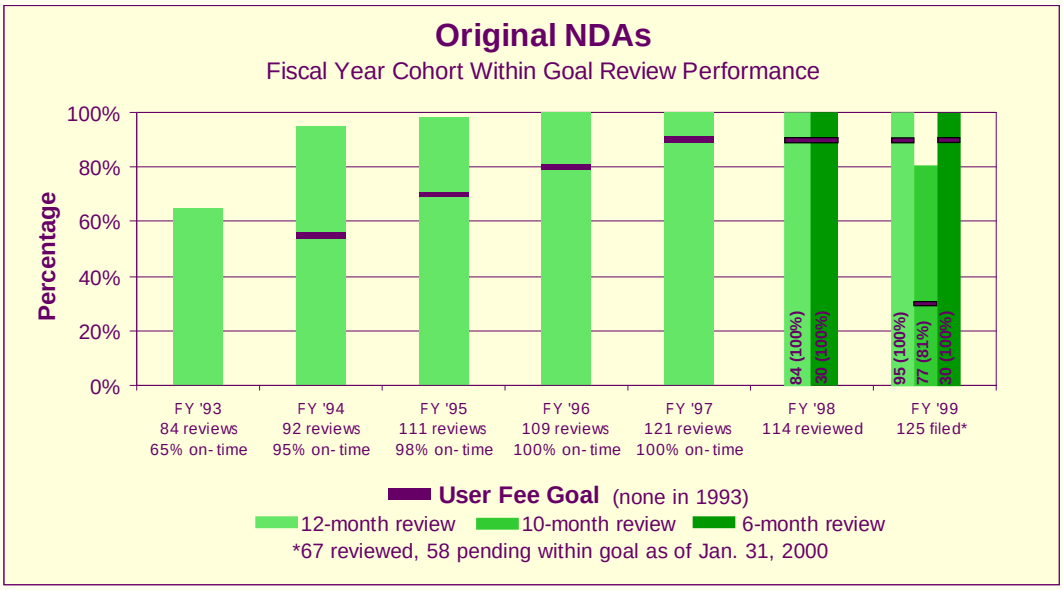
Manufacturing Supplements to Generic Drug Applications

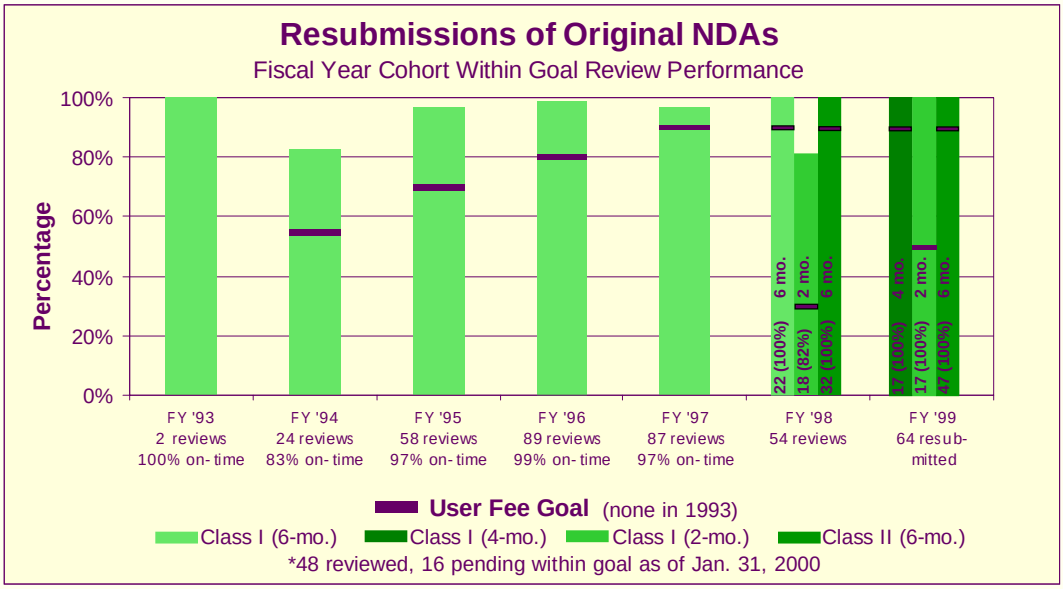
In 1999, we approved 2,293 manufacturing supplements to generic drugs applications. We received 2,499 manufacturing supplements during the year. In 1997, we began counting generic drug manufacturing supplements separately from all supplements to generic drug applications.

Note: Each product's supplement is tracked individually. A "global supplement" requires only one review but can apply to multiple products.

User Fee Review Performance

The quick and consistent level of drug reviews in recent years reflects the importance of our managerial reforms and the additional resources provided us under the Prescription Drug User Fee Act. The law was first enacted in 1992 and renewed for an additional five years in the 1997 FDA Modernization Act. Under the law, the drug industry pays user fees for new drug applications, efficacy supplements and some other activities. User fees helped us hire additional scientists to perform reviews.





Original NDAs

Improved performance goals were a key element of the reauthorization of user fees:

- **Standard drugs began a phase-in to 10-month reviews in fiscal year 1999.**
- **Priority drugs have a performance goal of 90 percent reviewed and acted upon within six months.**
- **New molecular entities have the same review performance goals as standard and priority drugs.**

Resubmissions of original NDAs

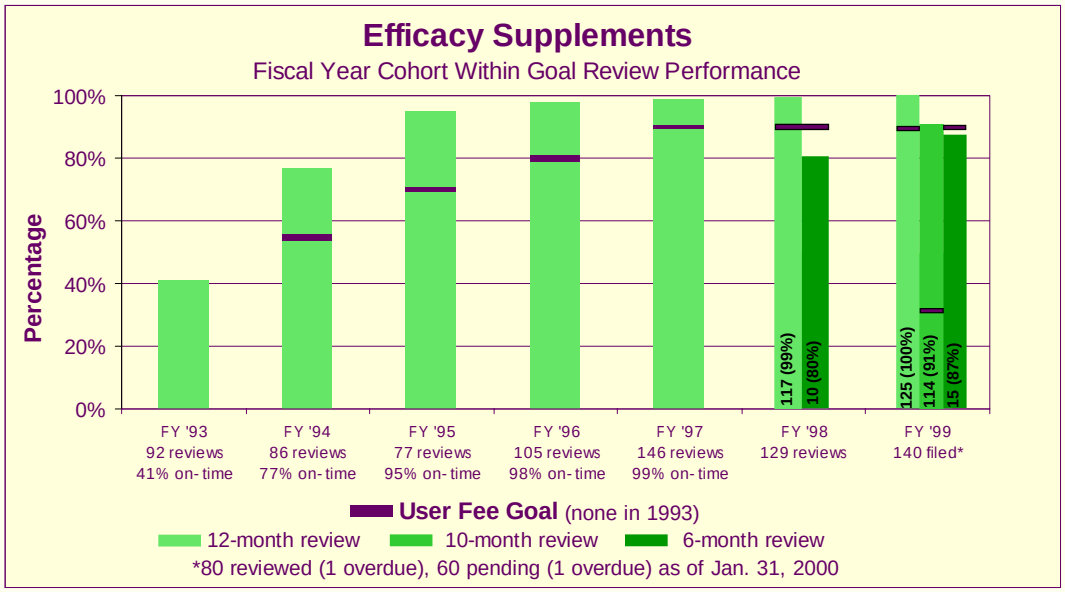
Beginning in 1998, resubmissions were divided into two classes:

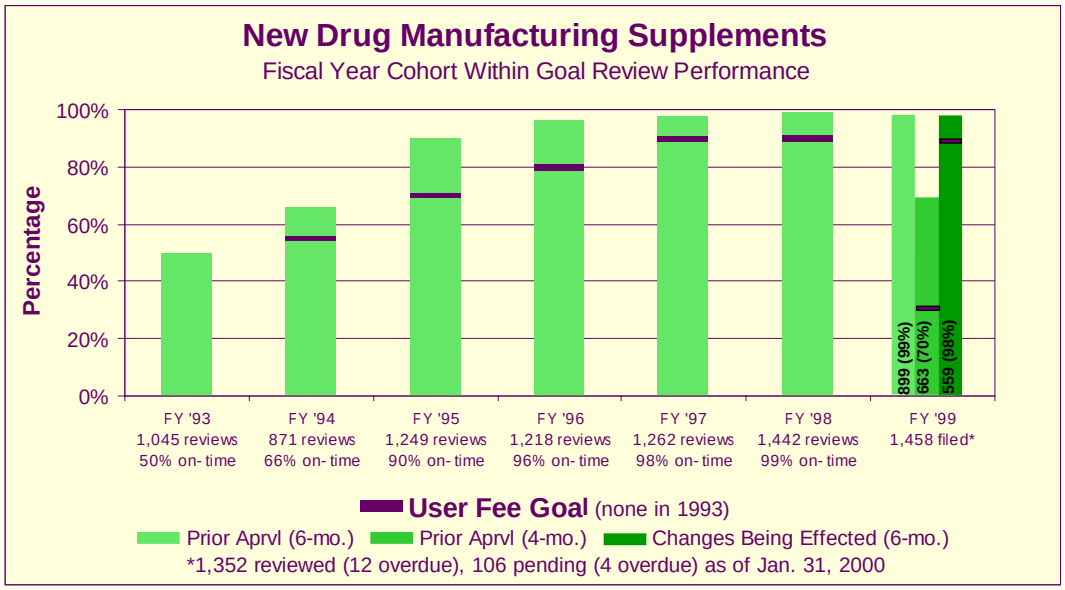
- **Class I, involving minor changes, are targeting 90 percent two-month reviews by fiscal year 2001.**
- **Class II, involving changes not specifically identified in the user fee goals document, retain a six-month review.**

In 1992, we agreed to specific performance goals for the prompt review of four categories of submissions:

- Original new drug applications.
- Resubmissions of original NDAs.
- Efficacy supplements to already approved marketing applications.
- Manufacturing supplements to already approved new drug marketing applications.

We exceeded the progressively more stringent user fee performance goals for each successive fiscal year except for one goal in fiscal year 1998.





Fiscal year cohorts

When comparing the fiscal year user fee performance charts with the calendar year performance charts, remember that work on one year's submission cohort is often performed in the following year.

Efficacy supplements

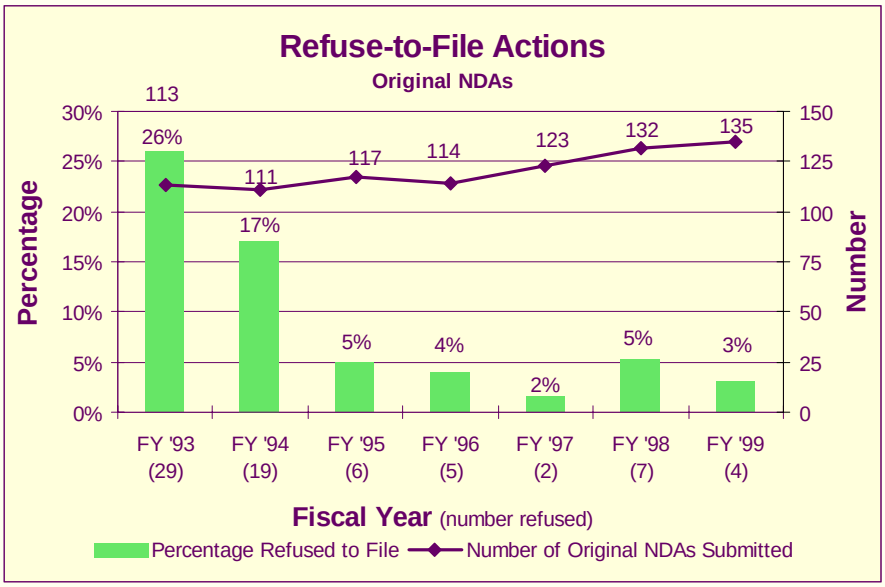
- **Standard efficacy supplements began a phase-in to 10-month reviews in fiscal year 1999.**
- **Priority efficacy supplements began a six-month performance goal in fiscal year 1998.**

Manufacturing supplements

- **Manufacturing supplements to NDAs that require our prior approval before implementation have a phase-in to a four-month review.**
- **The goal for those that don't require our prior approval—changes being effected—remains at 90 percent reviewed and acted on within six months.**

In 1997, Congress, with the industry's and our support, enhanced the user fee program and extended it for five years as part of the FDA Modernization Act. We have committed to goals that will help speed the time it takes for drugs to be appropriately tested and developed before submitting those results for FDA review.

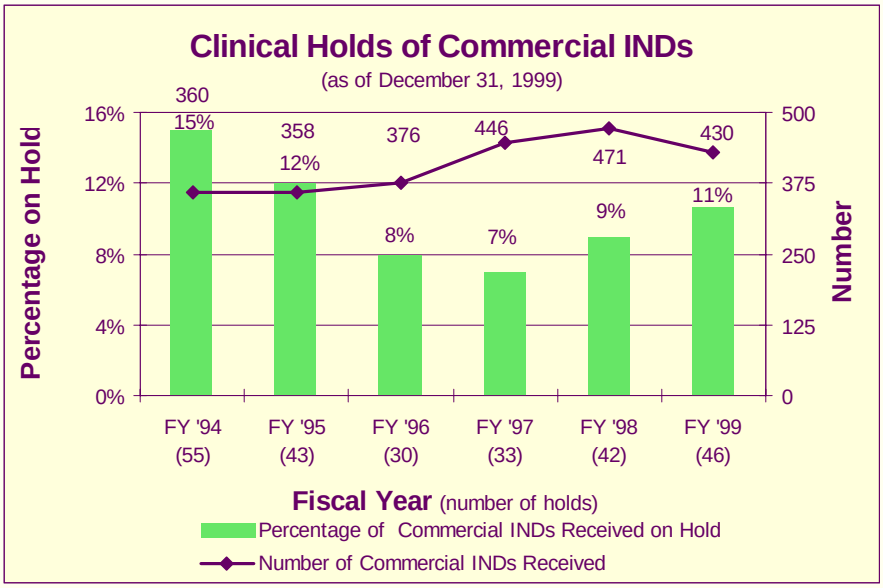
These new goals include those related to meeting management, clinical holds, resolving major disputes and reaching agreement on certain protocols. There are added expectations regarding electronic applications and submissions, simplification of action letters and expedited notification of deficiencies in applications.



Refusal to file an application

As a result of the user fee program, the quality of applications submitted by industry has improved. In addition we have exercised increased consistency in applying our authority to refuse to file an application. We refuse to file an application only when we determine there is a significant omission of needed information.

Before 1993, we were refusing to file approximately 25 percent to 30 percent of submitted original new drug applications. The percentage of refused-to-file applications has dropped steadily to approximately 4 percent in recent years.



Clinical Holds

By working with sponsors more closely, the percentage of commercial investigational new drug applications put on clinical hold has decreased dramatically.

A clinical hold temporarily halts the testing of a drug in humans because of concerns about safety.

We have developed and published procedures that outline specific responsibilities and timelines for handling clinical holds imposed on investigational new drugs.

