Center for Drug Evaluation and Research ***2000***

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.

This report is available on the Internet in Adobe Acrobat Portable Document Format and in hypertext markup language. The charts and graphs are available as Microsoft PowerPoint slides. The locations are:

- PDF: http://www.fda.gov/cder/reports/rtn2000/rtn2000.pdf
- HTML: http://www.fda.gov/cder/reports/rtn2000/rtn2000.htm
- Slides: http://www.fda.gov/cder/reports/rtn2000/rtn2000.ppt

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Graphs and Charts

DIRECTOR'S MESSAGE

Last year, we at the Center for Drug Evaluation and Research continued our efforts to strike the right balance in our programs. We have worked hard to provide rapid access to new therapies while maintaining rigorous safety and effectiveness standards; to listen to the voices of consumers, patients and health care professionals as well as those of regulated industry; to match the effort in premarket evaluation with a vigorous postmarket monitoring program; and, of course, to make sure we support the people in CDER as well as serving the outside world. In that regard, a highlight of the year was winning the W. Edwards Deming award for our scientific training program.

Many Americans are benefiting from last year's approvals of new drugs and new uses for already approved drugs. As a result of the new pediatric program, our youngest citizens—children—are starting to use therapies that have scientifically proven dosing regimens. In the process, we are expanding our knowledge of drug metabolism in the youngest patients.

We held a landmark public meeting last summer on over-the-counter drugs. We invited wide participation, and this will help us enormously as we evaluate policies for OTC drugs.

Our workload in reviewing applications for generic drugs continues to grow. This is good news for consumers. It means a steady supply of more affordable drugs that meet our uniform and stringent standards for safety, effectiveness and quality.

This decade will be known for a focus on drug safety. We have laid a strong foundation for the drug safety program of the future. We established the Office of Post-Marketing Risk Assessment, which utilizes a functioning Adverse Event Report System that is receiving direct electronic submissions. An enhanced medication errors program is in place.

We have made strenuous efforts to streamline our regulatory oversight of drug manufacturing. We hope we are beginning to see the payoff for these efforts as a downturn in manufacturing changes requiring our approval before implementation. This represents a reduction in workload for industry while ensuring the highest quality drug products for American consumers.

We are making strenuous efforts to come to grips with the reality of globalization in the marketplace. Cornerstones of our efforts are the International Conference on Harmonization, the Mutual Recognition Agreement with the European Union, and building relationships with the international regulatory community. We have begun work to promote harmonization within the Americas.

An urgent priority for us is improving our communications. Information is a key element in the safe and effective use of drugs. We are collaborating and leveraging with a broad spectrum of groups to improve information for prescribers and consumers. A highlight this year was publication of a proposed rule for a new format for the prescription drug package insert that is designed to improve

usability. In addition, the Internet is a tool that continues to grow in importance for our communications efforts.

This year, concerns have been raised about review times. Some groups contend they have slowed down, others claim they are too fast. Our data demonstrate that the time we take to review new drug applications is on target: neither too short nor too long. Much of this confusion is caused by analyzing the wrong groups of data. For example, concerning a potential review slowdown, when review times are analyzed based on the year in which applications were submitted, rather then when they were approved, they haven't changed. This *Report to the Nation* presents approvals based on the year in which the approval took place, regardless of when the application was submitted. As you can see from the graph on page 7 of the *Report*, more applications were approved in 2000 in a shorter time frame than in 1999. The longer median approval time for 2000 shown in the graph on page 8 of the *Report* refers to new molecular entities, which are drugs never before marketed in the United States. This longer NME approval time for 2000 vs. 1999 is a result of seven historically older applications approved in 2000, including several that received deficiency letters, which had a negative impact on the total approval time.

The concern about drugs being reviewed too fast links the user fee review times to the occurrence of drug withdrawals. It is misleading to analyze drug withdrawals based on the year of withdrawal. A drug approved in 1990 and withdrawn in 1999 does not reflect on the 1999 review process, because that drug would have been reviewed in the 1980s. When analyzed by year of approval, the evidence shows our withdrawal rates are remaining stable at about 3 percent. We also do not find a relationship between a withdrawal for safety reasons and time taken to review the original new drug application. Most of the drugs approved under the user fee program and subsequently withdrawn had longer than average review times.

We have many projects planned for the year ahead. We will continue to build our drug safety program by linking to new data sources and creating new partnerships and collaborations. A pilot electronic drug registration and listing system will be implemented. Additional standardization of review documents will occur under the Good Review Practices initiative, and we expect to be receiving new drug applications in the format of the new Common Technical Document developed under ICH.

As we look to the challenges ahead, we remain steadfast in our commitment to facilitate the availability of safe and effective drugs, keep unsafe or ineffective drugs off the market, improve the health of Americans and provide clear and easily understandable drug information for safe and effective use.

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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 and 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

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 may 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.**

and consumers. Sometimes, manufacturers run into production problems that might endanger the health 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.

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.

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.

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.

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.

2000 HIGHLIGHTS

We are pleased to present our fifth 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 have especially benefited from our approvals in 2000. Also, people with HIV, AIDS, cancer, heart disease and other serious conditions all benefited. We met our obligations to Congress for prompt and thorough review of drug applications supported by user fees. Our reviews of generic drugs have been prompt and predictable . We approved 98 new drugs, including 27 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 134 new or expanded uses of already approved drugs, 11 new or expanded uses for over-the-counter drugs and 244 generic drugs.

Drug safety and quality

All medicines have risks. 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. Last year, we processed and evaluated nearly a quarter million reports of adverse drug events. We issued more than 1,000 letters to help ensure that the promotion of drug products presents a fair balance of risks and benefits and isn't false or misleading. We mandated that five drug products be dispensed with specific consumer information that will help ensure the products are used safely and effectively. We issued a proposed rule to revise prescription drug labeling to improve its accessibility and enhance safe and effective prescribing and use. Our reviews of the safety profile of three approved drug products resulted in their voluntary withdrawal. We issued a public health alert about a once widely used decongestant that may cause strokes. The alert resulted in its withdrawal from the market by manufacturers.

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. We agreed to a final version of the Common Technical Document that can be used for seeking approval to market new drugs in the United States, the European Union and Japan. We began harmonization efforts among the countries of North and South America. We led the U.S. consultations with the European Union to allow for reciprocal reliance on manufacturing plant inspections.

Communications

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

We met almost weekly with outside experts on difficult scientific and public health issues.

We responded to more than 58,000 individual requests for information.

Our Internet information site averaged more than 406,000 visitors and about 6.7 million hits per month. We developed public education campaigns in areas such as risk management and buying prescription drugs over the Internet.

Drug withdrawals influence benefit-risk assessment

The recent market withdrawals of some drugs resulted, in part, from the U.S. health care system's inability to manage known and preventable risks.

These experiences have catalyzed an evolution in our thinking on risk management and the evaluation of new drugs for approval.

Our risk assessment must evaluate both a drug's intrinsic safety profile as well as the ability of the health care system to adequately manage known toxicities.

Unless effective risk management strategies and methods are brought to bear, additional effective drugs are likely to be withdrawn, and some drugs may never become available in the first place.

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.

Linking nonclinical and clinical studies

Key achievements in this area include:

- Establishing that biological markers for heart damage, such as troponin, are useful both experimentally and clinically to predict the incidence and extent of heart damage from exposure to certain drugs.
- Identifying unique biomarker proteins found in blood that cause heart damage and that are generated after treatment with certain drugs.
- Elucidating the molecular mechanisms operating in alternative transgenic mice that are used to test the cancer-causing potential of drugs. This understanding will make these models more rapid and reliable assessment tools.
- Developing an experimental model for detecting reactive metabolic products of drugs in cultured liver cells. This will facilitate mechanistic analysis of certain types of liver damage.

