Center for Drug Evaluation and Research

CDER 1998 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.

CONTENTS

GRAPHS AND CHARTS

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 you and your doctor will have the information you need to use medicines wisely. We also monitor drugs for problems once they are on the market.

Reviewing drugs before marketing. A drug company seeking to sell a drug in the United States must first test it. We monitor biomedical research to ensure that people who volunteer for clinical 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 regular reports about suspected problems from manufacturers, health care professionals and consumers. Sometimes, manufacturers run into production problems that might endanger the health of patients who

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.**

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 or 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 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 have just begun holding annual public meetings with consumer and patient groups, professional societies and pharmaceutical trade associations. These meetings will 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.

1998 HIGHLIGHTS

We are pleased to present our third 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.

Drug review

Children, older Americans, people with arthritis, cancer, AIDS and hepatitis all benefited from significant new drugs approved in 1998. We exceeded all our goals for the prompt review of drug applications supported by industry user fees. Approval times for generic drugs also continued their downward trend, despite a growing workload and the absence of user fees. We approved 90 new drugs, including 30 new molecular entities. New molecular entities contain an active substance never before approved for marketing in any form in the United States. We also approved 124 new or expanded uses of already approved drugs, eight over-the-counter drugs and 344 generic drugs.

Drug safety

All medicines have risks. Injuries from approved medicines rank among the top 10 causes of death in the United States. Last year, we significantly upgraded our ability to detect problems with a drug's safety profile once it has been approved for marketing. 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. Three drugs were removed from the market last year because their risks were discovered to outweigh their potential benefits.

International harmonization

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. Our experts and scientists worked with their international colleagues to develop a standardized vocabulary to be used in all phases of drug development and post-market follow-up. We are making significant progress toward agreement on a common technical document that can be used to submit a marketing application in all three regions.

Communications

We embarked on a significant and long-term effort to include greater input into our planning and decision making from consumers, patients, health-care professionals, academia and industry.

We held our first public meeting with our stakeholders to obtain their input into our priority setting.

We significantly enhanced our Internet site to include information on all new medicines approved since January 1998. This includes information in plain language for consumers and technical information for health professionals.

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

FDA Modernization Act

We began implementing the Modernization Act initiatives during 1998. We met nearly all of the law's deadlines and, in many cases, completed projects ahead of schedule. We issued more than two dozen documents implementing various portions of the law or providing guidance to manufacturers about the law.

Pediatrics. We took several actions to implement portions of the law that make it more likely that children will receive improved treatment. We have outlined how manufacturers can obtain incentives for doing studies that will provide doctors with more complete information on how drugs affect children and what age appropriate doses are needed.

Information technology. We expect to have the capability and capacity for electronic regulatory submissions and reviews by fiscal year 2002. We established a five-year plan for moving from today's environment to a paperless environment. We are already pursuing a program of structured data submissions, particularly in the areas of chemistry, manufacturing and controls; biopharmaceutics; and generic drugs. We deployed an electronic document management system that allows our reviewers to capture, sign and archive their regulatory review products.

Emerging Issues

Pregnancy Labeling. We have reviewed our current system of labeling products for use by pregnant women and are developing an improved, more comprehensive and clinically meaningful approach. We are integrating input from multiple government agencies, consumer groups, medical experts and the pharmaceutical industry.

Antibiotic Resistance. We are addressing the growing problem of antibiotic resistance and its effects on drug development and regulation. We held a public forum meeting with the industry and academia, attended by over 200 individuals, to identify specific issues of mutual concern. We also held a two-day advisory committee meeting to seek comment and foster discussion in the public domain on the clinical development and use of antibiotics to treat resistant organisms.

Toxicity studies. We are exploring a formal collaboration with industry and academia to improve the drug development process. Standard studies of a drug's long-term toxic effects are time-consuming and hard to evaluate. To support rapidly progressing clinical trials and drug reviews, this cooperative effort will provide improved guidance for conducting and evaluating toxicity studies that are less time-consuming and more scientifically informative.

Pharmacy Compounding

The Modernization Act provides conditions under which a licensed pharmacist or physician can compound drug products and be exempt from certain requirements of the Federal Food, Drug and Cosmetic Act.

We developed regulations, guidance documents and a model memorandum of understanding. The model memorandum will serve as the basis for agreements between the Agency and individual states for regulating the interstate distribution of compounded drug products.

1

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 all goals for reviews supported by manufacturer user fees. We approved 30 new medicines that have never been marketed before in this country, 344 generic versions of existing drugs and authorized eight medicines to be sold over the counter without a prescription. Highlights of new medication options for American consumers include:

- ❑ The first in a new class of drugs for asthma.
- ❑ A new AIDS medicine that is given once a day.
- ❑ The first new tuberculosis drug in 25 years.
- ❑ Two new drugs for arthritis.
- ❑ The first in a class of drugs for Parkinson's disease, a progressive and debilitating disease of the central nervous system.
- ❑ A new drug and an expanded use of an existing drug for breast cancer treatment.
- ❑ A drug for erectile dysfunction.
- ❑ Three treatments tested specifically for treating the AIDS virus in children as well as adults.
- ❑ The first over-the-counter treatment for mild to moderate migraine.
- ❑ The first-ever generic version of a drug used to prevent rejection of transplanted organs.
- ❑ The first-ever generic version of an over-the-counter medicine for ulcers.

1998 drug review accomplishments:

90 new drugs

30 new molecular entities

124 new uses for already approved drugs

7 over-the-counter drugs

1 new use for an over-the-counter drug

344 generic equivalents for prescription and over-the counter drugs

9 orphan drugs

New Drug Review

We took 199 actions on original new drug applications, of which 90 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:

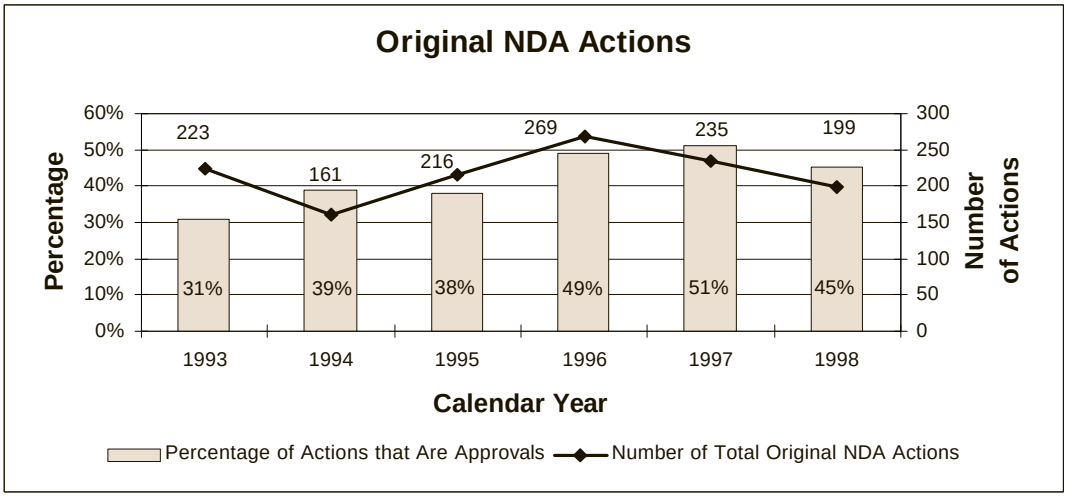
- **90 new drugs**
- **30 new molecular entities**
- **25 priority reviews**
- **Median total approval time: 12.0 months**
- **Median total FDA review time: 12.0 months**

Total original NDA approvals

Of these 199 actions, 90 were approvals of original new drug applications. The median total time to approval for new drugs acted on in 1998 was 12.0 months, 17 percent faster than the 14.4 months in 1997. Approval time represents the total review time at the Agency plus industry response time to the Agency's requests for additional information. The median review time—FDA time only—was also 12.0 months, 2 percent quicker than the year before.

Priority reviews

Last year's new drug approvals included 25 priority drugs. We perform an accelerated, six-month review on priority drugs because these drugs represent an advance in medical treatment. The median approval time for these priority applications was 6.4 months. The median review time was 6.2 months.



New molecular entity approvals

Thirty of the new original drugs were new molecular entities, and 16 received priority reviews. NMEs contain an active substance that has never before been approved for marketing in any form in the United States. The median total approval time for these products was 12.0 months, 10 percent faster than the 13.4 months in 1997. The median FDA review time was 11.9 months. Nine of the 39 NMEs approved in

Priority new drug approvals:

Abacavir sulfate (2 dosage forms)

Capecitabine

Celecoxib

Efavirenz

Eptifibatide

Fomivirsen sodium

Glucagon (rDNA origin)

Glucagon (rDNA origin), biosynthetic

Kit for the preparation of Tc 99m apcitide

Leflunomide

Lepirudin

Levonorgestrel/ ethinyl estradiol

Midazolam hydrochloride

Nevirapine

Octreotide acetate

Ribavirin and interferon alfa-2b

Rifapentine

Sacrosidase

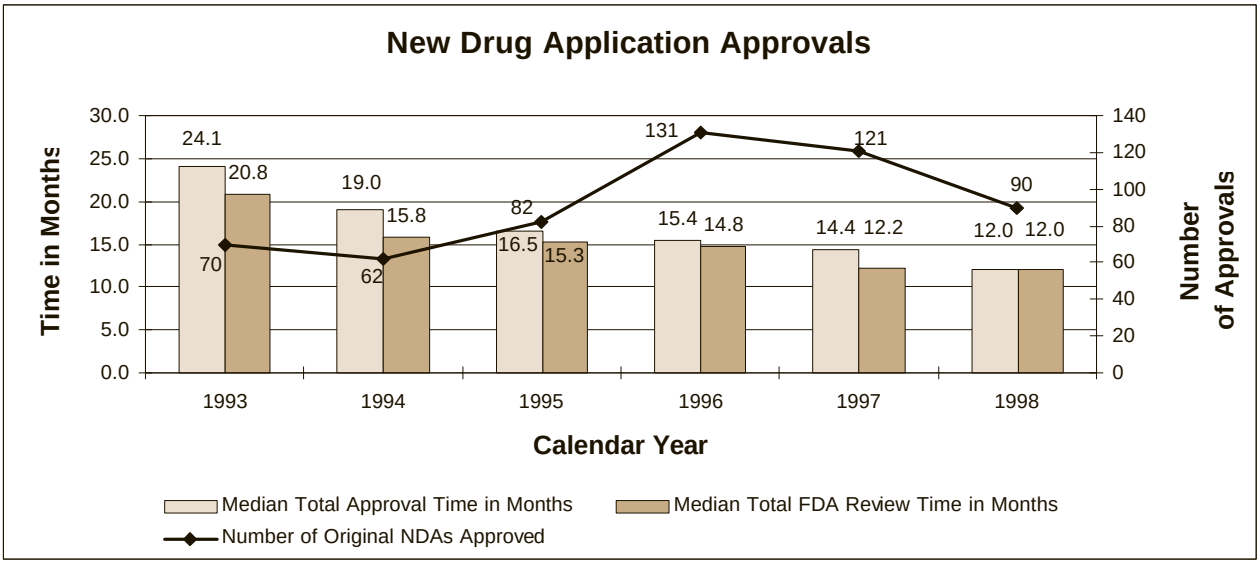
Sildenafil citrate

Thalidomide

Thyrotropin alfa

Tirofiban hydrochloride (2 dosage forms)

Valrubicin



1998 new molecular entities:

Abacavir sulfate

Brinzolamide

Candesartan cilexetil

Capecitabine

Celecoxib

Citalopram hydrobromide

Efavirenz

Eptifibatide

Fomivirsen sodium

Kit for the preparation of Tc 99m apcitide

Leflunomide

Lepirudin

Loteprednol etabonate

Modafinil

Montelukast sodium

1997, or 23 percent, received priority reviews. In 1998, slightly more than half the NMEs approved were priority reviews.