Drug Review Team

We use project teams to perform drug reviews. Team members apply their individual special technical expertise to review applications:

- *Chemists* focus on how the drug is manufactured. They make sure the manufacturing controls, quality control testing and packaging are adequate to preserve the drug product's identity, strength, potency, purity and stability.
- *Pharmacologists* and toxicologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies, including the potential based on animal studies for drugs to induce birth defects or cancer in humans.
- *Physicians* evaluate the results of the clinical trials, including the drug's adverse and therapeutic effects, and determine if the product's benefits outweigh its known risks at the doses proposed.
- *Project managers* orchestrate and coordinate the drug review team's interactions, efforts and reviews. They also serve as the review team's primary contact for the drug industry.
- *Statisticians* evaluate the designs and results for each important clinical study.
- *Microbiologists* evaluate the effects of anti-infective drugs on germs. These medicines—antibiotics, antivirals and antifungals—differ from others because they are intended to affect the germs instead of patients. Another group of microbiologists evaluates the manufacturing processes and tests for sterile products, such as those used intravenously.
- *Biopharmaceutists* evaluate the rate and extent to which a drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated. They also check for interactions with other drugs.
- *Clinical pharmacologists* evaluate factors that influence the relationship between the body's response and the drug dose. They assist physician members of the team in assessing the clinical significance of changes in the body's response to drugs through the use of exposure-response relationships.

Consumers benefit from user fee reforms

Two studies released last year document the benefits of FDA's review and approvals and indicate that Americans have an increasingly fast access to new medications of worldwide origin.

- **One of the studies (Tufts Center for Study of Drug Development, July 1999) showed that since the passage of the Prescription Drug User Fee Act of 1992, total development time for new drugs in the U.S. has dropped by 18 percent.**
- **Another study (*Ashton CMRI International News,* Spring 1999, Vol. 17, No. 1) found that, in 1998, about 75 percent of worldwide new molecular entities were first launched in the United States.**

2

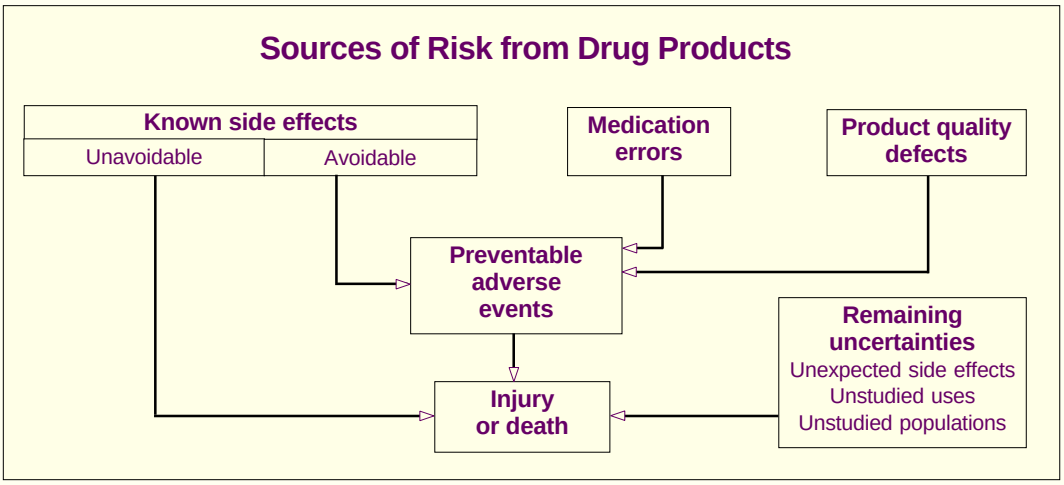
DRUG SAFETY AND QUALITY

Mission

Protect the public health by ensuring that human drugs are safe and effective.

The practical size of premarketing clinical trials means that we cannot learn everything about the safety profile of a drug before we approve it. Therefore, a degree of uncertainty always exists about both the benefits and risks from drugs. The trade-off for accepting these uncertainties is our continued vigilance along with that of the industry to collect and assess data during the postmarketing life of a drug.

We monitor the quality of marketed drugs and their promotional materials through product testing and surveillance. In addition, we develop policies, guidance and standards for drug labeling, current good manufacturing practices, clinical and good laboratory practices and industry practices to demonstrate the safety and effectiveness of drugs.



Risk management

For a 164-page report on current and recommended premarket and postmarket risk assessment procedures and surveillance programs, last year's FDA report, *Managing the Risks form Medical Product Use: Creating a Risk Management Framework,* is available on the World Wide Web at http://www.fda.gov/oc/tfrm/riskmanagement.pdf

Types of risks from medicines

Product quality defects. These are controlled through good manufacturing practices, monitoring and surveillance.

Known side effects. Predictable adverse events are identified in the drug's labeling. Known side effects cause the majority of injuries and deaths resulting from using medicines. There are avoidable and unavoidable side effects:

- *Avoidable*. In many cases drug therapy requires an individualized treatment plan and careful monitoring. Other examples of avoidable side effects are known drug-drug interactions.

- *Unavoidable.* Some known side effects occur with the best medical practice even when the drug is used appropriately. Examples include nausea from antibiotics or bone marrow suppression from chemotherapy.

Medication errors. The drug is administered incorrectly or the wrong drug or dose is administered.

Remaining uncertainties. These include unexpected side effects, long-term effects and unstudied uses and populations. For example, a rare event occurring in fewer than 1 in 10,000 persons won't be identified in normal

Drug Safety

We evaluate the ongoing safety profiles of drugs available to American consumers using a variety of tools and disciplines. We maintain a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process. We monitor adverse events such as adverse reactions, drug-drug interactions and poisonings. We use this information to update drug labeling and, on rare occasions, reevaluate the approval or marketing decision.

Adverse event reporting

Last year, we received 258,125 reports of suspected drug-related adverse events:

- 78,539 manufacturer 15-day (expedited) reports.
- 15,374 reports directly from individuals.
- 164,212 manufacturer periodic reports and other follow-up reports.

As we discover new knowledge about a drug's safety profile, we make risk assessments and decisions about the most appropriate way to manage any new risk or new perspective on a previously known risk. Risk management methods include new labeling, "Dear Health Care Practitioner" letters, restricted distribution programs or product marketing termination.

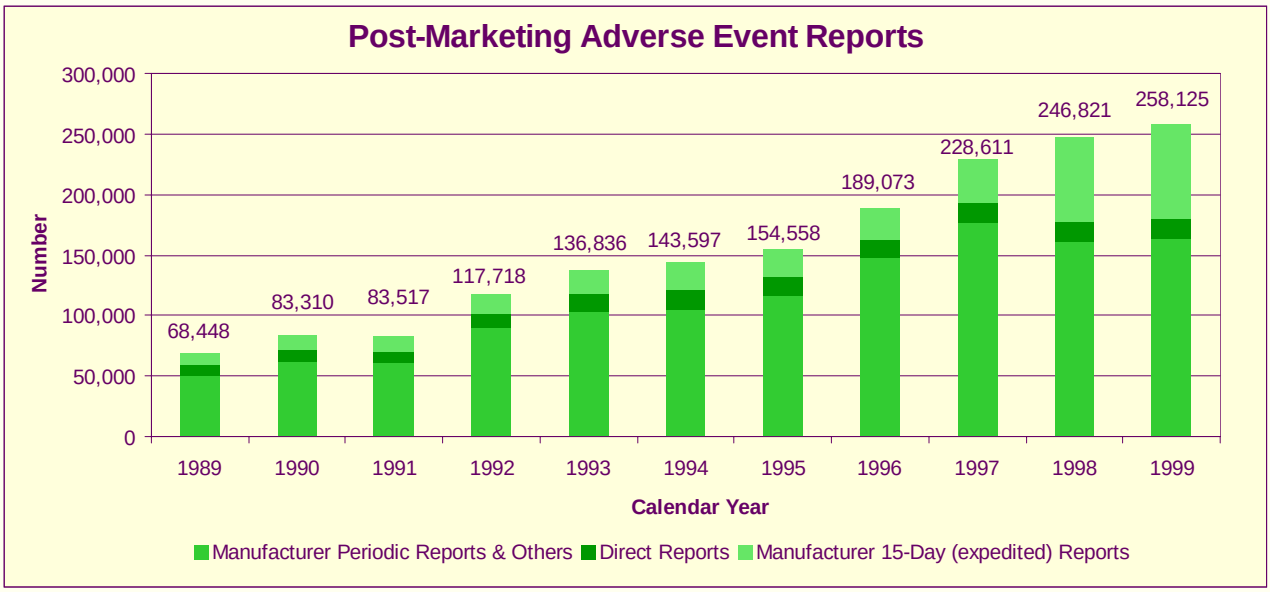
We enforce regulations on adverse event reporting to assure that reports are accurate, timely and complete. During fiscal year 1999, there were 50 inspections of foreign and domestic firms for adverse event reporting. In addition, we gave guidance on policy issues and held meetings with industry to discuss their adverse event reporting practices. We approved four warning letters and three untitled letters citing adverse event reporting deficiencies. The 50 inspections in fiscal year 1999 compare to 51 conducted in fiscal year 1998, 33 in fiscal year 1997 and 17 in fiscal year 1996.