Database building

Our work included:

- Developing and implementing an Internet-enabled pilot of FDA's toxicology knowledge base. This database is linked to an expanded chemical substance dictionary that permits searches using unique chemical structures as well as structural similarities.
- Developing and distributing new computational software that predicts birth defects from drugs in rodent laboratory models. This was done under a commercial research and development agreement.
- Developing computational toxicology software to predict the human no-adverse-effect level for a substance based on its chemical structure and extrapolation of information about the maximum therapeutic dose.
- Developing computational models that use the pharmaceutical properties and molecular structure of drugs to predict their bioavailability in humans when administered orally.

Leveraging scientific resources

The Product Quality Research Institute is a unique and innovative collaboration among our scientists and those from academia and industry. PQRI conducts research to establish better testing methods, standards and controls for assessing product quality and manufacturing and management processes **(PQRI 2000 update, page 34).**

The institute's research will help us develop consistent and reasonable requirements for product quality information in regulatory filings.

Leveraging scientific expertise in this way contributes to streamlining the drug development and approval processes for industry and ourselves while ensuring the highest level of product quality for American consumers.

Deming Award recognizes our scientific training

Our program of scientific training based on core competencies received the prestigious W. Edwards Deming Outstanding Training Award for 2000 presented by the Graduate School of the Department of Agriculture. **See page 19 for details.**

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 nearly all goals for reviews supported by manufacturer user fees.

We approved 27 new medicines that have never been marketed before in this country and 244 generic versions of existing drugs. We authorized eight medicines to be sold over the counter without a prescription.

We conducted 528 foreign and domestic inspections that help protect volunteers for clinical trials from research risks and validate the quality and integrity of data submitted to us.

Highlights of new medication options for American consumers include:

- Three new drugs to treat cancer.
- A first protease inhibitor approved to treat HIV infection in children as young as 6 months.
- Four drugs to treat heart disease and circulatory disorders.
- Three drugs to treat disorders of the nervous system.
- A malaria treatment effective in areas where the disease is resistant to other anti-malarial drugs.
- The first anti-inflammatory corticosteroid that can be used in a nebulizer by very young children.
- The first in a new class of antibiotics.
- The first thyroid replacement drug to undergo a stringent FDA review.
- Three new drugs and five new uses of existing drugs for "orphan" patient populations of 200,000 or fewer.
- 13 new pediatric uses for already approved adult drugs.

2000 drug review accomplishments

98 new drugs

27 new molecular entities

134 new uses for already approved drugs

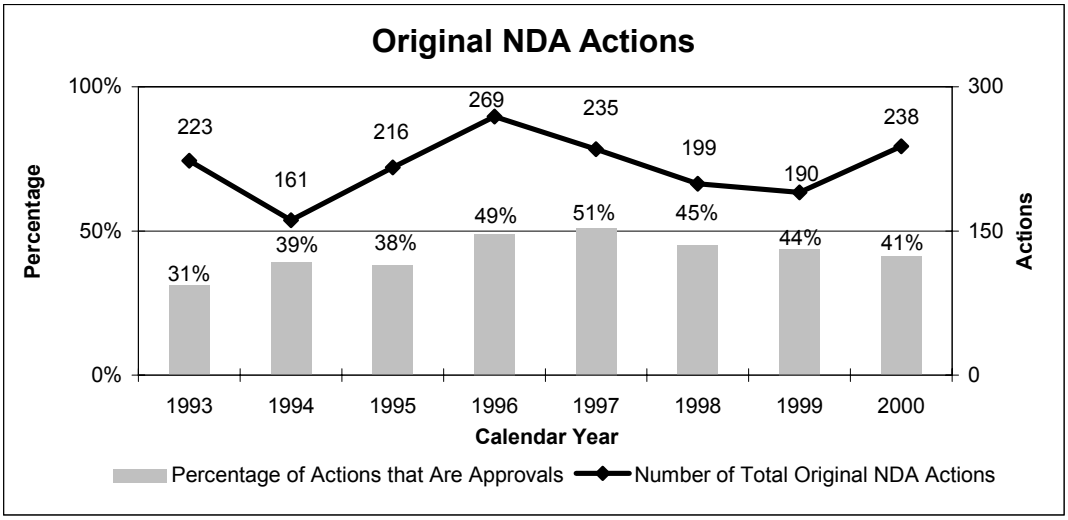
8 over-the-counter drugs

3 new uses for over-the-counter drugs

244 generic equivalents for prescription and over-the counter drugs

3 orphan drugs

5 orphan new uses



New Drug Review

We took 238 actions on original new drug applications, of which 98 were approvals. In 1999, we took 190 actions, of which 83 were approvals.

Total original NDA approvals

The median total approval time for new drugs in 2000 was 11.2 months, compared with 12.0 in 1999. Approval time represents our total review time plus industry response time to our requests for additional information. The 10.9-month median FDA review time—our time only—was 8 percent shorter in 2000 than the 11.8 months in 1999. Three of the NDAs were approved for "orphan" uses in patient populations of 200,000 or fewer. In 1999, we approved 12 NDAs for orphan uses.

Priority reviews

The new drug approvals in 2000 included 20 priority reviews. We perform a six-month review on priority drugs because they represent an advance in medical treatment. The median total approval time and the median FDA review time for these priority reviews were both 6.0 months. In 1999, there were 28 priority reviews.

New molecular entity approvals

Twenty-seven of the original new drugs we approved in 2000 were new molecular entities. NMEs contain an active substance that has never before been approved for marketing in any form in the United States. Nine of these received priority approvals.

The median total approval time for NMEs was 15.6 months, and the median FDA review time was 13.9 months. These times were longer than those for all NDAs. Last year the number of NDAs approved increased from the previous year, but the number of NMEs approved fell. Although user fee goals were met, the longer times for some drugs had a disproportionately larger effect on NME statistics. In 1999, there were 35 NMEs approved.

New drug statistics

- **98 new drugs**
- **27 new molecular entities**
- **3 orphan drugs**
- **20 priority reviews**
- **Median total approval time: 11.2 months**
- **Median FDA review time: 10.9 months**

Priority new drug approvals (N=NME)

Abacavir/lamivudine/ zidovudine (Trizivir)

Alosetron (Lotronex) (N)

Arsenic trioxide (Trisenox) (N)

Atovaquone/proquanil (Malarone)

Bexarotene (Targetin)

Budesonide (Pulmicort)

Didanosine (Videx EC)

Gentuzumab ozogamicin (Mylotarg) (N)

Levobetaxolol (Betaxon)

Levofloxacin (Quixin)