Notable 1998 new drug approvals

Last year's approvals benefited children, older Americans and people with AIDS and other disorders.

Children

- Some of the most vulnerable victims of the AIDS virus—children—now can get urgently needed help from three of last year's approvals. *Nevirapine* provides the first liquid formulation among this class of anti-HIV drugs. *Efavirenz* is one of two therapies approved last year for both adults and children. It was shown effective in combination with other agents in suppressing the HIV virus for at least two years in patients as young as 3 years old. *Abacavir*, the third new antiretroviral product, is an oral medication that also helps lower the amount of HIV in the blood, and can be taken by children as young as 3 months of age.
- *Midazolam syrup* offers an advantage over the previous intravenous-only compound for children who need sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures, or before induction of anesthesia. The approval of this product should also reduce the need for extemporaneous compounding of a liquid formulation of this drug.

Older Americans

- Last year's approvals included a breakthrough drug for erectile dysfunction, which affects primarily older men. *Sildenafil citrate* is an oral therapy for a condition that previously could only be treated locally with injections, pellets or implants. The drug includes augmented safety labeling to emphasize its risks for patients with a history of coronary problems and abnormal blood pressure as well as

1998 new molecular entities (continued)

Naratriptan

Paricalcitol

Rifapentine

Risedronate sodium

Rizatriptan benzoate

Sacrosidase

Sevelamer hydro-chloride

Sildenafil citrate

Telmisartan

Thalidomide

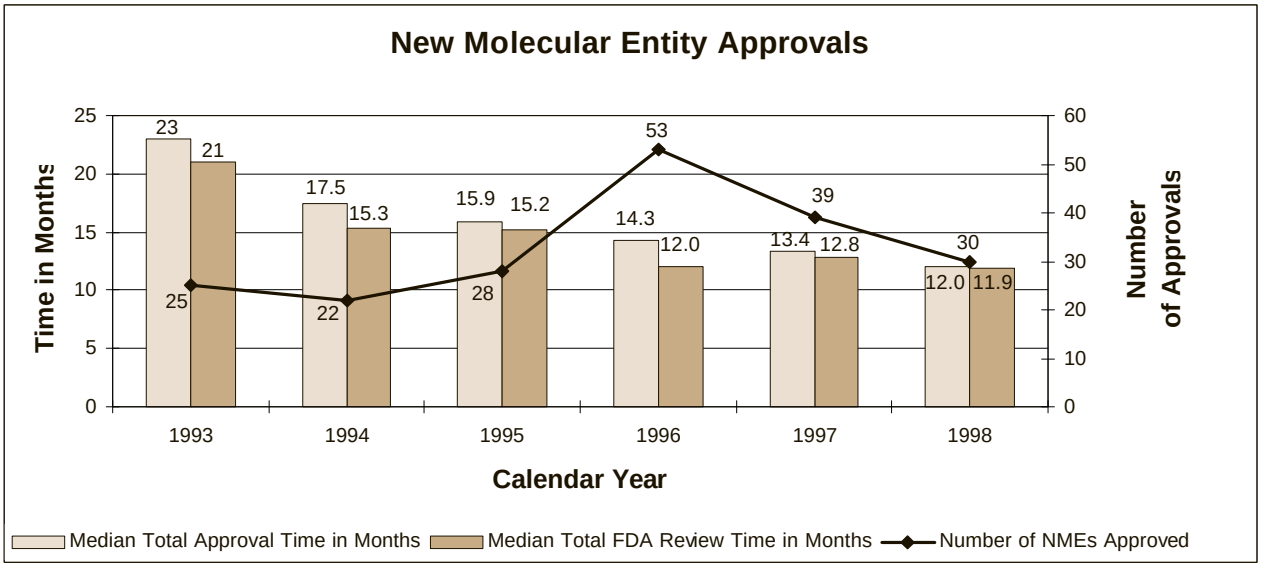
Thyrotropin alfa

Tirofiban hydrochloride

Tolcapone

Tolterodine tartrate

Valrubicin



a contraindication for use with medications containing nitrates.

- Other new treatments for older Americans include *tolterodine*, the first new drug therapy in several decades for incontinence, and *brinzolamide*, another treatment regimen for elevated intraocular pressure and open-angle glaucoma.

People with arthritis

- *Leflunomide* is the first oral drug that can relieve the symptoms and slow the progression of rheumatoid arthritis.
- *Celecoxib* is a new type of non-steroidal anti-inflammatory pain reliever that can be used for the treatment of both rheumatoid arthritis and osteoarthritis.

People with cancer

- *Fentanyl citrate* is a drug especially formulated to ease its administration to patients who are suffering from the agonizing pain that breaks through narcotic therapy.
- *Capecitabine* is an oral cancer treatment which is converted by the body to 5-fluorouracil (5FU), a drug that until now had to be administered intravenously. The product is used to treat advanced breast cancer that does not respond to other medications.
- *Valrubicin* is a new treatment for cancers of the bladder that cannot be removed immediately.
- *Thyrotropin alfa* is a new diagnostic tool for patients with thyroid cancer.

People with hepatitis

- Chronic hepatitis C infection can lead to cirrhosis, liver cancer and liver failure and is the most common reason for liver transplantation. An oral formulation of *ribavirin in combination with interferon alfa*-2b is a new treatment option that has higher sustained response rates than alfa interferon alone.

New molecular entity statistics

- **30 approvals**
- **16 priority reviews**
- **Median total approval time: 12.0 months**
- **Median total FDA review time: 11.9 months**

Note: **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.**

Other significant approvals

- *Rifapentine* is the first new medicine for pulmonary tuberculosis approved in a quarter of a century. The new drug can be taken in lower doses and less frequently than older products, thereby encouraging compliance.
- Another drug that serves a few, but very ill, patients is *thalidomide.* Two generations ago, FDA refused to approve it for the U.S. market, thereby preventing the tragic fetal deformities that beset thousands of victims elsewhere. Last July, we used unprecedented safeguards to clear the drug as treatment for a complication of Hansen's disease (leprosy), which affects about 100 people in this country. The approval, based on a wealth of data showing that the drug improves skin lesions in at least 70 percent to 80 percent of patients, restricts the prescribing of thalidomide to selected physicians. Its use is limited to patients who agree to comply with stringent protective measures, including a patient registry.

Safety first

In refusing to approve several applications, we may have prevented significant harm to American consumers. We were concerned about an antipsychotic's capacity to cause serious cardiovascular events, including death. This concern was prompted by an apparent increase in the rate of sudden unexplained death compared to that observed in other recent antipsychotic NDAs. European experience also appeared to show a greater risk of sudden death. The sponsor withdrew the application.

Another example was a drug to control high blood pressure. There was a signal that it might be more toxic to the liver than other drugs of its chemical class. Since the drug did not appear to provide an advantage over its chemical class siblings, we decided that we couldn't approve it without a substantially increased number of patients studied.

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 1998, these electronic submissions offset the equivalent of nearly 10 million paper pages. Beginning in 1999, drug companies will be able to submit the entire new drug application electronically in lieu of paper.

Orphan drug approvals

In 1998, we approved nine "orphan" products to treat disorders with patient populations of 200,000 or fewer:

***Sacrosidase,* the first treatment for patients with genetic deficiency of the enzyme sucrase, which is part of the congenital sucrase-isomaltase deficiency.**

***Lepirudin,* which provides the first available treatment for patients with heparin-induced markedly lowered platelet counts to help prevent further development of platelet emboli.**

***Octreotide acetate,* a new dosage form for patients with acromegaly, VIPoma or carcinoid. This new dosage form reduces the number of injections they require from two to four times a day to once a month.**

***Modafinil,* a new therapy for patients with narcolepsy.**

Orphan drug approvals (continued)

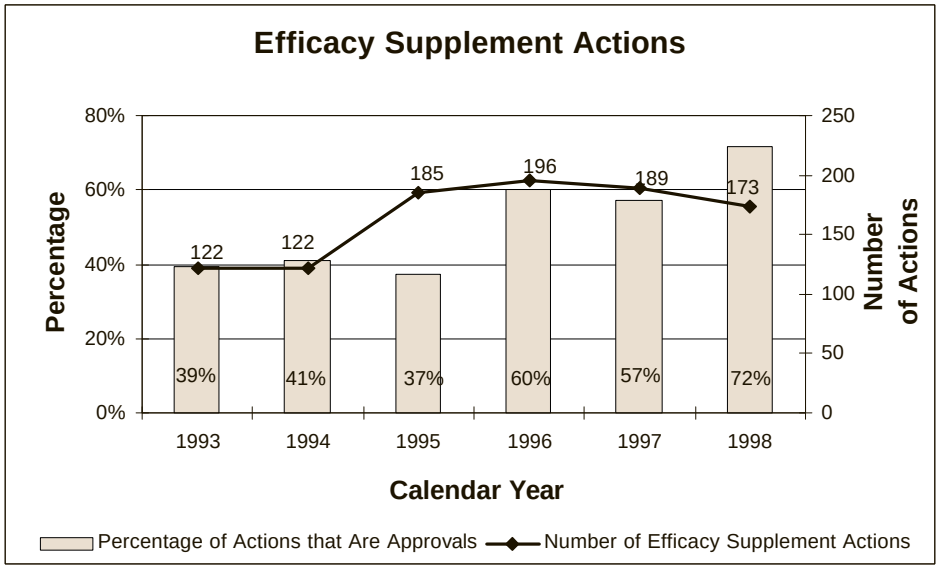
***Mafinide acetate,* for fighting bacterial infections in skin grafts for burns.**

***Thalidomide,* for treating a complication of leprosy.**

***Valrubicin,* for treating bladder cancer.**

***Thyrotropin alfa,* for use in imaging studies of people with thyroid cancer.**

***Rifapentine,* for treating pulmonary tuberculosis.**



New or Expanded Use Review

Last year we took action on 173 applications for new or expanded uses of already approved drugs. We approved 124, including 13 that were given priority reviews of six months or less. These applications, often representing important new treatment options, are formally called "efficacy supplements" to the original new drug application.