Medication errors

We help ensure the safe use of drugs we approve by identifying and avoiding brand names that contribute to problems in prescribing, dispensing or administration of the product.

Therapeutic inequivalence reporting

We identify and evaluate reports of therapeutic failures and toxicities that could indicate one produce is not equivalent to another similar product.



Information technology

A powerful tool for detecting signals is the computerized spontaneous reporting evaluation system. We have replaced our previous computerized system with a new, state-of-the-art system: the Adverse Event Reporting System. This system combines the voluntary adverse drug reaction reports from MedWatch and the required reports from manufacturers. These reports often form the basis of various "signals" that there may be a potential for serious, unrecognized, drug-associated events. After the signal is generated, further testing of the hypothesis is undertaken using various epidemiological and analytic databases, studies and other instruments and resources. The Adverse Event Reporting System offers paper and electronic submissions options, international compatibility and pharmacovigilance screening activities.

MedWatch

In 1999, we took over administration of MedWatch under which health professionals and the public can voluntarily report serious reactions and problems with all FDA-regulated medical products. Reports can be filed by mail, fax, telephone or the Internet. The program enhances the effectiveness of postmarketing surveillance by rapidly identifying significant health hazards associated with them and notifying health professionals and the public of these hazards. We educate health professionals and consumers about the importance of recognizing and reporting serious adverse events and product problems, including medication errors. We rapidly disseminate safety information through the World Wide Web and by e-mail notification available to both to health professionals and the public. Our education program includes speeches, articles and exhibits.

Internet resources

You can learn more about the Adverse Event Reporting System at http://www.fda.gov/cder/aers/index.htm.

The latest medical product safety information can be found on the MedWatch Website at http://www.fda.gov/medwatch/.

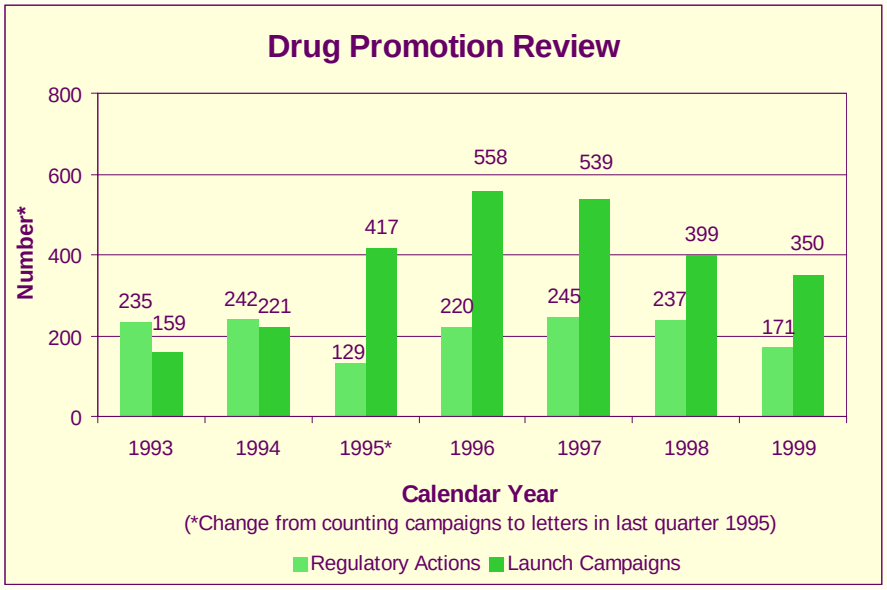
You can sign up for immediate e-mail notification of MedWatch safety information at http://www.fda.gov/medwatch/new.htm.

Report types

***15-day (expedited) reports:* Drug manufacturers report serious and unexpected adverse events to us soon as possible and within 15 days of discovering the problem.**

***Direct reports from MedWatch:* An individual, usually a health-care practitioner, notifies us directly of a suspected adverse event.**

***Manufacturer periodic reports and others:* Drug manufacturers report all other adverse events, for example, those that are less than serious or described in the drug's labeling. Reports are submitted quarterly for the first three years of marketing and annually after that. When additional information is required, a follow-up report is submitted.**



Drug Promotion Review

The information about a drug available to physicians and consumers is just as important to its safe use as drug quality. We promote and protect the health of Americans by ensuring that drug advertisements and other promotional materials are truthful and balanced. The Center operates a comprehensive program of education, surveillance and enforcement about drug advertising and promotion.

In some instances, we review drug advertisements and other promotional materials before drug companies launch marketing campaigns that introduce new drugs or introduce new indications or dosages for approved drugs. In 1999, the Center issued 337 advisory letters to companies regarding their promotional materials for launch campaigns.

We issued 171 regulatory action letters to pharmaceutical companies for prescription drug promotions determined to be false, misleading or lacking in fair balance. These were either "untitled" letters for minor violations or "warning" letters for serious or repeat violations. The Center also issued 773 other advisory, acknowledgment or closure letters to the industry regarding prescription drug promotional materials.

Direct-to-consumer advertising

We issued 247 combined advisory and regulatory action letters regarding direct-to-consumer promotion. We issued a final guidance on direct-to-consumer broadcast advertisements that covered human and animal prescription drugs and human biologics. We completed a national

Risk vs. benefit communications research

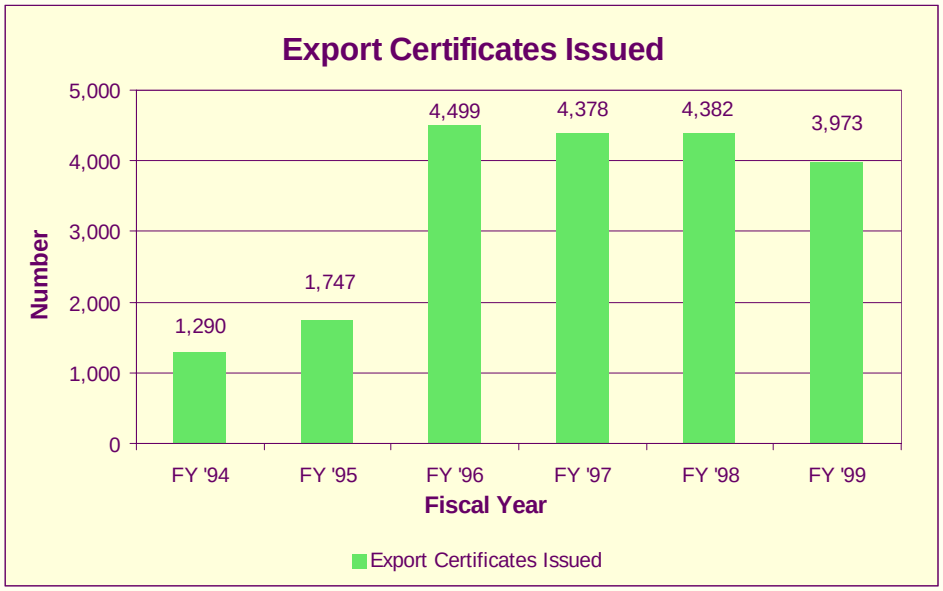
We are conducting research to assess the public's ability to understand risk and benefit information.