Linezolid (Zyvox) (3 NDAs approved, 1 as NME) **(N)**

Lopinavir/ritonavir (Kaletra) (2 NDAs approved, 1 as NME) **(N)**

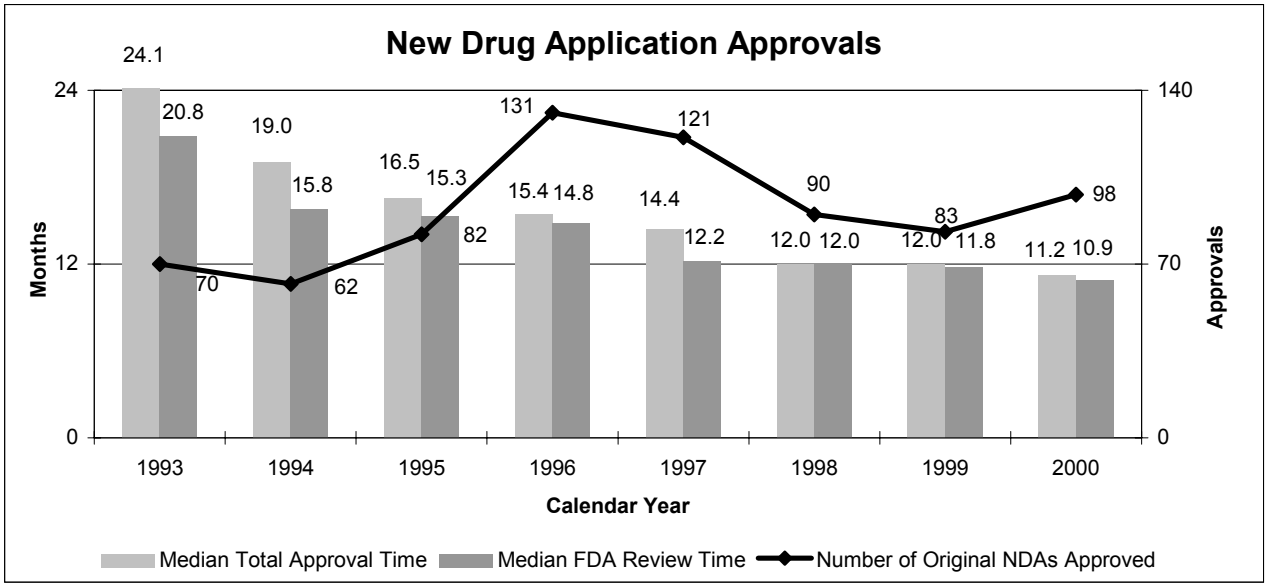
Mifepristone (Mifeprex) (N)

Oseltamivir (Tamiflu)

Skin Exposure Reduction Paste Against Chemical Warfare Agents (N)

Unoprostone (Rescula) (N)

Verteporfin (Visudyne) (N)



Notable 2000 new drug approvals

Last year's approvals benefited people with cancer, HIV, diabetes, heart disease and disorders of the circulatory and nervous systems.

People with cancer

Arsenic trioxide (Trisenox) treats acute promyelocytic leukemia, a cancer of white blood cells, in patients whose disease has recurred or who have failed to respond to standard therapy. Trisenox, a priority drug and an orphan drug, was approved in six months. The product's total development time for this use was only three years. *Gemtuzumab ozogamicin (Mylotarg),* a monoclonal antibody, is a priority orphan drug for treating CD33 (an antigen on certain leukemia cells) positive acute myeloid leukemia in patients 60 years or older who have relapsed for the first time and are not suitable candidates for the standard but poorly tolerated cytotoxic therapy. *Triptorelin pamoate (Trelstar Depot)* is for the palliative treatment of advanced prostate cancer. It represents a new alternative for patients with prostate cancer in whom orchiectomy or estrogen administration is not indicated or is unacceptable.

People with HIV and AIDS

A combination of *lopinavir and ritonavir (Kaletra)* received accelerated approval as a protease inhibitor for the treatment of HIV infection in adults and children in combination with other antiretroviral agents. The product, indicated for twice daily dosing with a total of six capsules per day, is the only protease inhibitor approved for use in children as young as 6 months.

People with heart and circulatory diseases

Argatroban (Acova) is an anticoagulant for the prevention or treatment of thrombosis (abnormal blood clotting) associated with heparin-induced thrombocytopenia, a serious immune disorder caused by heparin, a common anticoagulant used to prevent blood clots. *Bivalirudin (Angiomax)* is an anticoagulant for use in patients with unstable angina who are

New molecular entities in 2000

Alosetron (Lotronex) (withdrawn by manufacturer, page 30)

Argatroban (Acova)

Arsenic Trioxide (Trisenox)

Articaine/epinephrine (Septocaine)

Balsalazide disodium` (Colazal)

Bivalirudin (Angiomax)

Cetrorelix acetate (Cetrotide)

Cevimeline (Evoxac)

Colesevelam (Welchol)

Docosanol (Abreva)

Gemtuzumab ozogamicin (Mylotarg)

Insulin aspart recombinant (NovoLog)

Insulin glargine (Lantus)

Linezolid (Zyvox)

Lopinavir/ritonavir (Kaletra)

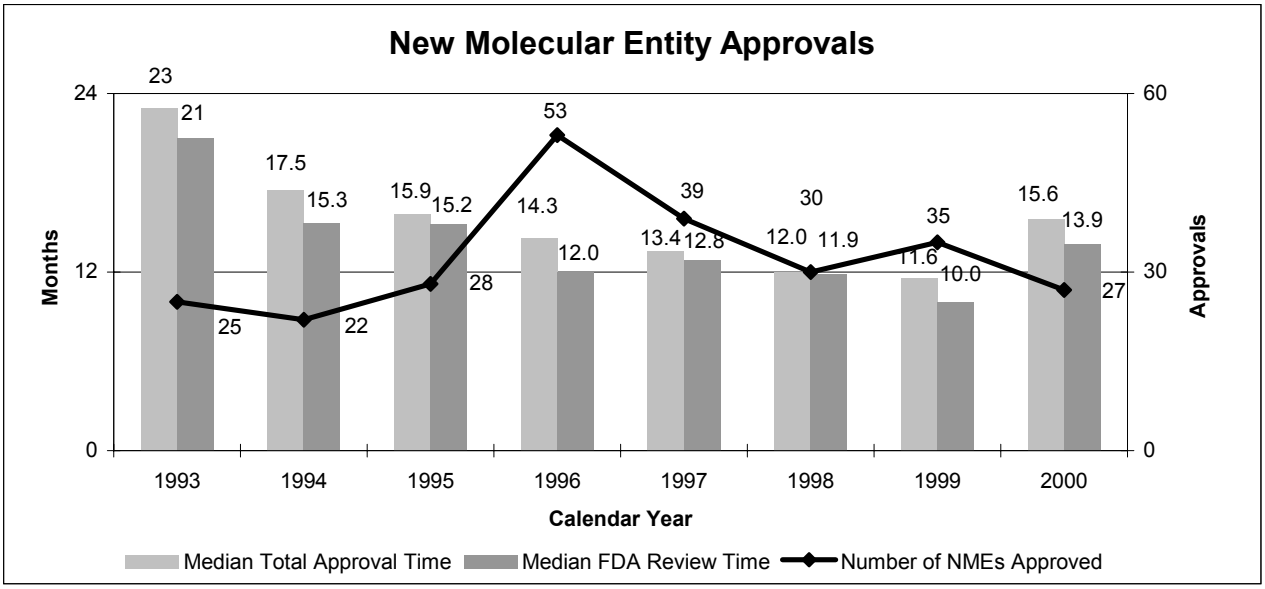
Meloxicam (Mobic)

Mifepristone (Mifeprex)

Nateglinide (Starlix)

Oxcarbazepine (Trileptal)

Pantoprazole



New molecular entities in 2000
(continued)

(Protonix)

Perfluoropoly-methylisopropyl ether/ polytetra-fluoroethylene (Skin Exposure Reduction Paste Against Chemical Warfare Agents)

Rivastigmine Tartrate (Exelon)

Tinzaparin sodium (Innohep)

Triptorelin pamoate (Trelstar Depot)

Unoprostone isopropyl (Rescula)

Verteporfin (Visudyne)

Zonisamide (Zonegran)

undergoing coronary angioplasty. It is to be used with aspirin. *Colesevelam (WelChol)* is used in conjunction with diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia. The novel, non-absorbed, lipid-lowering agent is to be administered alone or in combination with an HMG-CoA reductase inhibitor (statin). *Tinzaparin (Innohep),* a low-molecular-weight heparin, is a once-daily treatment for deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin.