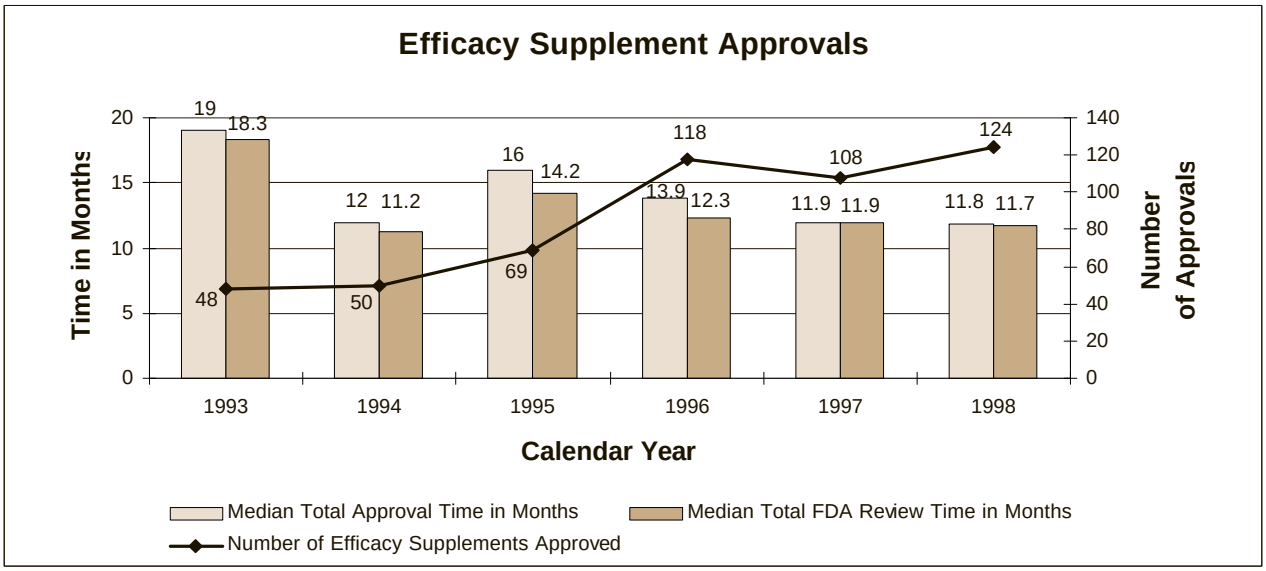
The median total approval time was 11.8 months, and median FDA review time was 11.7 months.

Efficacy supplement statistics:

- **124 approvals**
- **13 priority reviews**
- **Median total approval time: 11.8 months**
- **Median total FDA review time: 11.7 months**

Notable 1998 new or expanded use approvals

- *Tamoxifen citrate,* a well-established breast cancer drug in use for



more than 20 years, is now approved for the reduction of breast cancer risk in women who have a great likelihood to get the disease.

- *Lamivudine*, in tablets and oral solution, provides the first orally available treatment for chronic hepatitis B infection. Approval of this indication makes available an important therapeutic alternative to interferon, which is administered by injection.

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.

Drug labeling: joint responsibility

All drug review team members make sure the label is accurate and provides clear instruction to health care practitioners for prescription medicines or to consumers for over-the-counter medicines.

Applied research

In focused research to improve the drug development and review process, our scientists are developing:

- **An electronic knowledge base that can be useful in predicting the cancer-causing potential of new molecules based on their structure and comparisons to more than 700 pharmaceuticals in a relational database.**
- **Data to support use of troponin T as a biomarker to detect drug-induced myocardial damage.**
- **A biopharmaceutical classification system based on research we performed on high**

Over-the-Counter Drug Review

In 1998, we approved seven new drugs and one new use for over-the-counter marketing, including:

- The first OTC drug product for the relief of migraine headache pain.
- Drugs used for relief of pain and fever.
- Vaginal antifungal drug products and combinations.
- Drugs for treating and preventing heartburn.
- Smoking cessation aids.

Aspirin professional labeling published

We published 15 documents in the *Federal Register*. A highlight was the final rule establishing professional labeling for oral drug products containing aspirin. These products are used to treat pain, fever and inflammation. The professional labeling reflects the latest information on using these products to prevent and treat specific cardiovascular, cerebrovascular and rheumatologic diseases.

Other documents published in 1998, included:

- Amendments to require specific warning statements for ophthalmic vasoconstrictors; camphor or menthol-containing topical drug products and inhalers; and pain relievers.
- A final rule to limit the container size for sodium phosphates oral laxatives.
- Notices to reclassify ingredients, including laxatives, nasal decongestants and malaria treatments.
- Notices to establish new conditions for specific products used to treat lice and UVA sunscreens.
- A draft guidance to industry for labeling OTC topical drug products for the treatment of vaginal yeast infections.

Over-the-counter drug statistics:

- **7 new drug approvals**
- **1 new use approval**
- **15 rules or notices**

Past performance

In 1995, we approved 10 new drugs or conditions for OTC marketing. We published 21 rulemakings in the *Federal Register*.

From 1996 to 1998, we approved an average 15 new drugs or conditions each year. We published and more than 56 notices, monographs or rules that affected over-the-counter drug products.

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.

Meetings with expert advisors

In 1998, the Nonprescription Drugs Advisory Committee met jointly with other FDA advisory committees and as the Dental Subcommittee on six occasions. Subjects included:

- Effectiveness testing for final formulations of health-care antiseptic drug products relative to performance expectations for these products.
- Vaginal antifungal class labeling requirements.
- Advice on new OTC drug applications.
- Completion of the review of antigingivitis and antiplaque drug ingredients that will serve as the basis of an advanced notice of proposed rulemaking.

Improved labels for OTC drugs

Two years ago, we proposed standardized over-the-counter drug label formats. We completed testing of label prototypes and finalized the regulation for publication in March 1999.

OTC drug mongraphs

We have been evaluating the ingredients and labeling of older OTC products.

Our goal is to publish OTC drug monographs that establish acceptable ingredients, doses, formulations and consumer labeling for these older active ingredients.

Products that conform to a final monograph may be marketed without further FDA clearance.

Generic Drug Review

We approved 344 generic products in 1998, including 46 that represent the first time a generic drug was available for the brand name product. The median approval time for generic drugs continued a downward trend and stood at 18.0 months last year.

Initiatives to streamline the generic drug review process have paid off in a steady downward trend in approval times. The 18.0-month median approval time last year compares to 19.3 in 1997; 23 in 1996; and 27 in 1995.

We have also seen a drop in the number of review cycles needed to approve abbreviated applications for generic drugs. In 1998, the average application required 2.6 cycles before being approved. This was down from 3.6 in 1996 and 2.9 in 1997.

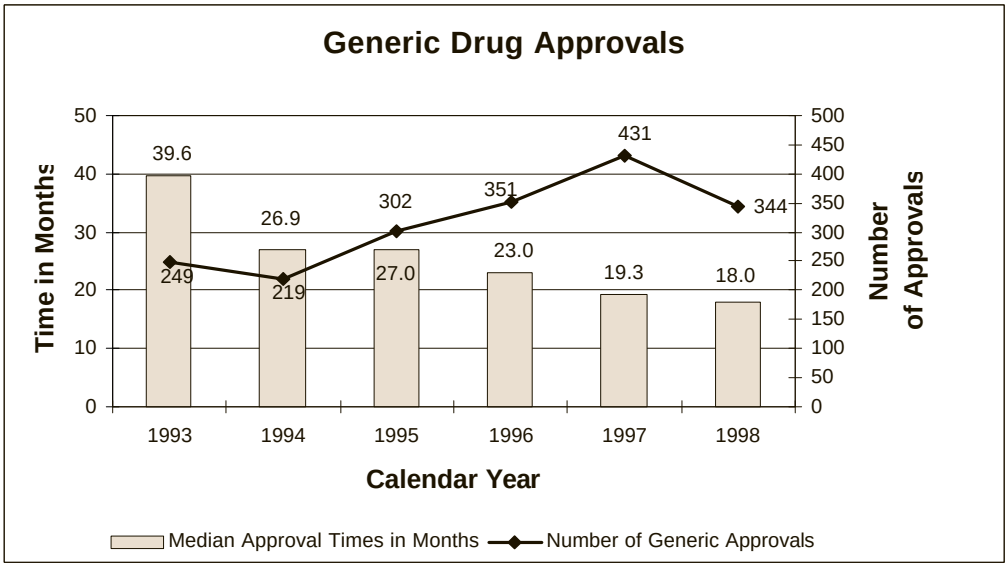
These downward trends occurred despite a continuing growth in workload. From 1991 to 1993, submissions remained relatively stable at approximately 323 applications each year. In each of the years since, there has been an increase in applications: 411 in 1995; 453 in 1996; 464 in 1997; and 564 last year.

1998 generic drug statistics

- **344 generic drug approvals**
- **Median approval time: 18.0 months**

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



Notable 1998 generic drug approvals

- Cyclosporine, used to prevent rejection of transplanted organs.
- Cimetidine, used in the treatment of ulcers.

The approval of generic versions of these products and other generic approvals in 1998 could save the American people and the federal government hundreds of millions of dollars.

Electronic submission initiative

Last year, we received 38 electronic submissions of bioequivalence data and 43 electronic submissions of chemistry, manufacturing and controls data. For comparison, only nine bioequivalence electronic submissions were received before 1998 and none with CMC data.