The goal is to develop useful and meaningful ways of presenting important information about a drug's known risks and benefits.

telephone survey of patient attitudes and behaviors in relation to direct-to-consumer advertising, focusing on the patient-physician interaction. We also began research to examine how consumers interpret specific direct-to-consumer advertisements.

Improved patient information for prescription drugs

We continued our research, education and outreach activities in support of the private plan to provide patients with useful information about their prescription drugs. We have been working with industry, nonprofit agencies and academic groups to ensure that 75 percent of patients receive useful information about their new prescriptions by the year 2000. We completed a study examining the current status of the private sector plan's progress toward achieving the year 2000 goal. We issued a final rule that requires FDA-approved patient labeling (medication guides) for especially risky prescription drug products.



What export certificates do

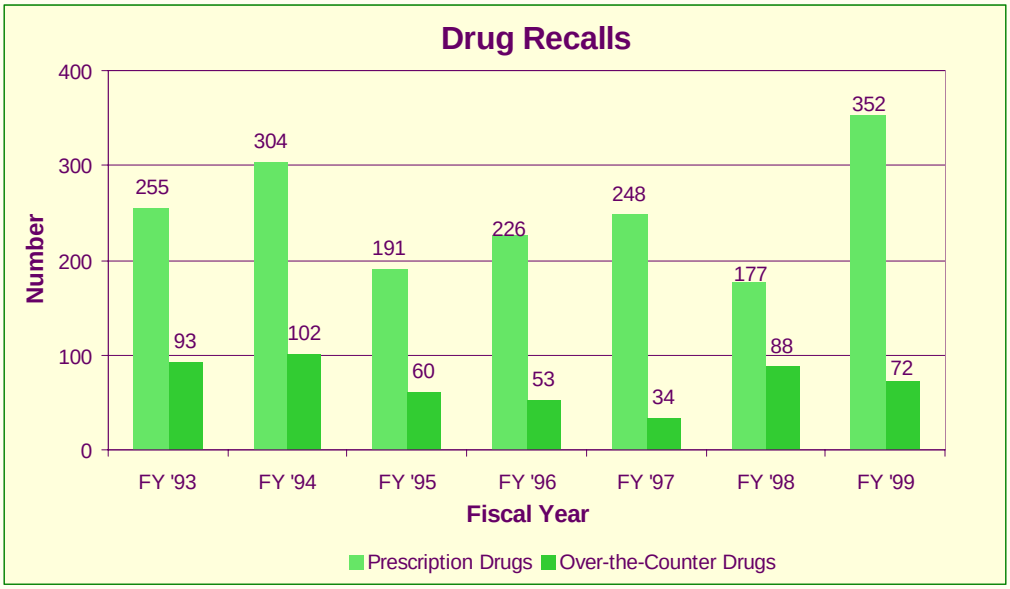
Export certificates verify that the drug products being exported:

- **Were freely marketed in the United States.**
- **Were in compliance with U.S. laws and regulations.**
- **Met certain national or international standards, such as quality standards.**
- **Were free of specific contaminants.**

Export Certificates

We promote goodwill and cooperation between the United States and foreign governments through the Export Certificate Program. These certificates enable American manufacturers to export their products to foreign customers and foreign governments. The demand for certificates by foreign governments remained high due to expanding world trade, ongoing international harmonization initiatives and international development agreements.

The certificates attest that the drug products are subject to inspection by the FDA and are manufactured in compliance with current good manufacturing practices.



Top 10 reasons for drug recalls in fiscal year 1999:

- **Failure or inability to validate drug analysis methods**
- **Subpotency**
- **Stability data failing to support expiration date**
- **Failure or inability to validate manufacturing processes**
- **Deviations from good manufacturing practices**
- **Failure of drug to dissolve properly**
- **Labeling mix-ups**
- **Marketed without a new or generic approval**
- **Lack of assurance of sterility**
- **Cross-contamination with other products**

Drug Recalls and Withdrawals

We coordinate drug recall information and prepare health hazard evaluations to determine the risk to public health by products being recalled. We classify recall actions in accordance to the level of risk, and we participate in determining recall strategies based upon the hazard and other factors including distribution patterns and market availability. We determine the need for public warnings and assist the recalling firm with public notification.

In some cases, drugs are withdrawn from the market. Last year, manufacturers withdrew these two drugs for safety reasons:

- *Astemizole (Hismanal),* a prescription antihistamine approved in 1988, voluntarily withdrawn after new adverse reaction data had required a series of labeling changes and warnings.
- *Grepafloxacin (Rexar),* an oral flurorquinolone antibiotic first marketed in 1997, voluntarily withdrawn when the company observed a small number of severe cardiovascular events.

The record of withdrawal of drugs approved in recent years compares favorably to previous periods when we were criticized for taking too long to review drug applications. Nonetheless, the increased number of drugs and the large number of patients taking multiple drugs have created the potential for more drug safety problems. We are exploring these issues in a systematic manner with our partners in industry, academia, state and local

Voluntary recalls

A recall is a voluntary action taken by a manufacturer or distributor to carry out their responsibility to protect the public health when they need to remove or correct a marketed drug product that presents a significant risk to public health. A voluntary recall is more efficient and effective in assuring timely consumer protection than an FDA initiated court action or seizure.

Safety-based NME withdrawals

The record of withdrawal of drugs approved in recent years compares favorably to previous periods when we were criticized for taking too long to review drug applications.

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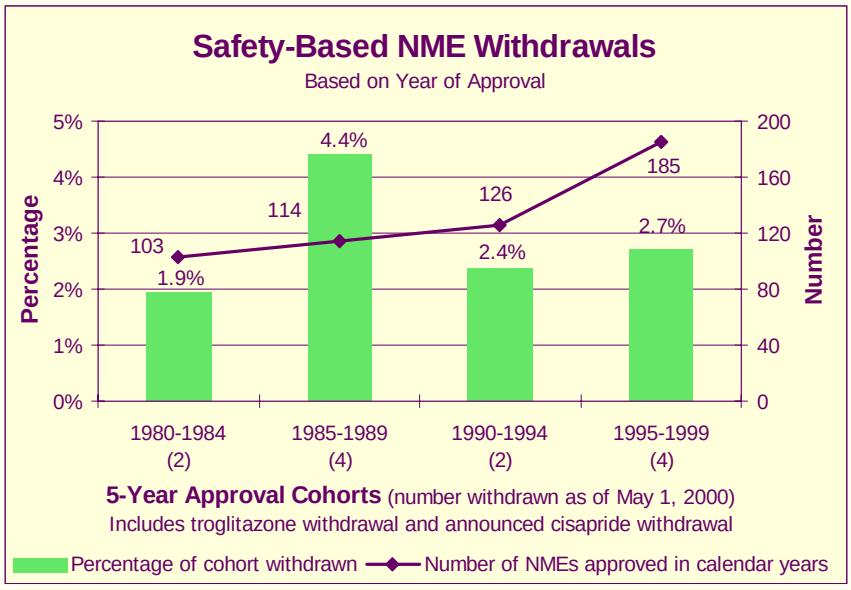


Drug Product Quality

We provide comprehensive regulatory coverage of the production and distribution of drug products. This helps ensure that drugs are safe, effective and in compliance with applicable current regulations for good manufacturing practices. We manage inspection programs designed to minimize consumer exposure to defective drug products. We have two basic strategies to meet this goal:

- Evaluating the factory inspections that include collection and analysis of associated samples and the conditions and practices under which drugs are manufactured, packed, tested and stored.
- Monitoring the quality of finished drug products in distribution through sampling and analysis.