People with diabetes

Insulin aspart recombinant (NovoLog) is for the treatment of type 1 and type 2 diabetes. *Insulin glargine (Lantus)* is a long-acting recombinant human insulin for type 1 and type 2 diabetes. *Nateglinide (Starlix),* the first in a new class of drugs, is for the treatment of type 2 diabetes.

People with gastrointestinal disorders

Alosetron (Lotronex) was to treat irritable bowel syndrome in women whose predominant bowel symptom is diarrhea, but the drug was withdrawn by the manufacturer (page 30). *Balsalazide disodium (Colazal)* is for the treatment of mild to moderately active ulcerative colitis, a chronic and debilitating inflammatory disease of the gastrointestinal tract. *Pantoprazole (Protonix),* a proton pump inhibitor, is a delayed-release tablet for the short-term (up to 16 weeks) treatment in the healing and symptomatic relief of erosive esophagitis.

People with neurological disorders

Oxcarbazepine (Trileptal) is for treatment of epileptic partial seizures as monotherapy in adults or as adjunctive therapy in adults and children as young as 4. *Rivastigmine tartrate (Exelon),* a cholinesterase inhibitor, treats mild to moderate Alzheimer's disease. *Zonisamide (Zonegran)* is for adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

New molecular entity statistics

- **27 approvals**
- **9 priority reviews**
- **Median total approval time: 15.6 months**
- **Median FDA review time: 13.9 months**

Median time

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

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

Orphan drug approvals

In 2000, we approved three "orphan" products to treat disorders with patient populations of 200,000 or fewer:

Arsenic trioxide (Trisenox) **treats acute promyelocytic leukemia, a cancer of white blood cells, in patients whose disease has recurred or who have failed to respond to standard therapy.**

Somatropin, recombinant (Norditropin) **is indicated for the long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.**

Gemtuzumab ozogamicin (Mylotarg) **treats CD33-positive acute myeloid leukemia in patients 60 years or older who have relapsed for the first time and are not suitable candidates for the standard but poorly tolerated cytotoxic therapy.**

Infectious diseases

Docosanol (Abreva) is an over-the-counter topical treatment for recurrent oral-facial herpes simplex infections, commonly known as cold sores or fever blisters. *Linezolid (Zyvox)* is the first antibiotic in a new class in 35 years (the oxazolidinones) to treat infections caused by gram-positive bacteria. Gram-positive bacteria are regarded as one of the greatest challenges in hospitals. *Oseltamivir (Tamiflu*) oral suspension was approved for prevention of influenza virus in adults and adolescents aged 13 years and older. *Zanamivir (Relenza)* treats uncomplicated influenza A and B in adults and children 7 years and older.

People with thyroid disease

Levothyroxine sodium (Unithroid), a thyroid replacement drug, is the first single-ingredient oral levothyroxine product approved for the treatment of hypothyroidism, a disease that causes mental and physical sluggishness, including stunted growth. Although oral levothyroxine drugs products have been marketed in the United States since the 1950s, this product meets FDA's standards for safety and effectiveness as well as its standards for manufacturing processes, purity, potency and stability.

People with eye disease

Verteporfin for injection (Visudyne) is the first therapy to slow vision loss in people with the classic type of wet age-related macular degeneration, a disease that can cause blindness. *Unoprostone isopropyl (Rescula)* treats open-angle glaucoma or ocular hypertension.

People with severe eczema

Tacrolimus (Protopic) is an ointment for patients with moderate or severe eczema for whom standard eczema therapies present potential risks or who are not adequately treated by or do not tolerate standard eczema therapies.

Children with asthma

Budesonide inhalation suspension (Pulmicort Respules) is approved for children 1 to 8 years old with asthma. The product is the first anti-inflammatory corticosteroid formulated for inhalation using a nebulizer in this age group. This is important because toddlers frequently cannot use metered-dose inhalers.

Other NME approvals

Articaine 4 percent and epinephrine hydrochloride (Septocaine) is a local anesthetic to be used for simple and complex dental and periodontal procedures. *Cetrorelix acetate (Cetrotide)* prevents premature ovulation in women undergoing controlled ovarian stimulation for assisted reproductive treatment. *Meloxicam (Mobic)* tablets are a once-daily treatment for the pain and stiffness associated with osteoarthritis. *Mifepristone (Mifeprex)* is to terminate pregnancies of 49 days or less from the beginning of a woman's last menstrual period. *Perfluoropolymethylisopropyl ether/ polytetrafluoroethylene (Skin Exposure Reduction Paste Against Chemical Warfare Agents),* when used with Mission Oriented Protective Posture gear, reduces or delays the absorption of such agents through the skin when the paste is applied prior to exposure.

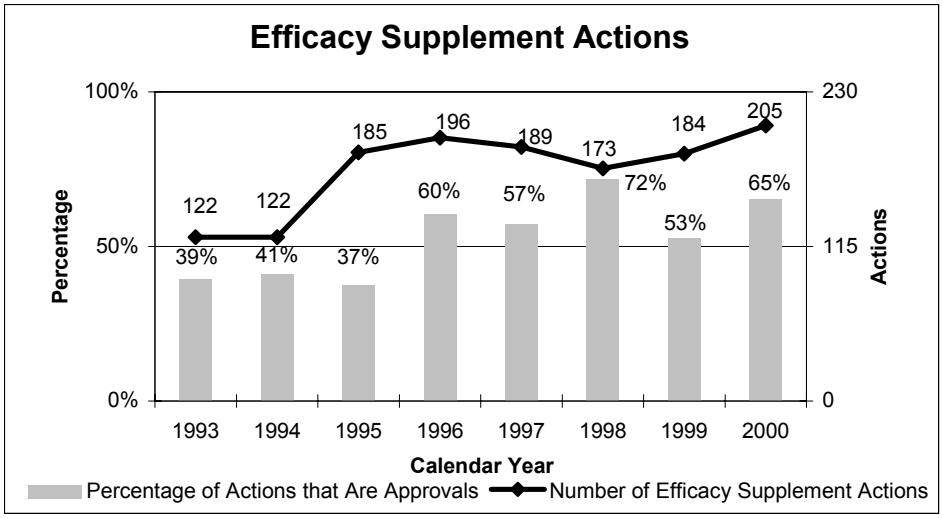
Malaria treatment

A combination of *atovaquone and proguanil (Malarone)* is for the prevention and treatment of acute, uncomplicated malaria. It has been shown to be effective in regions where the disease has become resistant to other anti-malarial drugs.

PET drug initiative

We approved F-18 FDG, an injected radiopharmaceutical drug that localizes areas with abnormal glucose metabolism to assist in cancer assessments and in identifying reversible cardiac dysfunction.

It was approved as part of an initiative under the FDA Modernization Act of 1997, which included consultations with the public and an advisory committee, a review of literature and a *Federal Register* notice describing how the drug could be found to be safe and effective for certain indications.