In continued support of the electronic submissions initiative, we have:

- ❑ Promoted electronic submissions directly to industry and trade groups.
- ❑ Held training sessions for industry.
- ❑ Formed a joint industry-CDER workgroup to facilitate feedback on the program and assess potential enhancements.

"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, also known as the Waxman-Hatch Act.

Generics are not required to replicate the extensive clinical trails that have already been 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 set for bioavailability, which is the extent and the rate at which the body absorbs the drug.

Scientists measure the time it takes the 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.

Total manufacturing supplement approvals:

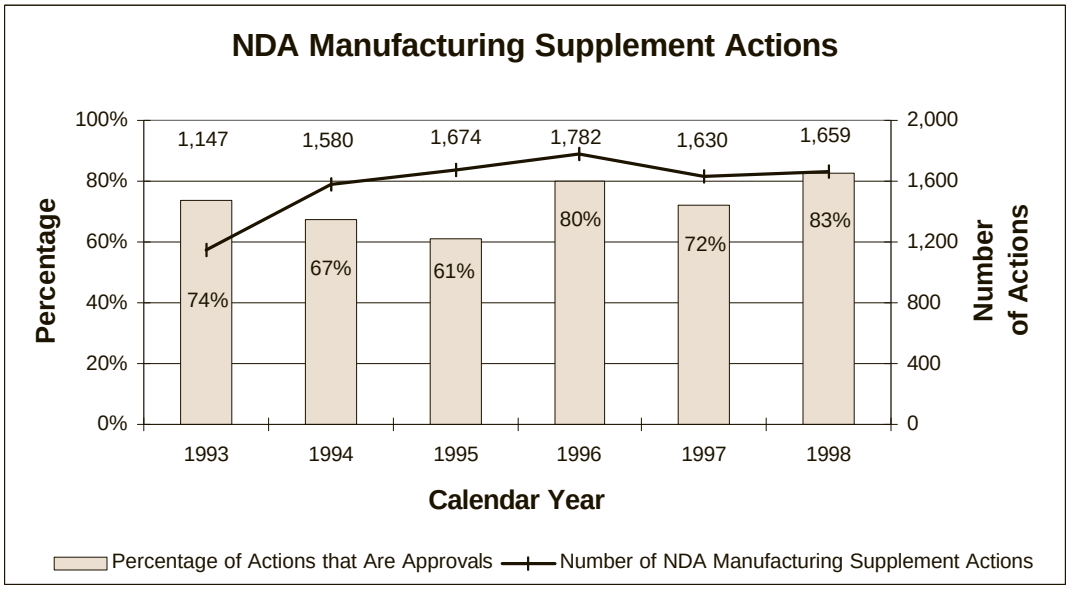
- **1998: 3,659 approvals**
- **1997: 3081 approvals**

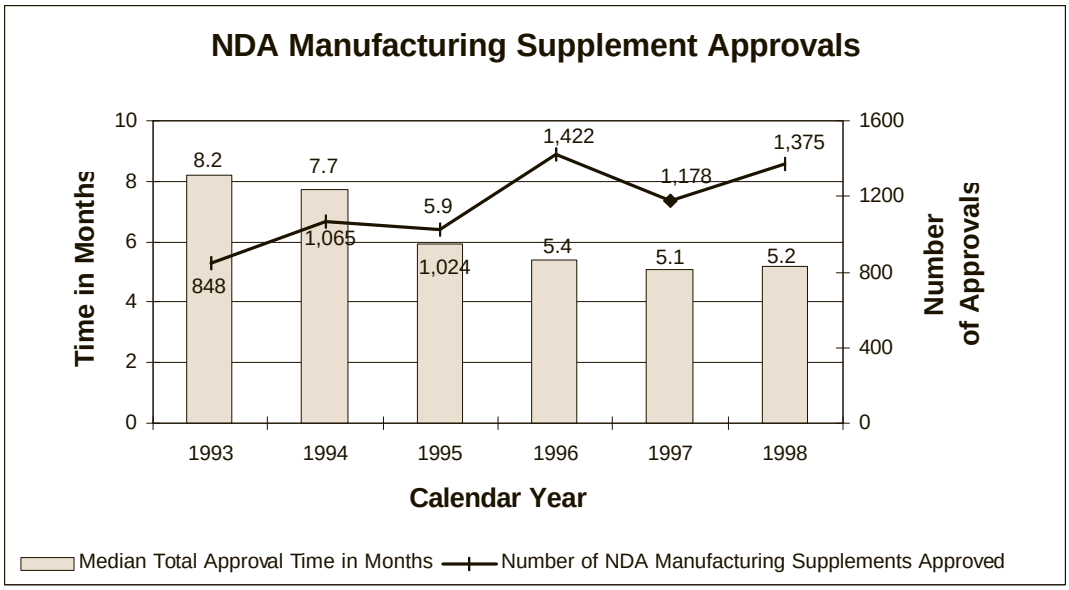
Manufacturing Supplements to New Drug Applications

In 1998, we took action on 1,659 manufacturing supplements, of which 1,375 were approvals.

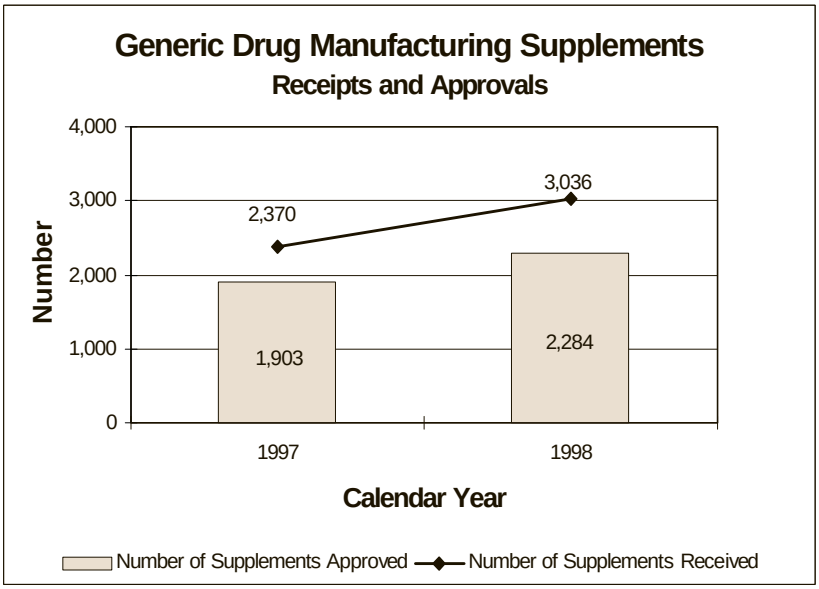
NDA manufacturing supplement statistics

- **1,375 approvals**
- **Median total review time: 5.2 months**





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

- **2,284 approvals**
- **3,036 receipts**

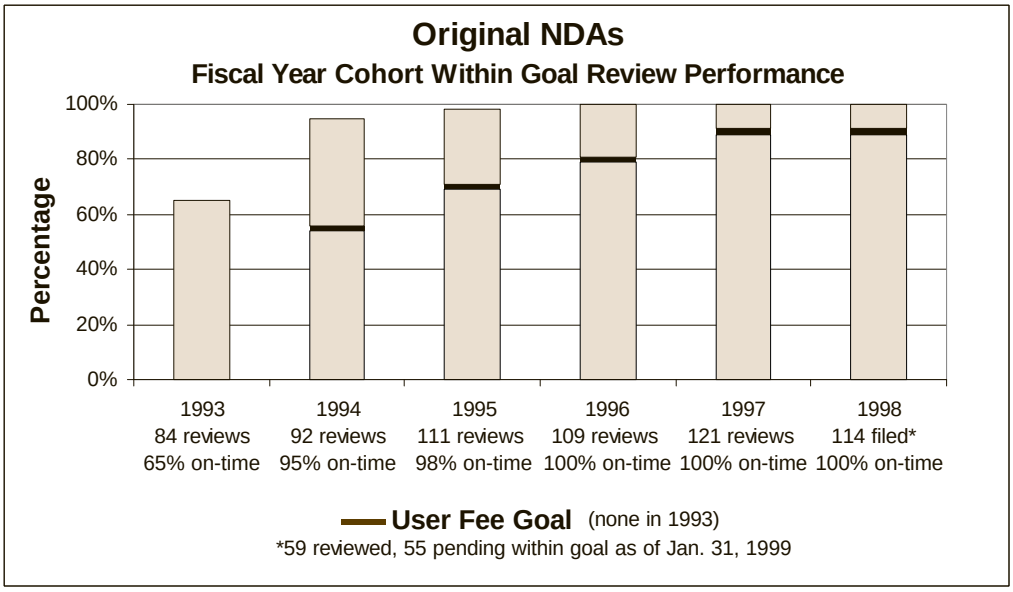
Manufacturing Supplements to Generic Drug Applications

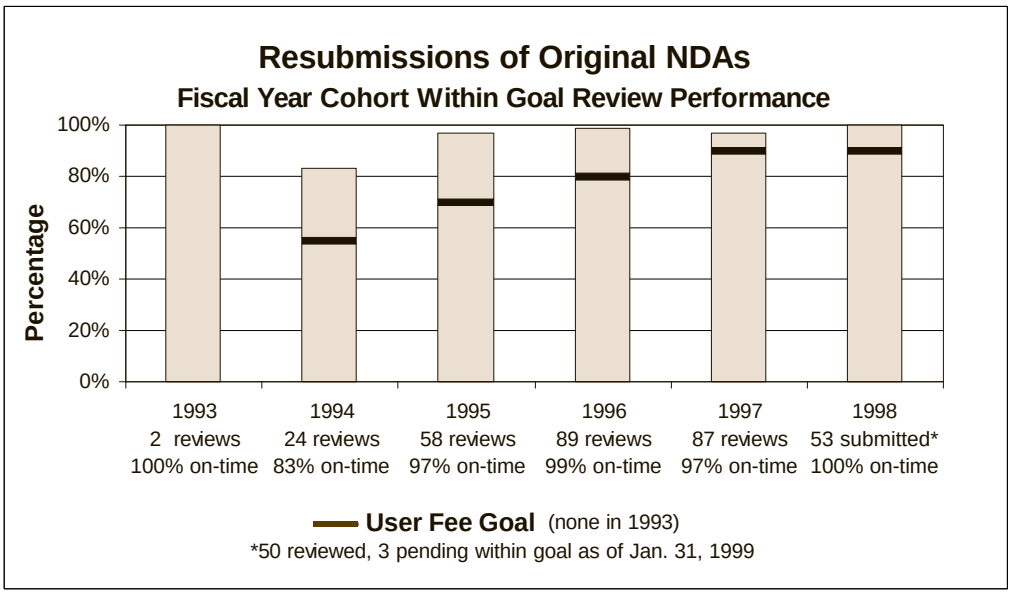
In 1998, we approved 2,284 manufacturing supplements to generic drugs applications. We received 3,036 manufacturing supplements during the year. In 1997, we began counting generic drug manufacturing supplements separately from all supplements to generic drug applications.