We identify, evaluate and analyze inspection findings for trends. We develop guidances to assist drug manufacturers in gaining a better understanding of our regulations. We communicate the expectations of compliance through outreach programs. We review all international pharmaceutical inspection reports. We determine which foreign manufacturers are acceptable to supply active pharmaceutical ingredients or finished drug products to the U.S. market.

OTC drug quality

We ensure that all marketed over-the-counter drugs medicines are safe and effective for their intended uses and are labeled accurately.

When we find OTC drug products that fail to meet the appropriate standards of labeling or formulation, we advise firms in writing of the violations in the hope that voluntary corrections will be made.

In some instances it is necessary to seize violative products to ensure that consumers are protected.

Manufacturing plant inspections

FDA field offices conduct inspections of plants that manufacture, test, package and label drugs. There are more than 18,000 of these plants in the United States. Before a drug is approved, FDA investigators must determine if data submitted in the firm's application are authentic and if the plant is in compliance with good manufacturing practices. After a drug is approved, FDA conducts an inspection to make sure a firm can consistently manufacture the product. Finally, routine inspections evaluate the firm's entire operations.

- *Preapproval inspections.* During fiscal year 1999, FDA evaluated 773 domestic plants in support of new drug applications. No user fee goals were missed. Also, FDA evaluated 1,775 domestic firms in support of generic drug applications.
- *Postapproval inspections.* There were 1,844 good manufacturing practice inspections, and these resulted in 103 warning letters. We reviewed 34 of these letters before they were issued, and the remaining 69 were issued directly by the field. We also reviewed 44 field recommendations for regulatory action and approved 30. These included two injunctions, 20 seizures and eight warning letters. We reviewed more than 200 foreign establishment inspection reports. These reviews resulted in six warning letters and two import alerts. Import alerts prevent violative foreign drug products from entering the United States.

Reporting systems for drug quality problems

Two important tools help us rapidly identify significant health hazards associated with the manufacturing and packaging of drugs:

- *Field Alert Reports.* Firms are required to notify FDA promptly of significant problems they discover that may represent safety hazards for their marketed drug products. Last fiscal year, our review of these reports resulted in 60 drug product recalls, 15 voluntary corrective actions, two products withdrawn from the market and 12 products discontinued.
- *Drug Quality Reporting System.* We analyze voluntary reports on drug product quality problems submitted by health care practitioners through MedWatch and other systems. We maintain these reports in a central database to aid in detecting problem areas and identify trends requiring regulatory action. Last fiscal year, our review of more than 2,000 of these voluntary reports resulted in nine recalls and 29 corrective actions.

Drug shortages

We attempt to prevent or alleviate shortages of medically necessary drugs. We coordinated responses to 10 drug shortage situations in fiscal year 1999. These efforts assured the availability of necessary drug products for the treatment several serious and life-threatening diseases, such as myasthenia gravis, tuberculosis, AIDS and cancer.

Surveillance sampling of drugs

The Drug Quality Surveillance Sampling Program helps determine the quality of imported and domestic drugs distributed in the United States. Samples of drug products are tested for conformance with quality specifications to ensure that the nation's drug supply is safe and effective and to provide rapid identification of emerging problems.

We have intensified surveillance of imported drug products because of the increased number of imports.

During fiscal year 1999, we surveyed 56 drug products. The analysis of 216 samples was complete as of May 1, 2000. Twenty samples failed various quality specifications including impurity tests, dissolution requirements, net content and the limit for free salicylic acid. Although investigational follow-up is in-process for some samples, compliance achievements to date include packaging and manufacturing revisions and other recommendations.

Unsubstantiated claims, fraudulent and hazardous products

We encounter many products that are vitamins, minerals, amino acids and herbal preparations with labeled drug claims. These products may be labeled as dietary supplements but make claims that they are safe and effective for the prevention, treatment or cure of such diseases as AIDS or cancer. Because these claims are unsubstantiated, they could present a health hazard when consumers delay or avoid seeking appropriate medical care.

- We take enforcement action when these products are likely to cause serious injury.
- We identify fraudulent or hazardous drug products and assist in developing enforcement strategies involving counterfeit drugs.

Party drugs seized

The so-called "party drugs" GHB (gamma-hydroxybutyrate), GBL (gamma-butyrolactone) and 1-4 butanediol are examples of ingredients that have been promoted for illicit activities including date rape.

We have seized dietary supplements and other products that contain these ingredients because they pose a significant risk of injury or death.

Sampling criteria

We chose drugs for the sampling program based on the following criteria:

- **New molecular entities.**
- **Drugs with dissolution issues.**
- **Highly active drugs that have effects in low doses.**
- **Drugs with a history of quality problems, field alerts or recalls.**
- **Suspected counterfeit drugs.**

3

INTERNATIONAL ACTIVITIES

Mission

We participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.

International Conference on Harmonization

Harmonization—making the drug regulatory processes more efficient and uniform—is an issue that is important not only to Americans, but to drug regulatory agencies and pharmaceutical companies throughout the world. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has worked to bring together government regulators and drug industry experts from innovator trade associations in the European Union, Japan and the United States.

We are leading the FDA's collaboration with the ICH. This work will help make new drugs available with minimum delays not only to American consumers but also to patients in other parts of the world.

The drug regulatory systems in all three regions share the same fundamental concerns for the safety, efficacy and quality of drug products. However, many time-consuming and expensive technical tests have had to be repeated in all three regions. The ICH goal is to minimize unnecessary duplicate testing during the research and development of new drugs. The ICH process results in guidance documents that create consistency in the requirements for product registration. The ICH model applies the most advanced scientific knowledge and coincides with our top priority of using state-of-the art science as the basis for efficient and rigorous drug reviews.

Four areas of focus

The ICH areas of harmonization are efficacy, safety, quality and regulatory communications. These terms are used somewhat differently than similar American terms.

- ***Efficacy*** **refers to what we know as clinical safety and efficacy.**
- ***Safety*** **refers to preclinical safety testing.**
- ***Quality*** **refers to our terms for production control or good manufacturing practices.**
- ***Regulatory communications*** **focuses on medical terminology and standards for the electronic transmission of regulatory information and data.**

Standard terminology

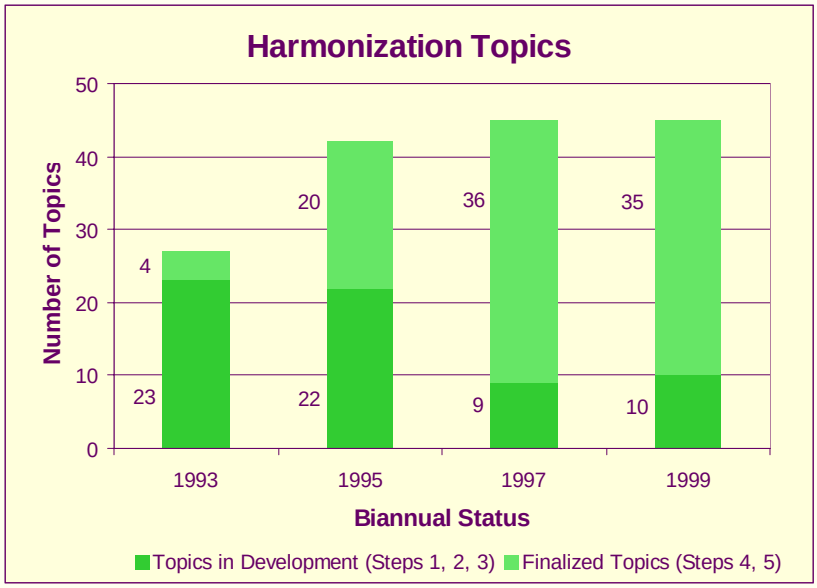
The ICH Medical Dictionary for Regulatory Activities supports the classification, retrieval, presentation and communication of medical information throughout a drug's life cycle. It will be particularly important in the electronic transmission of adverse event reporting, both in the pre- and postmarketing areas, as well as in the coding of clinical trial data. We expect MedDRA to become the accepted standard for all regulatory activities. The terminology serves a vital public health need: to facilitate the collection, presentation and analysis of regulatory information on medical products during clinical and scientific reviews and marketing.