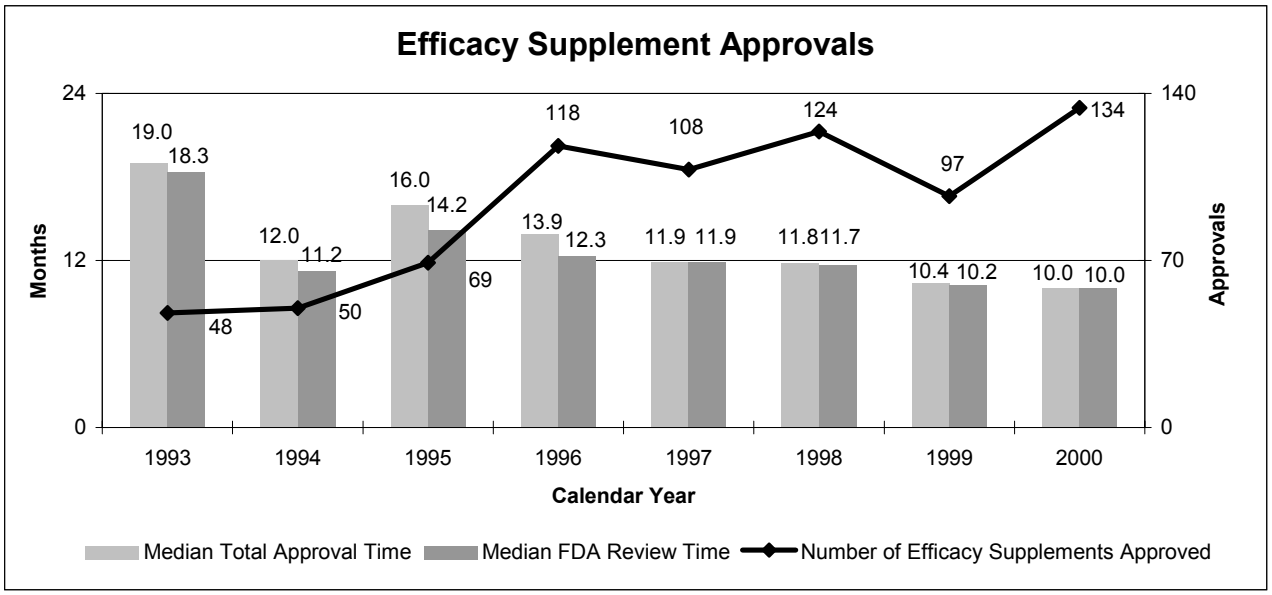
Efficacy supplement statistics

- **134 approvals**
- **18 priority reviews**
- **5 orphan new uses**
- **Median total approval time: 10.0 months**
- **Median FDA review time: 10.0 months**

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 205 applications for new or expanded uses of already approved drugs. We approved 134, including 18 that were given priority reviews of six months or less. Five of the approvals were for orphan uses in patient populations of 200,000 or fewer.



Priority efficacy supplement approvals

Ciprofloxacin (Cipro) (5 supplements)

Enoxaparin (Lovenox)

Epoprostenol (Flolan)

Irinotecan (Camptosar)

Mitoxantrone (Novantrone)

Nimodipine (Nimotop)

Olopatadine (Patanol)

Oseltamivir (Tamiflu)

Paclitaxel (Taxol)

Risedronate (Actonel) (2 supplements)

Somatropin, recombinant (Genotropin)

Tamoxifen (Nolvadex)

Zanamivir (Relenza)

Notable 2000 new or expanded use approvals

We added pediatric use to the labeling of 13 adult drugs including *ibuprofen (Motrin* and *Advil), ranitidine (Zantac)* for stomach acid reflux and *cromolyn (Nasalcrom)* for asthma and hay fever.

Ciprofloxacin (Cipro), an antimicrobial product, was designed to reduce the incidence or progression of inhalational anthrax following exposure to *Bacillus anthracis.* Inhalational anthrax is an extremely rare disease, usually resulting from exposure to contaminated animal hides and hairs in an industrial setting, but the causative organism can be used as a biological weapon.

Irinotecan (Camptosar) has a new use as a first-line therapy in combination with 5-fluorouracil and leucovorin (5-FU/LV) to treat metastatic colorectal cancer. The combination showed a clear survival advantage compared to 5-FU/LV alone.

Tamoxifen (Nolvadex) was approved for use to reduce the risk of invasive breast cancer for women with preinvasive cancer of the ducts.

Orphan efficacy supplement approvals

Epoprostenol (Flolan)

Follitropin alfa (Gonal-F)

Fomepizole (Antizol)

Mitoxantrone (Novantrone)

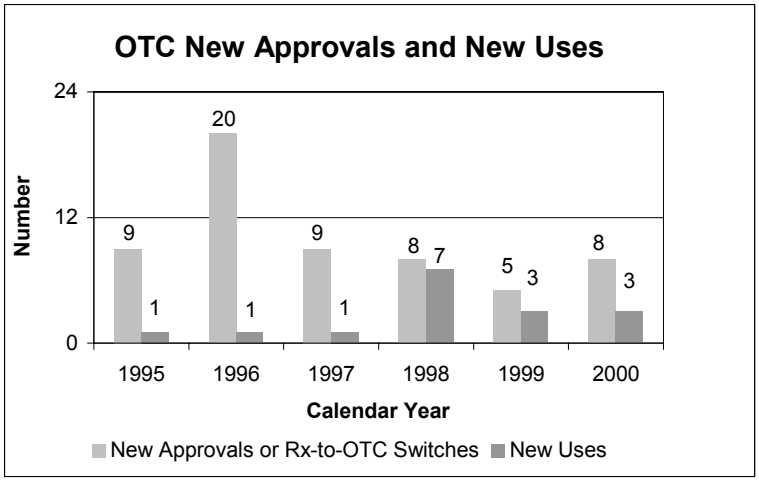
Somatropin, recombinant (Genotropin)

Electronic Submissions

We have been receiving new drug application case report forms and case report tabulations in electronic format in place of paper since November 1997. In February 1999, we started receiving the archival copy of the entire new drug application in electronic format in place of paper.

The number of new drug electronic submissions has steadily increased. Last year, we received more than 500 electronic NDA submissions. Currently, we average more than 100 submissions per month. About 75 percent of original new drug applications have some component in electronic format, and about 35 percent are entirely in electronic format. Since the program began, we have seen a 50 percent reduction in the average number of paper volumes for new drug applications.

We have a pilot program for receiving post-marketing expedited safety reports in electronic format and have published a draft guidance for providing advertising and promotional material in electronic format. We also have a pilot program for receiving generic drug applications in electronic format (page 14). We are working on the ability to accept all of these submissions, along with investigational new drug applications and drug master files, in electronic format without paper in 2002.



Over-the-counter drug statistics

- **8 new drug or Rx-to-OTC switch approvals**
- **3 new use approvals**

Over-the-Counter Drug Review

In 2000, we approved eight new drugs and three new uses for over-the-counter marketing.

New OTC medicines and new uses

- *Antacid and famotidine (Pepcid Complete Chewable Tablet)* is the first antacid and H_2 blocker combination product for heartburn.
- *Chlorhexidine gloconate (ChloraPrep)* is a topical antimicrobial.
- *Clotrimazole (Trivagizole 3 Vaginal Cream)* is an antifungal.
- *Docosanol (Abreva Cream)* is a cold sore and fever blister treatment.
- *Ibuprofen (Advil Migraine Liqui-Gels)* is for the treatment of migraine headache.
- *Ibuprofen (Infants' Advil Concentrated Oral Drops)* is now indicated for children ages 6 months to 23 months.
- *Ibuprofen (Motrin Migraine Pain)* is for the pain of migraine headache.
- *Ibuprofen and pseudoephedrine (Children's Motrin Cold Suspension)* is a pain reliever, fever reducer and decongestant.
- *Loperamide and simethicone (Imodium Advanced Caplet)* is for diarrhea and gas.
- *Piperonyl butoxide and pyrethrins (Rid Mousse)* is a topical treatment for head and body lice and is the first OTC product approved as a new drug "deviation" to the pediculicide monograph.
- *Terbinafine hydrochloride (Lamisil AT Spray Pump and Solution Dropper)* treats athlete's foot, jock itch and ringworm.

Public meeting airs OTC drug issues

We are open to the possibility of having more and different kinds of OTC medicines available to consumers. We explored these issues with more than 300 stakeholders at a two-day public meeting.

Discussions included how we determine which drugs should be available over the counter, who should initiate Rx-to-OTC switches and safety concerns about OTC availability of medicines for chronic conditions without symptoms.