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. Coupled with management reforms, user fees have helped us meet or exceed all the performance deadlines we agreed to with Congress and the industry.





On-time review performance

The on-time review performance charts show our results exceeded the review performance goals.

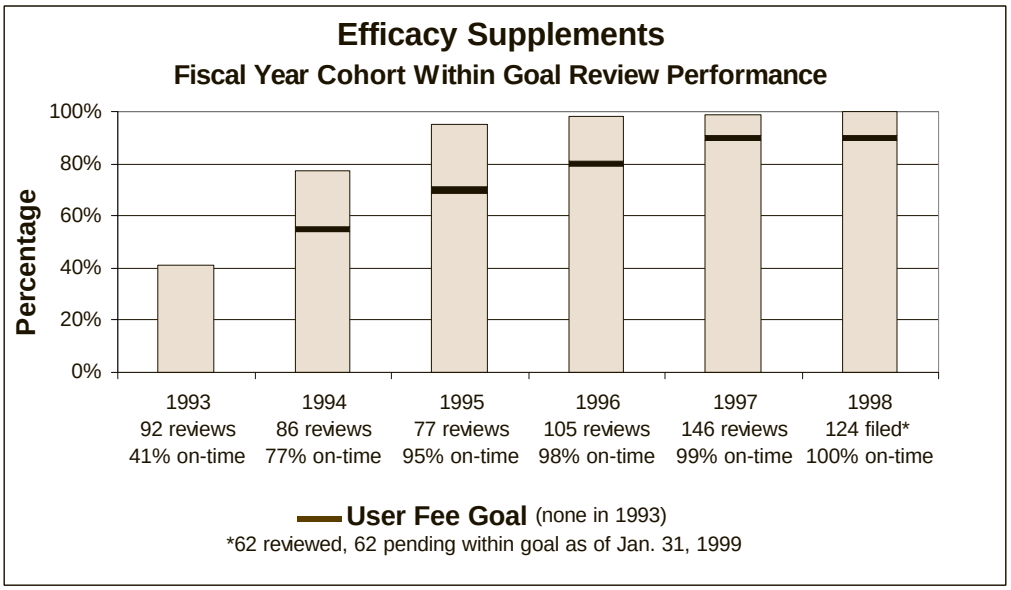
When comparing the fiscal year performance charts with the calendar year performance charts, remember that work on one year's submission cohort is often performed in the following year.

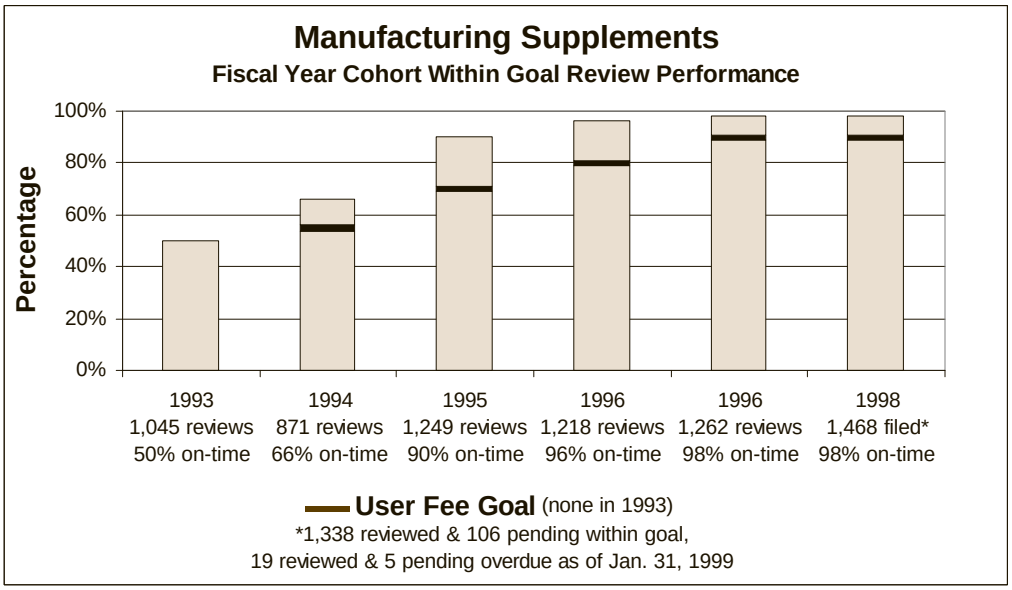
User fee goals

In 1992, we agreed to specific performance goals that require 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 marketing applications.

We have exceeded the progressively more stringent PDUFA performance goals agreed to for each successive fiscal year.





User fee reauthorization

In 1997, Congress, with the Center's and the industry's support, enhanced the user fee program and extended it for five years as part of the FDA Modernization Act. The act changes how fees are assessed and collected. Fees are waived for first applications for small businesses, orphan products and pediatric supplements.

A phase-in to a 10-month review time by fiscal year 2002 for standard new drug applications and efficacy supplements highlights an expanded list of review performance goals. Performance goals for priority drugs remain at six months.

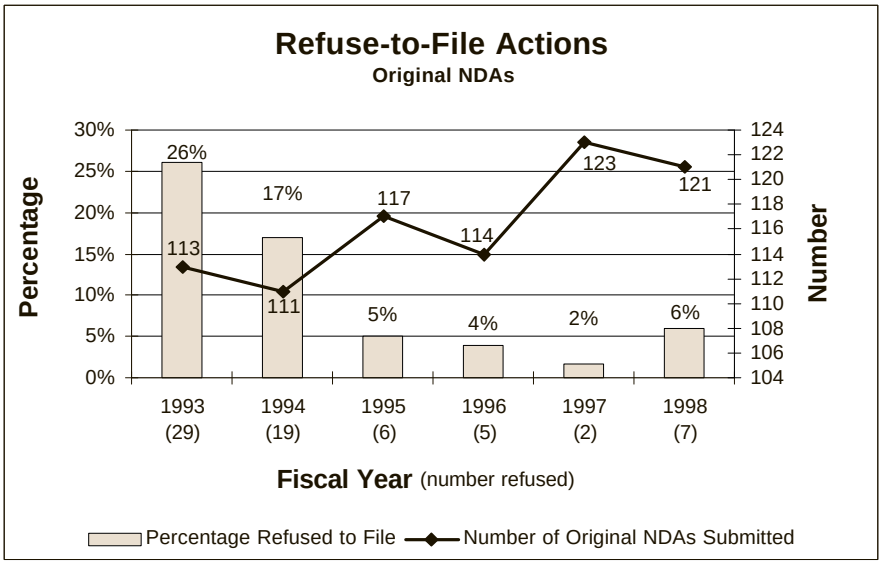
We have committed to goals that will help speed the time it takes for drugs to be appropriately tested and developed before submitting those results for FDA review.

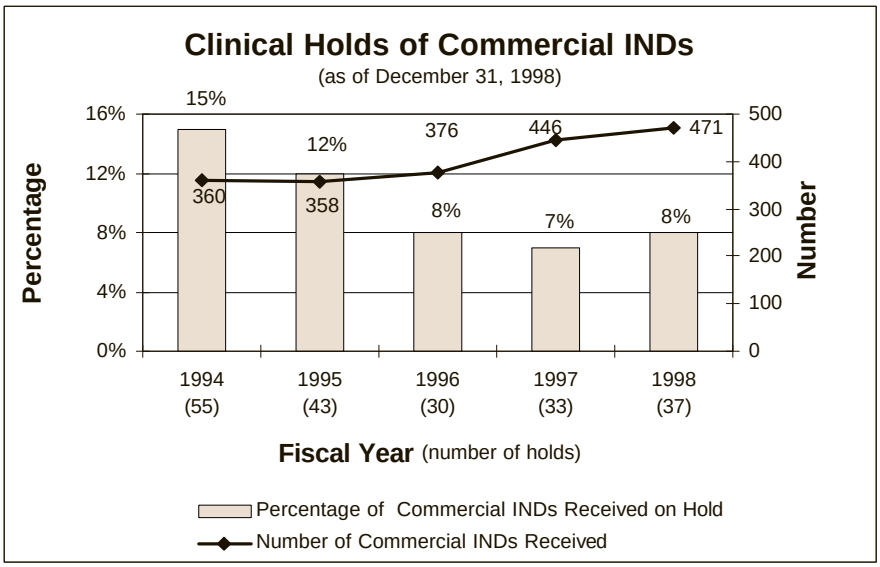
These new goals include those related to meeting management, clinical holds, resolving major disputes and reaching agreement on certain protocols. There are added expectations regarding electronic applications and submissions, simplification of action letters and expedited notification of deficiencies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





Overdue Reduction

One of our goals for the user fee program was to reduce the number of overdue reviews and create a review program that stays current with the workload and has a minimum of overdue applications at any given time.

On Dec. 31, 1998, the number of applications on hand, including those submitted but not yet officially filed, and the number overdue were:

- **Original NDAs: 120 on hand, none overdue.**
- **Efficacy supplements: 112 on hand, one overdue.**
- **Manufacturing supplements: 612 on hand, five overdue.**

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.