Common Technical Document

An important goal of harmonization is to define a standardized format for submitting information about a new drug. Our objective is to reach agreement on an information package of technical data, in the same format and with the same content, that would be submitted to drug review

Mansfield fellowships

Two of our scientists have received two-year fellowships from The Mansfield Center for Pacific Affairs. The fellowships involve one year of Japanese language and area studies training and a second year in Japan working with drug regulators in the Japanese government.



The 5-step ICH process

1. An expert working group develops a draft guidance.

2. We obtain comments from citizens, industry, academia and others.

3. The regulatory members of the expert working group revise the draft based on comments received and pass it on to the ICH steering committee.

4. The steering committee approves the guidance and hands it over to the regional regulatory authorities.

5. The regulatory authorities implement the guidance in their regions according to their own national procedures. In this country, we follow good guidance practices, publish the guidances in the *Federal Register* and post them on our Web site.

authorities in all three ICH regions. The project is well on target with a final document expected in November 2000. Work on making the Common Technical Document suitable for electronic submission will take about six months longer.

Second phase launched

The ICH has embarked on a second phase of activities and agreed to broaden representation to other parties. The second phase of harmonization will have implications for already marketed drugs, over-the-counter drugs and generic equivalents. To keep pace with scientific advances, several guidances are being revised or considered for revision.

U.S.-European Union Mutual Recognition Agreement

This agreement provides for reciprocal reliance on inspection systems in the United States and the 15 member nations of the European Union. The globalization of the pharmaceutical industry is outpacing our resources to inspect pharmaceutical manufacturing plants worldwide. Once fully implemented, the agreement will allow us to base our regulatory decisions on inspection data from "equivalent authorities" in the European Union. Equivalent authorities are those have regulatory systems for good manufacturing practices that we assess and determine will achieve a comparable level of public health protection.

While the agreement will allow us to use an inspection report from one or our European counterparts as though it were our own, the actual regulatory decision will be up to us. Last year marked the first year of a three-year transition period to implementation. Our experts in good manufacturing practices are leading the FDA team working with a team from the European Union to implement this agreement. We held a public meeting in December to advise our stakeholders about progress on the agreement.

Internet sources

We publish the ICH documents as guidances to industry. These can be found on our Internet site at: http://www.fda.gov/cder/guidance/index.htm.

More information about ICH activities can be found on the World Wide Web at: http://www.ifpma.org/ich1.html.

The Mutual Recognition Agreement can be found on FDA's Website at http://www.iep.doc.gov/mra/mra.htm and at the European Union's Website at http://dg3.eudra.org/. Information about the most recent public meeting can be found at http://www.fda.gov/oia/homepage.htm.

4

COMMUNICATIONS

Mission

Carry out our mission in consultation with experts in science, medicine and public health and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of human drugs.

Public Participation

We participated in the FDA program of public meetings with our stakeholders. Top issues that emerged included risk management, drug safety, direct-to-consumer advertising and of our processes. We received valuable input from consumer groups, professional societies, industry and trade association on these issues. A number of groups expressed a willingness to partner with us in meeting our objectives, especially in the area of providing information to consumers and health care professionals. Many of these issues will involve us in an on-going dialogue with our stakeholders as we seek consensus on directions and priorities.

We confer with panels of outside experts about difficult scientific issues. These advisory committees met almost weekly last year, and we assure that patient representatives are included on committees considering medicines for HIV, AIDS, cancer and other serious disorders. In addition to analyzing required public comments on proposed new rules, we sought and received comments on our nonbinding guidances to industry.

Stakeholders in drug development and review

We work closely with many organizations during the drug development and review process:

- **Industry and trade associations**
- **Consumers and consumer groups**
- **Universities, hospitals and health care professionals**
- **Patients, families, care-givers and patient groups**
- **Federal, state and local government agencies**
- **Foreign governments**

Consumer and Industry Outreach Efforts

We use a number of modern communication methods to reach our stakeholders including making information available on the Internet; leveraging with consumer and patient groups to publish brochures; using videoconferencing and satellite television broadcasting; disseminating information about new and existing medicines; and making public service announcements available to print and broadcast media. Highlights of these activities include:

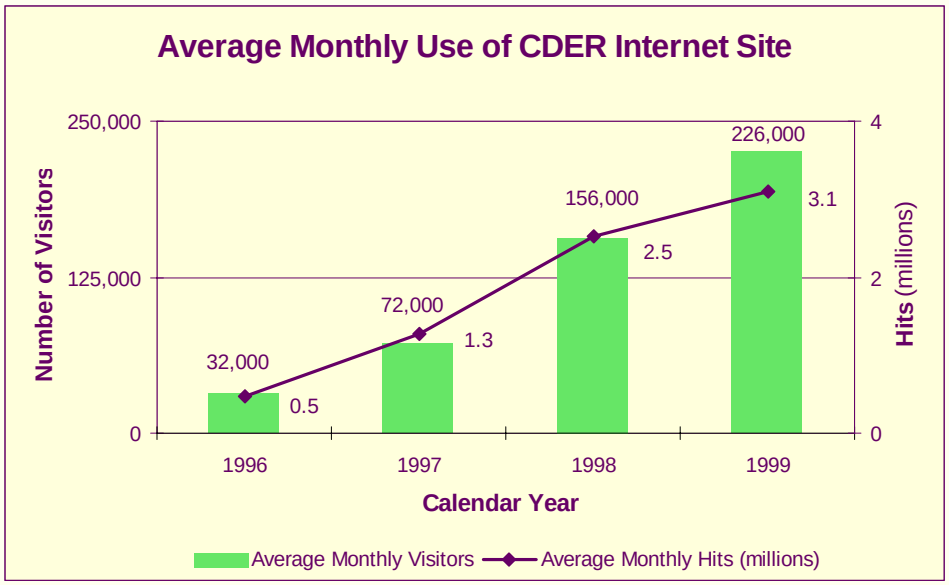
- Warning consumers about the dangers of products and dietary supplements that contain the party drug GHB and related substances. We issued warning flyers and posters to more than 2,500 health and fitness organizations, health care associations, amateur and professional sports organizations and health care publications.
- Surveying and auditing the pharmaceutical industry to assess their readiness for the year 2000 transition. To help Americans prepare for YK2, we developed an education campaign designed to alleviate the concerns of consumers, health care professionals and other special populations about drug product shortages. The campaign discussed the steps drug manufacturers had taken to assure a sufficient supply of drug products to meet demand. Messages were channeled through radio, newspapers, magazines, brochures and FDA's Website.
- Responding to more than 1,250 telephone and e-mail requests from

Consumer information

The FDA Modernization Act requires us "to maximize the availability and clarity of information for consumers and patients concerning new products."

specialized media that concentrates on the pharmaceutical industry. This was a 25 percent increase from the previous year.

- Completing successful showings our exhibit and information program at 13 national health care conferences and meetings, nearly double last year's number.
- Conducting about 100 domestic and foreign videoconferences for academia, industry and associations, about the same as last year.