A brief report of the meeting is available at: http://www.fda.gov/cder/pike/july2000.htm#OTC.

Improved labels for OTC medicines

American consumers last year began to see new, easy-to-understand labels on nonprescription drugs.

Titled "Drug Facts," the new labels are the result of a regulation we issued in 1999.

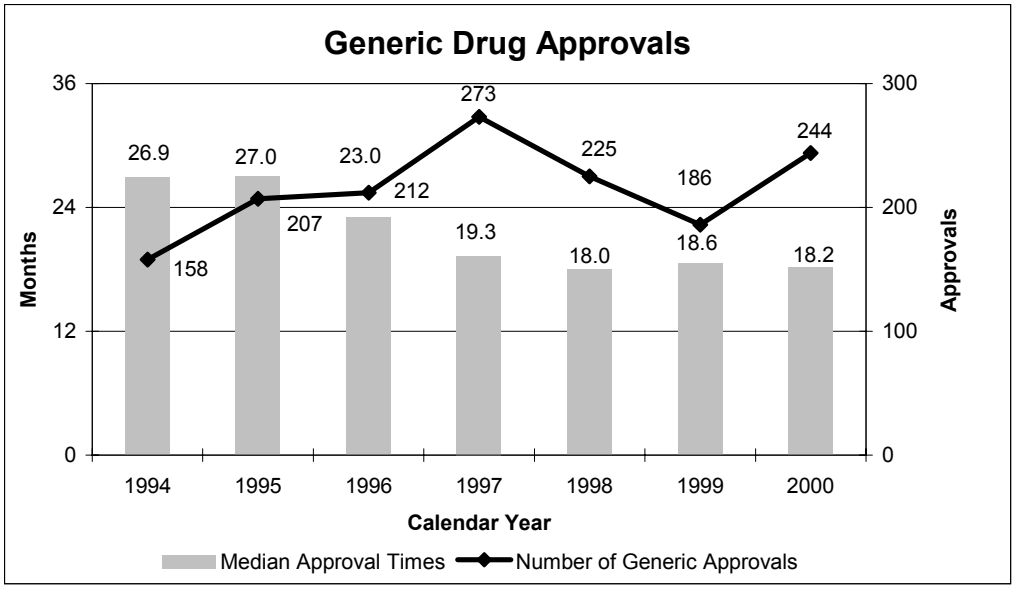
These new labels will improve a consumer's ability to use an OTC drug safely and properly and to find and understand its benefits and risks.

How we regulate OTC drugs

We 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 prior FDA clearance.

Drugs can also be approved for OTC sale through the new drug review process.



2000 generic drug statistics

- **244 generic drug approvals**
- **Median approval time: 18.2 months**

Generic Drug Review

We received 365 submissions and approved 244 generic products in 2000, including 34 separate molecules in 52 products that represent the first time a generic drug was available for the brand-name product. The median approval time for generic drugs was 18.2 months.

Initiatives to streamline the generic drug review process have resulted in an overall downward trend in approval times since 1994. We have also seen a drop in the number of review cycles needed to approve abbreviated applications for generic drugs. In 2000, the average application required 2.8 cycles to reach approval.

We also issued 61 tentative approvals last year. 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.

Our approval of generic drugs last year could save the American people and the federal government hundreds of millions of dollars.

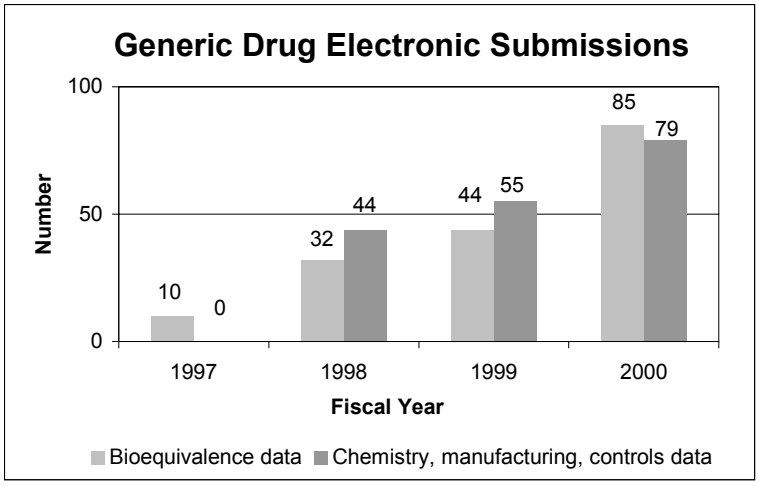
Generic drug submissions

- **2000: 365**
- **1999: 296**
- **1998: 345**
- **1997: 330**
- **1996: 307**
- **1995: 283**
- **1994: 199**
- **1993: 215**

Notable 2000 generic drug approvals

Examples of first-time approvals include:

- ***Doxazosin mesylate tablets,* used in treating benign prostatic hyperplasia and hypertension.**
- ***Paclitaxel injection,* used in treating various ovarian and breast cancers.**
- ***Nifedipine extended release tablets,* used in treating angina and hypertension.**



Generic drug electronic submission initiative

Last year, for original submissions, we received 85 electronic submissions for bioequivalence data and 79 electronic submissions for chemistry, manufacturing and controls data. 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.

Quicker approvals without user fees

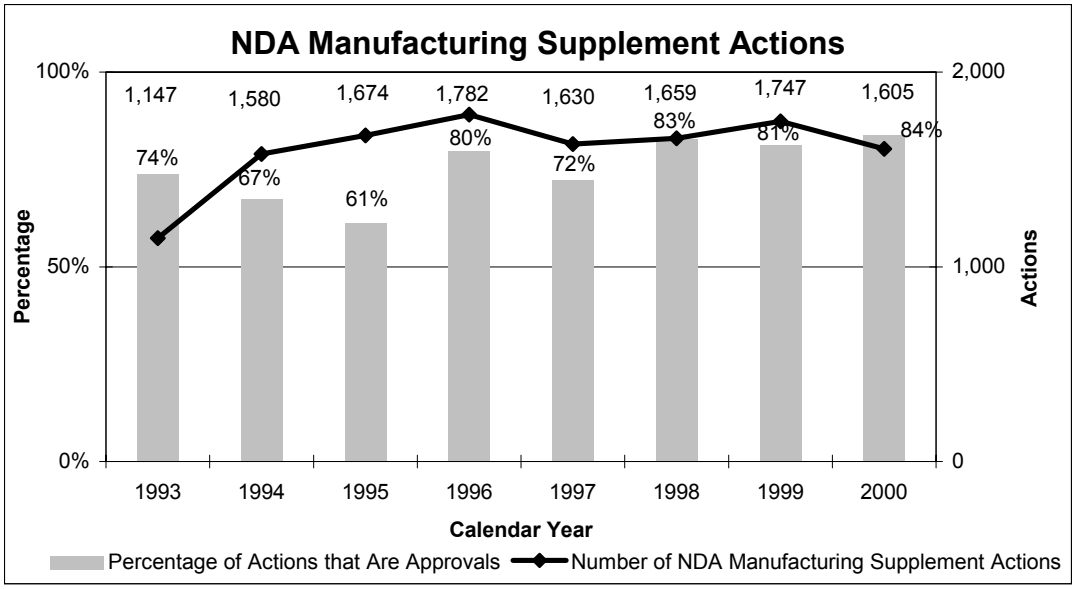
We don't receive user fees to review applications for marketing generic equivalents of prescription or over-the-counter drugs.

How we approve generic drugs

Generics are not required to repeat the extensive clinical trials used in the development of the original, brand-name drug. Instead, they must show bioequivalence to the brand-name reference listed drug.