2

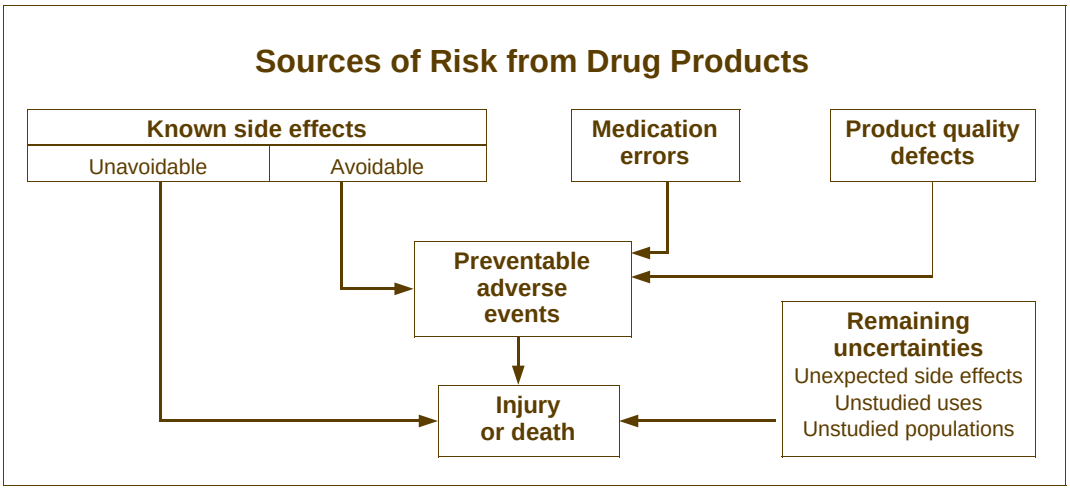
DRUG SAFETY AND QUALITY

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 tradeoff for accepting these uncertainties is our continued vigilance along with that of the industry to collect and assess data during the post-marketing 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.



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:

- A*voidable*. 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 premarket testing.

Drug Safety

We evaluate the ongoing safety profiles of drugs available to American consumers using a variety of tools and disciplines. This program underwent many enhancements in 1998, including:

- Elevation of the Division of Pharmacovigilance and Epidemiology to become the new Office of Postmarketing Drug Risk Assessment.
- Formation of drug risk assessment teams serving the drug review divisions and providing specialized attention to high risk drug areas
- Integration of triage, data entry and risk analysis in processing adverse event reports.
- Initial efforts to formalize drug error reporting.
- Rollout and implementation of a state-of-the-art information technology system for receiving, storing, and analyzing the nearly 250,000 individual reports of suspected drug-related adverse events we receive annually
- Initiation of the electronic submission of adverse event reports from drug manufacturers.
- Exploration of new databases, such as hospital audit systems.
- Initiation of new methodologies including data mining tools.
- Implementation of a monthly videoconferences with Canadian health authorities and a similar arrangement with the European Union.

Internet resources

The latest drug safety information can be found on FDA's MedWatch Website at http://www.fda.gov/medwatch/.

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

Applied research

Our scientists completed research to support a guidance to industry on data expected by the FDA for drug metabolism and drug interactions.

Adverse event reporting

Last year, we received 232,470 reports of suspected drug-related adverse events:

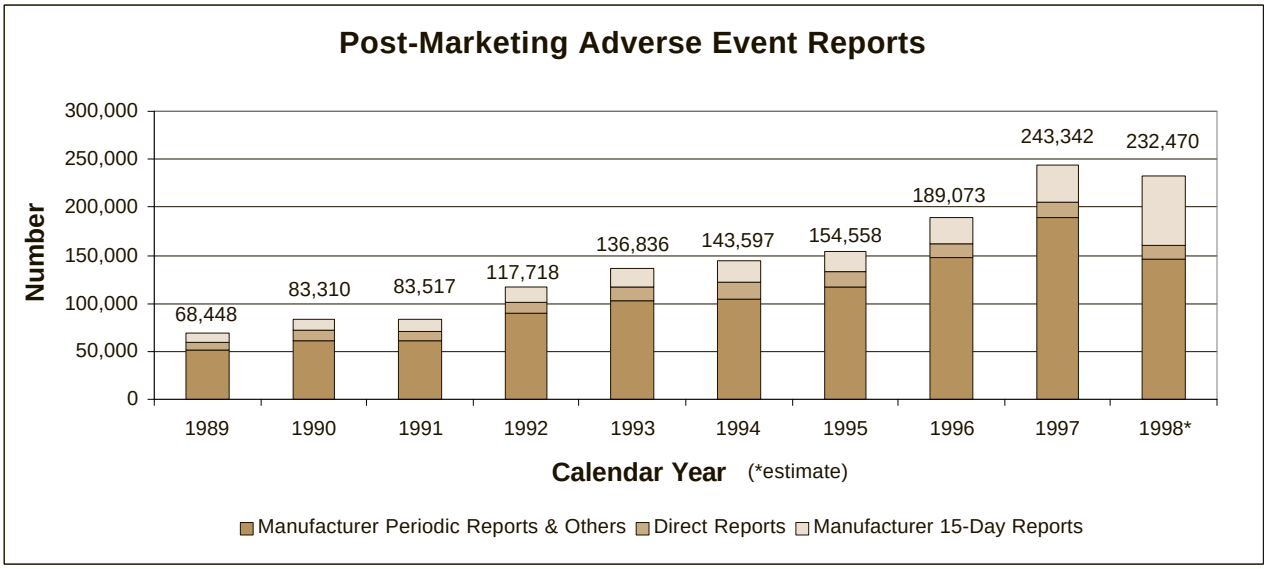
- 71,464 manufacturer 15-day reports.
- 15,456 reports directly from individuals.
- 145,550 manufacturer periodic reports and other follow-up reports.

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

Drug Shortages

We coordinated responses to a wide variety of drug shortage situations in 1998.

These have ranged from treatments for tuberculosis and AIDS to therapy for serious varicose veins to multi-vitamins used for nutritional support in hospitalized patients.



Safety relabeling

Our review of adverse events led to relabeling or warnings for these drugs:

***Troglitazone,* for use in Type II diabetes, due to liver toxicity.**

***Tolcapone,* for use in Parkinson's disease, due to liver toxicity.**

***Ticlopidine,* for stroke prevention, due to bleeding events.**

***Enoxaparin,* for prevention of deep vein thrombosis, due to epidural hematoma.**

***Cisapride,* used for gastroesophageal symptoms, due to heart arrhythmias.**

***Isotretinoin,* for the treatment of acne, due to reports of depression, psychosis and suicide.**

management methods include new labeling, "Dear Health Care Practitioner" letters, restricted distribution programs or product marketing termination.

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 adverse drug reaction reports from FDA's MedWatch program 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.

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 1998, the Center issued 399 advisory letters to companies regarding their promotional materials for launch campaigns.

Report types

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

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

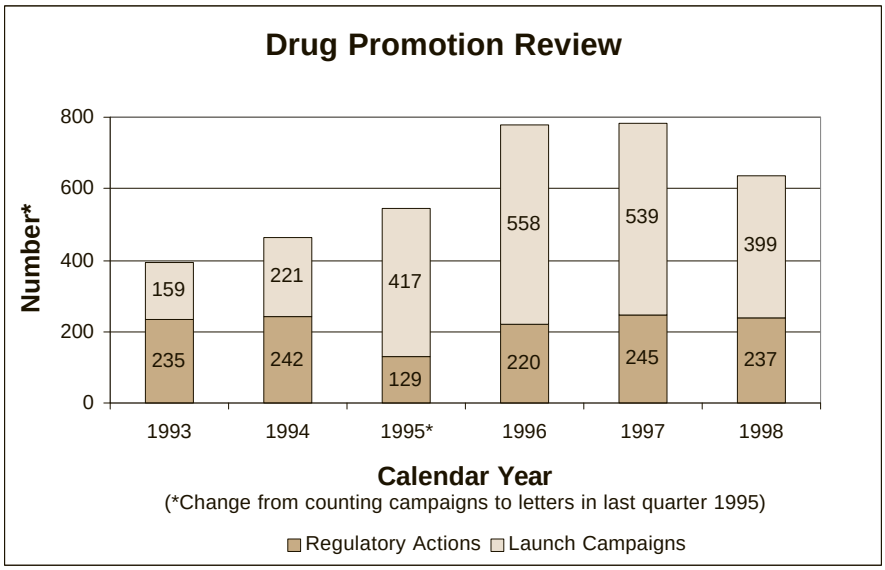
***Manufacturer periodic reports and others:* Drug manufacturers report all other adverse events, for example, those that are less than serious or described in the drug's labeling. Reports are submitted quarterly for the first three years of marketing and annually after that. When additional information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

We issued 237 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 724 other advisory, acknowledgment or closure letters to the industry regarding prescription drug promotional materials.

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.



Direct-to-consumer advertising

We issued 282 letters regarding direct-to-consumer promotion. We also began research to evaluate the effects of direct-to-consumer advertising on the patient-physician interaction.

Patient medication guides for certain medicines

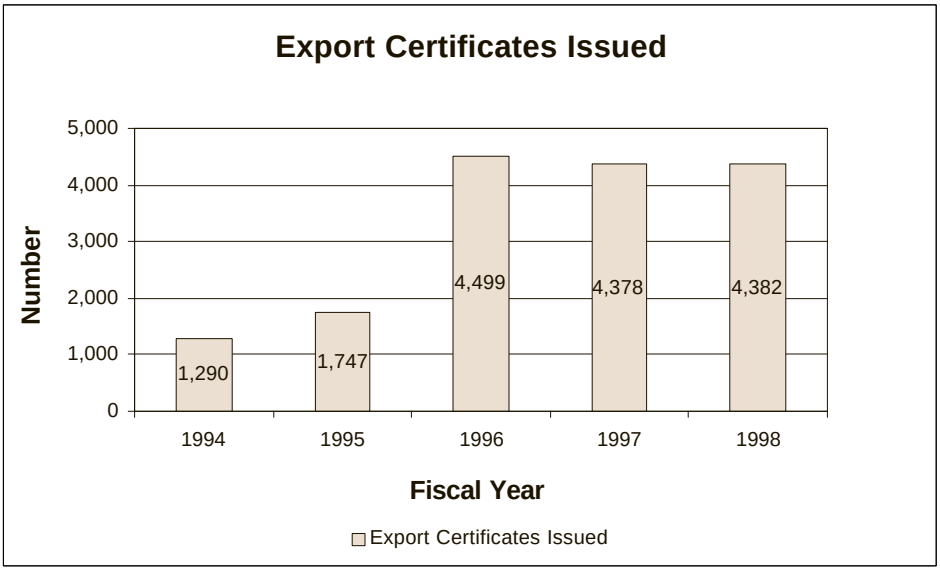
We published regulations that require FDA-approved patient labeling, called medication guides, to be distributed for certain rare products that pose a serious and significant public health concern. The medication guide would have to be considered necessary for the safe and effective use of the product before this rule applied.

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, non-profit agencies and academic groups to ensure that 75 percent of patients receive useful information about their new prescriptions by the year 2000. We also began a study that will test the methods to be used to evaluate the private plan.

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



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.**

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.

Product Quality Research Institute

We are working with academia and industry to develop an efficient mechanism to conduct research for improving the quality of drug products available to the American consumers.