OTC drug labeling campaign

We developed and executed the first phase of a public service campaign designed to promote awareness and understanding of the new over-the-counter drug labels. We explained the format the new labels and their benefits for making informed decisions.

We developed and produced two black-and-white print public service announcements, two radio PSAs, five live-read radio scripts and an exhibit display. The PSAs were distributed to more than 200 nationwide publications, more than 10,000 newspapers, 6,000 radio stations and 1,000 television stations. Results from the campaign indicate:

- The radio PSAs were played more than 25,300 times, reaching a total of more than 135 million listeners and amassing more than $1.3 million worth of free air time.
- The print PSA appeared in more than 1,000 newspapers across the country and in *Time*, *Women's Day*, *Family Circle* and other national magazines.

Dissemination Activities

We provide the most current information FDA-regulated drug products and our processes, policies and regulations in a timely and accurate manner.

- We updated *From Test Tube to Patient: Improving Health through Human Drugs*, a popular FDA publication for consumers that describes new drug development in the United States and highlights our consumer protection role. The publication consolidates accurate and timely data about the drug development and review process in an easy-to-understand format. The report has been requested by more than 5,000 individuals and is responsible for a large number of Internet "hits."
- In conjunction with a nonprofit industry information association, we conducted three two-hour satellite television broadcasts for industry called "CDER Live!" Our scientific and regulatory experts engaged in a panel discussion about electronic submissions, user fees, risk management, product quality, drug safety and other topical issues in drug development and manufacturing. Each show is broadcast to about 50 sites across the country. About 5,000 industry executives, scientists and managers view each telecast.
- Our visible presence on the World Wide Web led to an increase in the number of general information requests by electronic mail from consumers, patients and health care professionals. We responded to more than 18,200 e-mail requests last year, triple the number from the previous year.
- In addition, we answered nearly 21,000 telephone inquiries, 4,000 faxes and 2,100 written requests from consumers, pharmacists, doctors, nurses, pharmaceutical and insurance companies, government agencies and others. Finally, we responded to more than 9,500 requests for documents and guidance publications..
- We developed consumer-friendly, Web-based fact sheets about new molecular entities. The fact sheets outline the products' labeling, approval dates, uses, possible side-effects, directions for use, any warnings and other information. In addition, we wrote 33 consumer information sheets about various drug topics.

Ombudsman's activity

In its fourth year of operations CDER's Ombudsman's Office handled a number of activities designed to settle situations among employees, the Center, health professionals and consumers.

The office handled about 80 complaints.

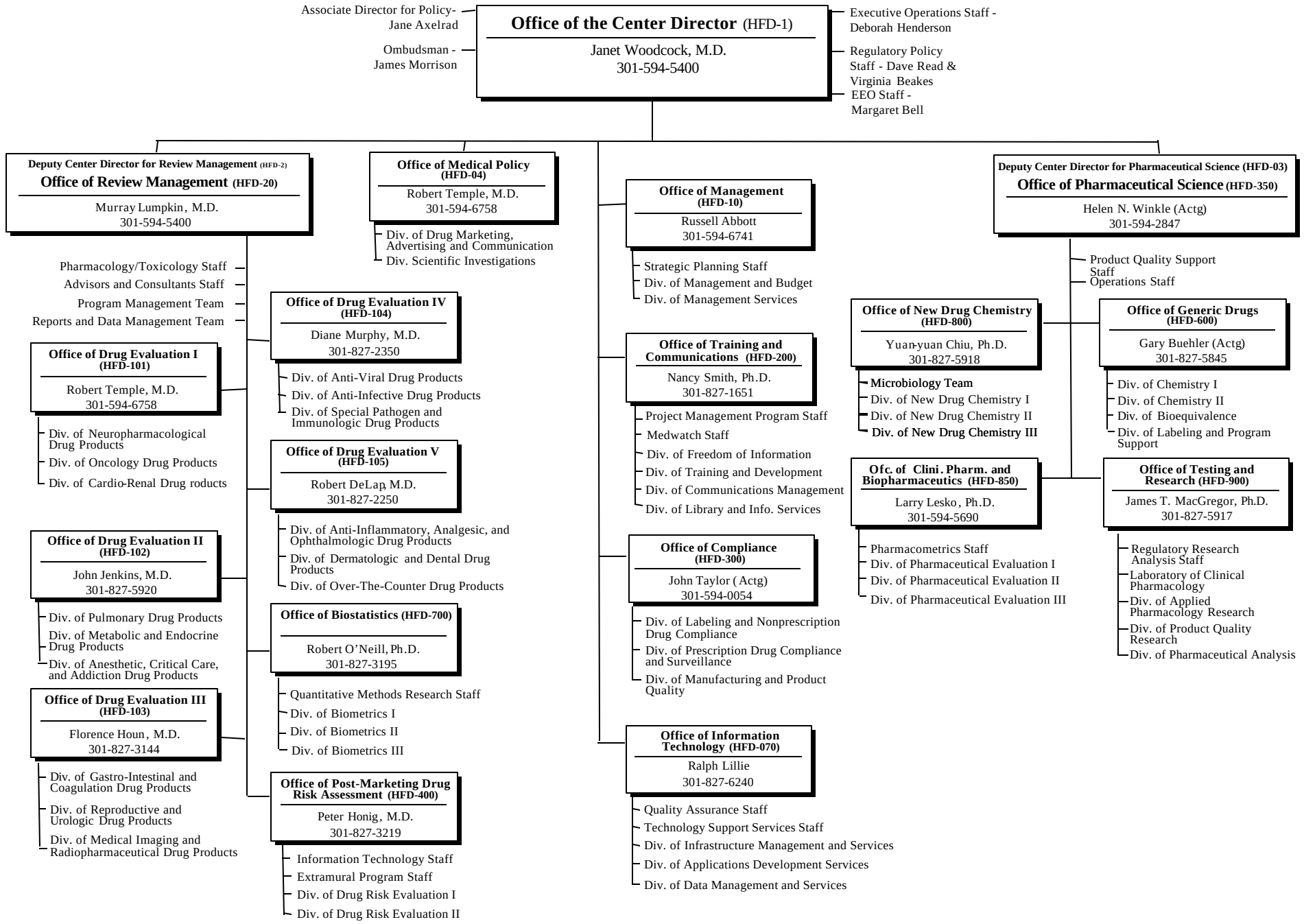
It answered:

- **More than 500 e-mails, mostly from consumers and health professionals.**
- **Approximately 2,000 telephone calls and 20 letters.**

In addition, the office held about 50 meetings with external parties.

AS OF: 04/26/00

CENTER FOR DRUG EVALUATION AND RESEARCH



Where to Find More Information

Selected Internet sites

- FDA Internet home page: http://www.fda.gov/
- CDER Internet home page: http://www.fda.gov/cder/
- MedWatch safety information and to report serious adverse events: http://www.fda.gov/medwatch/
- CDER's consumer drug information sheets for new medicines approved since January 1998: http://www.fda.gov/cder/consumerinfo/default.htm
- FDA Modernization Act of 1997 CDER-related documents: http://www.fda.gov/cder/fdama/default.htm
- *From Test Tube to Patient: New Drug Development in the United States:* http://www.fda.gov/fdac/special/newdrug/ndd_toc.html
- CDER *Handbook:* http:// www.fda.gov/cder/handbook/index.htm

Telephone

We respond to specific questions about prescription, over-the-counter and generic drugs for human use. You can telephone us toll free at 1-888-INFO FDA or directly at 301-827-4573.

E-mail

We can be contacted at DRUGINFO@CDER.FDA.GOV.

Regular mail

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Center for Drug Evaluation and Research

1999 Report to the Nation

Improving Public Health Through Human Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research