Scientists measure the amount of the generic drug that reaches the bloodstream and how long it takes to get there. This rate and extent of absorption is called bioavailability. The bioavailability of the generic drug is then compared to that of the brand-name reference listed drug.

The generic version must deliver the same amount of active ingredients into a patient's bloodstream and in the same time as the brand-name reference listed drug. Brand-name drugs are subject to the same bioequivalency tests as generics when their manufacturers reformulate them.

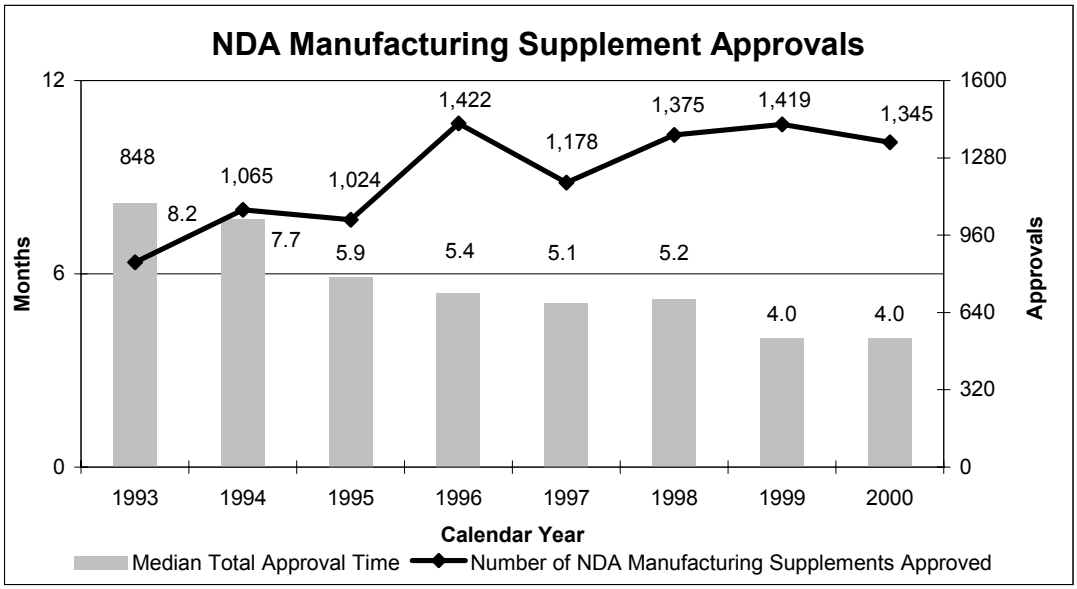


New drug manufacturing supplement statistics

- **1,345 approvals**
- **Median FDA review time: 4.0 months**

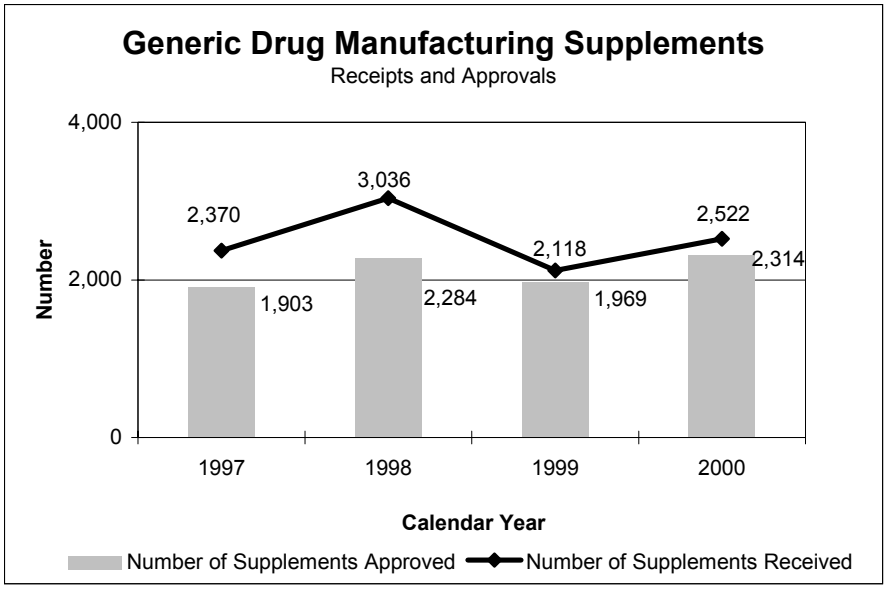
Manufacturing Supplement Review

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 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.



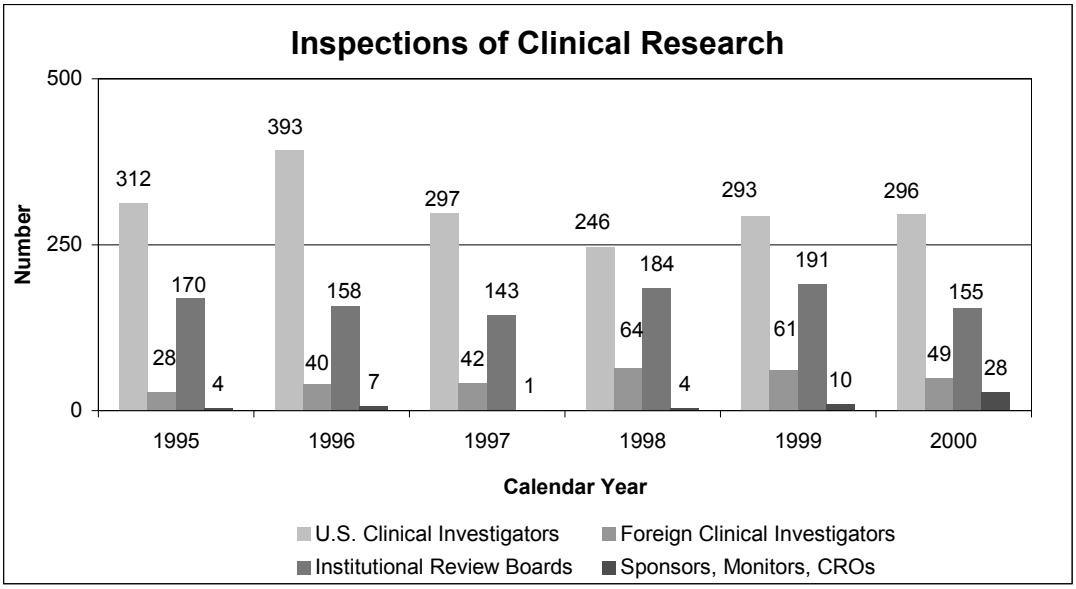
Generic drug manufacturing supplement statistics for 2000

- **2,314 approvals**
- **2,522 receipts**



Manufacturing supplements to generic drug applications

In 2000, we approved 2,314 manufacturing supplements to generic drug applications. We received 2,522 manufacturing supplements during the year.



Inspections of clinical research in 2000

We conducted a total of 528 inspections last year.

- **296 U.S. clinical investigators**
- **49 foreign clinical investigators**
- **155 institutional review boards**
- **28 sponsors, monitors or contract research organizations**

Assessing Data Quality, Research Risks

To protect the rights and welfare of volunteers and verify the quality and integrity of data submitted for our review, we perform on-site inspections of clinical trial study sites, institutional review boards, sponsors, study monitors and contract research organizations. Our programs to protect volunteers are challenged by increases in the number of clinical trials; the types and complexity of products undergoing testing; and the increased number of trials performed in countries with less experience and limited or no standards for conducting clinical research.

When obtaining data about the safety and effectiveness of drugs, sponsors rely on human volunteers to take part in clinical studies. Protecting volunteers from research risks is a critical responsibility for us and all involved in clinical trials, including manufacturers, institutional review boards, study sponsors, clinical investigators and their staffs, monitors, contract research organizations, hospitals and other institutions.