The Product Quality Research Institute will bring together scientists from academia, industry and the FDA.

They will collaborate on research in the areas of drug chemistry, biopharmaceutics and science management.

The goal is to identify better test methods for assessing quality of drugs and improved manufacturing and management processes.

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:

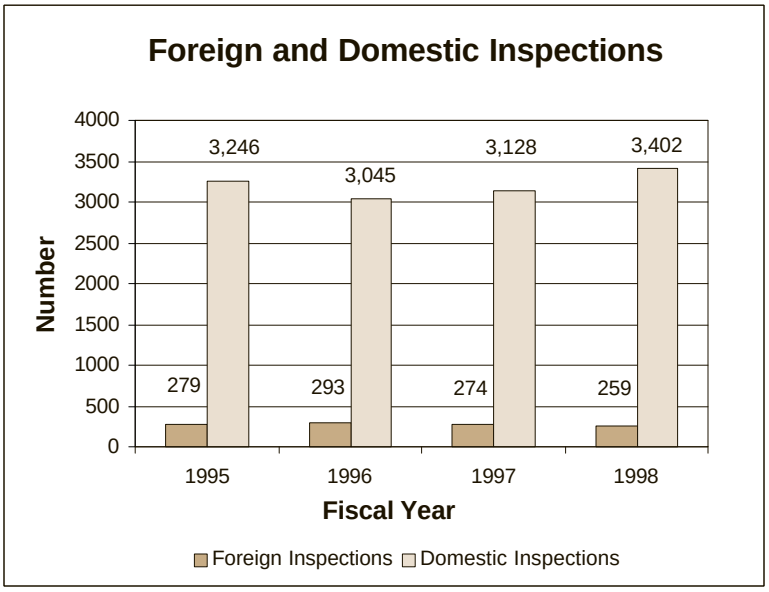
- Evaluating the factory inspections that include collection and analysis of associated samples and the conditions and practices under which drugs are manufactured, packed, tested and stored.
- Monitoring the quality of finished drug products in distribution through sampling and analysis.

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.

We ensure that all marketed over-the-counter drugs medicines are safe

Applied research

Our scientists are completing research to support a guidance to industry on qualifying near infrared spectroscopy equipment, a new technology that holds great promise for improved drug quality.



Number of foreign inspections by country
(fiscal years 1995 to 1998)

- **Japan: 130**
- **Italy: 115**
- **United Kingdom: 114**
- **Germany: 95**
- **France: 92**
- **Canada: 87**
- **Switzerland: 56**
- **Ireland: 52**
- **China: 41**
- **India: 33**
- **Spain: 32**
- **All others: 258**

and effective for their intended uses and are labeled accurately. We determine if a product complies with the OTC Review.

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.

Drug Recalls and Withdrawals

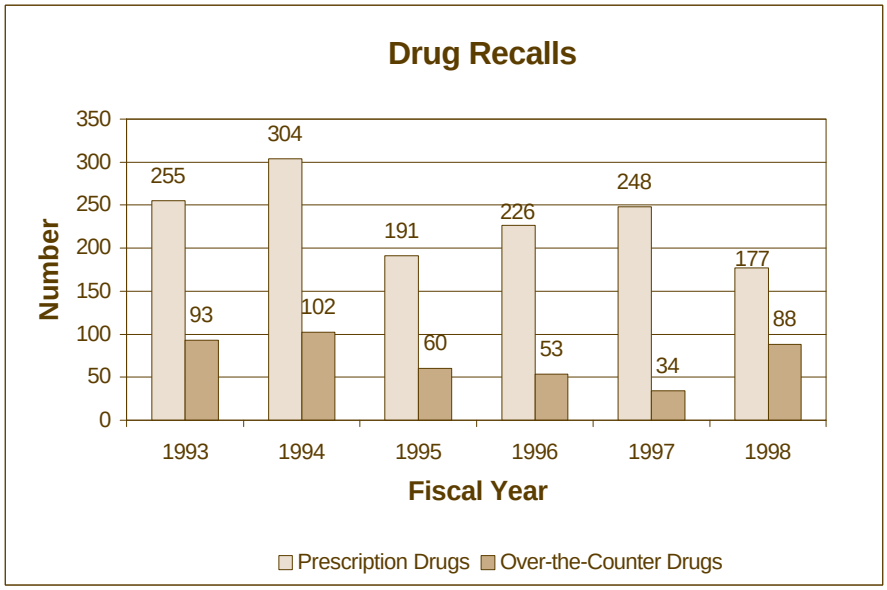
We coordinate drug recall information and prepare health hazard evaluations to determine the risk to public health by products being recalled. We classify recall actions in accordance to the level of risk, and we participate in determining recall strategies based upon the hazard and other factors including 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. Based on reports that we reviewed in consultation with the manufacturers, these drugs were withdrawn from the U.S. market last year:

- *Mibefradil*, an antihypertensive, withdrawn because it interacts, sometimes dangerously, with many other drugs.
- *Bromfenac sodium*, a nonsteroidal anti-inflammatory, withdrawn due to liver toxicity.

Voluntary recalls

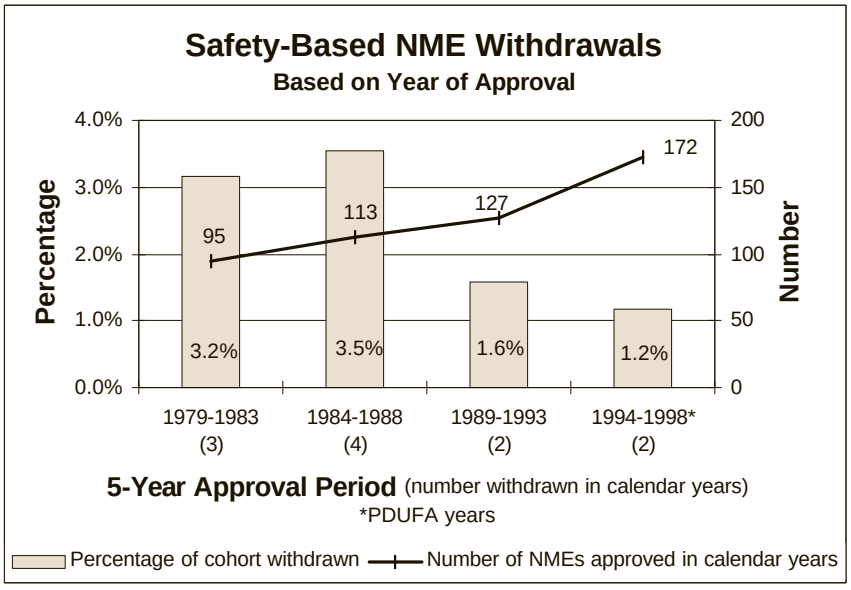
A recall is a voluntary action taken by a manufacturer or distributor to carry out their responsibility to protect the public health when they need to remove or correct a marketed drug product that presents a significant risk to public health. A voluntary recall is more efficient and effective in assuring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



- *Terfenadine*, an antihistamine, withdrawn because it can cause heart arrhythmias when used with drugs that block its metabolism.

One drug, *loratadine/pseudoephedrine*, an antihistamine/decongestant, was reformulated and the original withdrawn due to an association with throat blockages.

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 governments and professional and consumer associations.



Most common reasons for drug recalls:

- **Deviations from good manufacturing practices**
- **Subpotency**
- **Stability data failing to expiration date**
- **Discrepancies from conditions specified in the FDA approval**
- **Failure to dissolve properly**
- **Labeling mix-ups**
- **Uniformity failures**
- **Presence of foreign substances**
- **Failure on pH testing**
- **Microbial contamination of non-sterile products**

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

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.**

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 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.

Standard terminology adopted

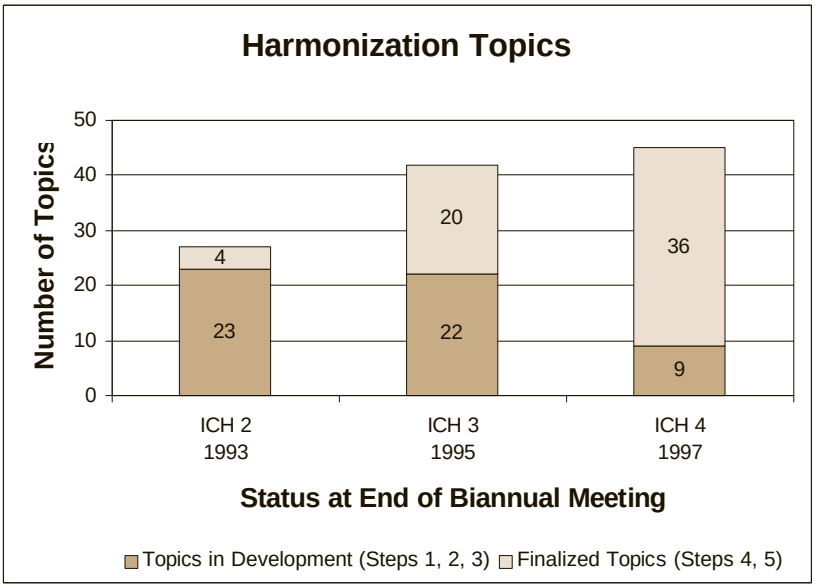
Applied research

Our scientists have conducted research to support development of an ICH guidance on alternative models to test the cancer-causing potential on drugs.

The ICH Medical Dictionary for Regulatory Activities is a new international medical terminology adopted last year. The dictionary is designed to support 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 post-marketing 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.

Progress made on 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 authorities in all three ICH regions. Representatives are nearing



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.

consensus on harmonizing the table of contents as well as the content of clinical and non-clinical summaries and tabulations. The project is well on target with a final document expected by the year 2000. Work has already begun on making the Common Technical Document suitable for electronic submission.

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.

In particular, ICH has committed to develop a guidance on active ingredients used in medicines. This project should result in a single international set of principles that can be implemented globally. This will provide greater assurance of the quality of the active ingredients used to manufacture medicines.

U.S.-European Union Mutual Recognition Agreement

This agreement provides for reciprocal reliance between "equivalent authorities" upon information gathered by their systems. 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. Last year, our experts in good manufacturing practices cooperated in preparing a plan for implementing the agreement and helped prepare the agreement for publication as a final FDA rule in December.

Internet sources

We have published 35 ICH documents as guidances to industry. These can be found on our Internet site at: http://www.fda.gov/cder/guidance/index.htm. Another 10 guidances are in development.

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#frame and at the European Union's Website at http://dg3.eudra.org/.

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

As part of the implementation of the FDA Modernization Act, we held our first public meeting with our stakeholders in August. This will be an annual event. We received valuable input from consumer groups, professional societies, industry and trade association on our priorities. 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. Issues such as direct-to-consumer advertising and risk vs. benefits in new drug approvals 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. We have expanded our use of open public meetings to obtain input on important public health policy issues. For example, we held a two-day advisory committee meeting and spearheaded the FDA's efforts to conduct an open public forum on antibiotic resistance. That forum with industry and academia was attended by more than 200 individuals.

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**
- **Federal, state and local government agencies**
- **Foreign governments**

In addition to analyzing required public comments on proposed new rules, the Center sought and received comments on its non-binding guidances to industry.

Consumer information

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

Consumer and Industry Outreach Efforts

In conjunction with a non-profit industry information association, we produced a two-hour satellite television broadcast to industry called "CDER Live." Our scientific and regulatory experts engaged in a panel discussion about our efforts to implement the FDA Modernization Act and the state-of-the-art Adverse Event Reporting System. The show was broadcast to approximately 60 sites across the country. Approximately 2,000 industry executives, scientists and regulatory affairs experts viewed the telecast.

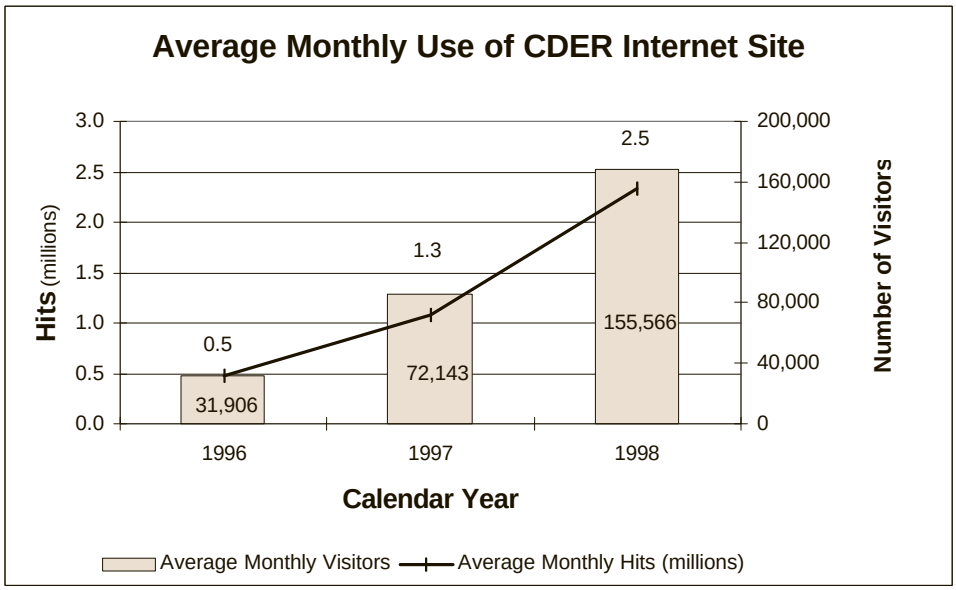
We implemented a "pharmacist education outreach" program to teach pharmacists about the drug approval process so that they may better explain it to consumers.

Our scientists and regulatory affairs experts participated in numerous workshops, training programs and conferences sponsored by professional societies. This not only helps us present our position and viewpoint on specific topics, it also helps us gather information to assist in the guidance development process.

In cooperation with FDA's Office of External Affairs, we conducted five briefings for health associations to explain in detail specific actions with a high degree of public health impact.

Our exhibit and information program completed successful showings at seven national health care conferences.

We conducted about 100 domestic and foreign videoconferences for academia, industry and associations.



Dissemination Activities

We have invested heavily in the technology to make information about our activities widely available to individuals, the media and industry. We make extensive use of traditional methods of communication as well as the World Wide Web.

We have established partnerships with several non-profit agencies to develop a series of brochures and drug information sheets to help communicate information about drugs to consumers.

We use the Internet to publish information on new and innovative drugs approved since January 1998. For consumers, we have easy-to-understand plain language summaries. For health care professionals, we have the labeling and and other technical information.

We implemented a searchable, Web-based version of the *Approved Drug Products with Therapeutic Equivalents*. This publication, known as the "Orange Book," serves as a national reference for drug product selection.

Medicare and the Department of Defense purchase programs use it as a reimbursement guide. The Web-based version has resulted in substantial cost reductions for our customers and us.

Partly a result of our expanded presence on the World Wide Web, we are receiving an increasing number of general information requests by electronic mail from consumers, patients and health care professionals. Our Ombudsman, Executive Secretariat and Drug Information Branch responded to nearly 6,000 e-mail requests last year.

We have created an over-the-counter site on the Internet to provide information for consumers and industry about non-prescription drugs.

Use of our Internet Web site, http://www.fda.gov/cder, has grown tremendously since it started in mid-1996. From 10,000 hits and several hundred visitors a month, our monthly averages have grown steadily. Currently, we have nearly 3 million hits from more than 215,000 visitors.

Our Electronic Freedom of Information Reading Room provides Internet users ready access to its most frequently requested documents.

Our Drug Information Branch answered nearly 32,000 telephone inquiries and 1,400 written requests from pharmacists, doctors, nurses, pharmaceutical and insurance companies, consumers, Federal agencies and others. We provided the most current drug information in a timely and accurate manner.

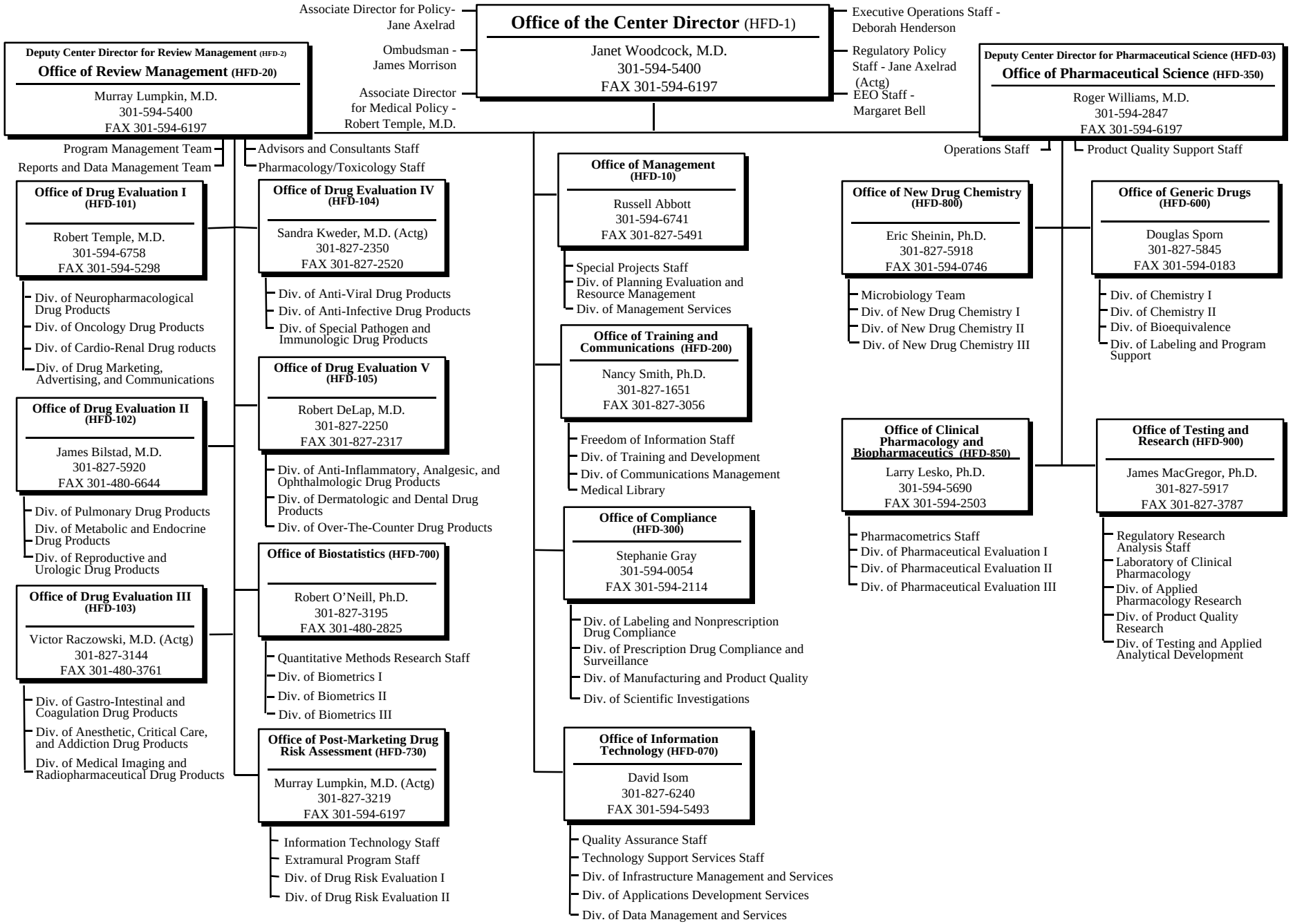
Our scientists, regulatory and communications experts participated in the development of eight Department of Health and Human Services press releases and 23 FDA talk papers. They took part in numerous media interviews related to these activities. In addition, we responded to about 1,000 requests from specialized publications serving the pharmaceutical industry.

Ombudsman's Activity

In its third year of operation, our Ombudsman's office handled about 100 interactions, about 90 percent from outside the Center. The Ombudsman provides a mechanism for people inside and outside the Center to seek solutions to problems and to suggest better ways for us to do our work.

AS OF: 03/31/99

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/.
- 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.
- FDA Consumer special issue, *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

Our Drug Information Branch responds to specific questions about prescription, over-the-counter and generic drugs for human use. You can contact them at 1-888-INFO FDA or 301-827-4573.

Fax-on-demand

In addition to the Internet, we have placed hundreds of our documents on a fax-back system at 1-800-342-2722 or 301-827-0577.

E-mail

Our Drug Information Branch can be contacted at DIB@CDER.FDA.GOV.

Regular mail

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Drug Information Branch
HFD-210, Room 12B-31
5600 Fishers Lane
Rockville, MD 20857

Improving Public Health Through Human Drugs

CDER 1998 Report to the Nation

Center for Drug Evaluation and Research

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

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