Sponsors and clinical investigators protect volunteers by ensuring that:

- Clinical trials are appropriately designed and conducted according to good clinical practices.
- Research is reviewed and approved by an institutional review board.
- Informed consent is obtained from participants.
- Ongoing clinical trials are actively monitored.

Special attention is given to protecting vulnerable populations, such as children, the mentally impaired or prisoners.

We require sponsors to disclose financial interests of clinical investigators who conduct studies for them. This helps identify potential sources of bias in the design, conduct, reporting and analysis of clinical studies.

International inspections

We have conducted 422 inspections in 45 countries from 1980 to 2000.

We participate in international efforts to strengthen protections for human volunteers worldwide and encourage clinical investigators to conduct studies according to the highest ethical principles.

These efforts include our work with the International Conference on Harmonization **(page 36)** **and the Declaration of Helsinki.**

Top 5 deficiency categories for clinical investigator inspections

- **Failure to follow the protocol**
- **Failure to keep adequate and accurate records**
- **Failure to report adverse events**
- **Failure to account for the disposition of study drugs**
- **Problems with the informed consent form**

Pediatric Exclusivity

Pediatric exclusivity statistics

□ 218 proposed pediatric study requests received

□ 188 written requests issued

The 1997 FDA Modernization Act authorized us to grant six months of marketing exclusivity to manufacturers who conduct and file pediatric studies in response to our written requests. Pediatric exclusivity has helped us uncover important new information that will help pediatricians and other prescribers use drugs to treat children more safely and confidently.

As of April 1, 2001, we had received 218 proposed pediatric study requests and had issued 188 written requests. These studies could potentially involve more than 20,000 children. In less than three years, more than 58 pediatric studies have already been conducted. Reports from these studies have been submitted, and exclusivity granted to 28 drugs.

Drugs that have or soon will have pediatric use information in their labeling are used to treat conditions such as:

- Diabetes mellitus.
- Gastroesophageal reflux disease.
- Hypertension.
- Juvenile rheumatoid arthritis.
- Obsessive compulsive disorder.
- Pain.
- Depression.
- HIV infection.
- Seizures.
- Anesthesia and sedation.

A full report on our experiences with pediatric exclusivity is at http://www.fda.gov/cder/pediatric/reportcong01.pdf. Our pediatric medicine page is at http://www.fda.gov/cder/pediatric/index.htm.

Pregnancy labeling

We have reviewed the current system of labeling drugs for use by pregnant women and are developing an improved, more comprehensive and clinically meaningful approach.

We are consulting with multiple government agencies, medical experts, consumer groups and the pharmaceutical industry to develop this new labeling format.

Antimicrobial Resistance

The emergence of drug-resistant bacteria is considered to be a major threat to the public health.

We play an active role in the federal government's efforts to address this growing problem 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.

Details of our efforts and other resources are at http://www.fda.gov/cder/drug/antimicrobial/default.htm.

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.

Scientific training for reviewers

Our systematic training program for reviewers in science, policy and job-related skills is based on core competencies, learning pathways and individual development plans.

The program grew from seven courses offered in 1997 to more than 20 currently offered. Existing courses were also revised.

Reviewer participants increased six-fold, from about 250 in 1997 to 1,500 currently.

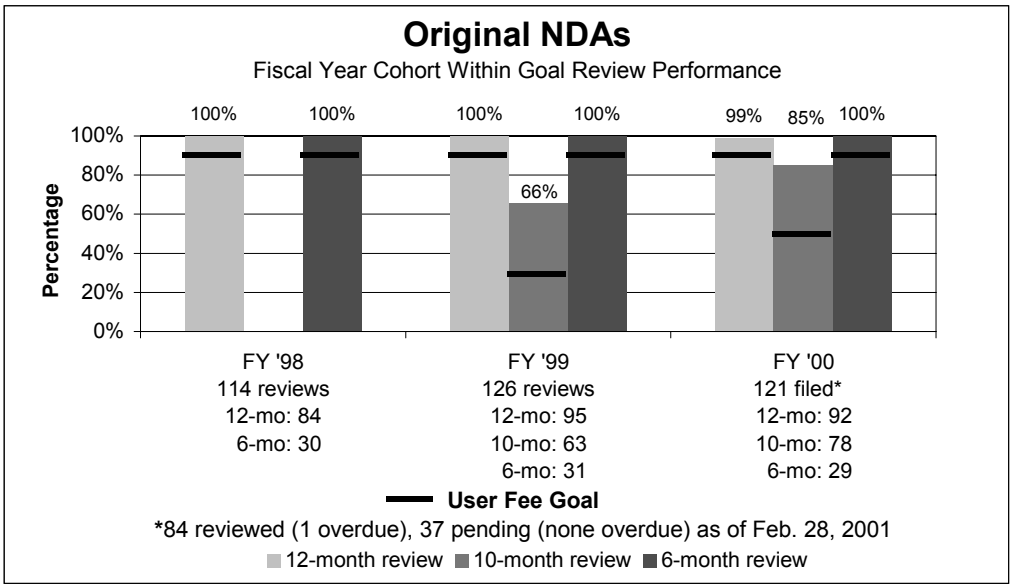
Reviewer training hours quadrupled from 4,000 hours a year in 1997 to 16,000 hours currently.

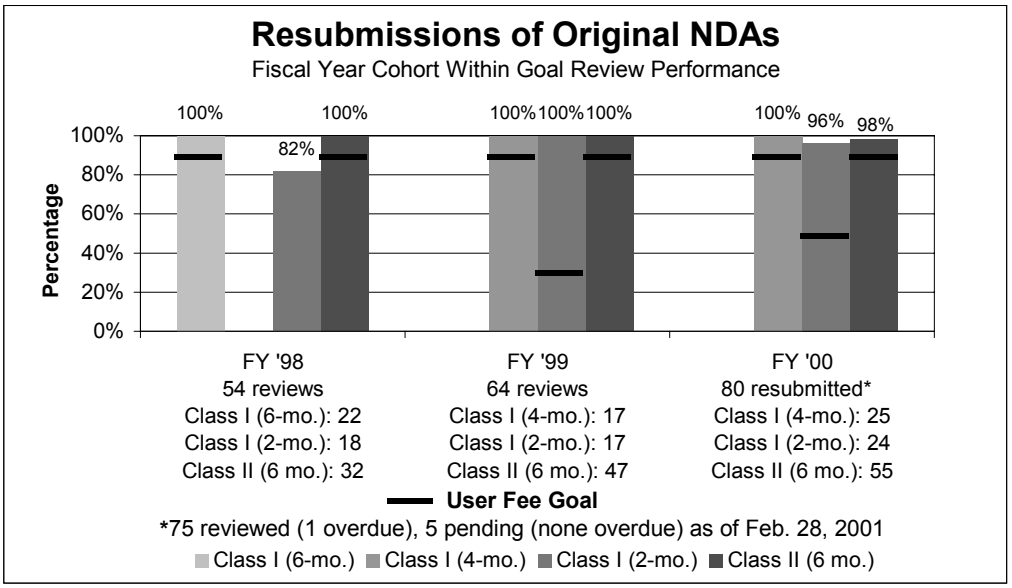
Training costs were reduced through partnerships with pharmaceutical firms, associations, academic institutions and foreign governments.

User Fee Review Performance

The timely performance of high-quality 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, first enacted in 1992, was 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.

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





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.**
- **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

Resubmissions are divided into two classes:

- **Class I, involving minor changes, are phasing in two-month reviews.**
- **Class II, involving changes not specifically identified in the user fee goals document, retain a six-month review.**

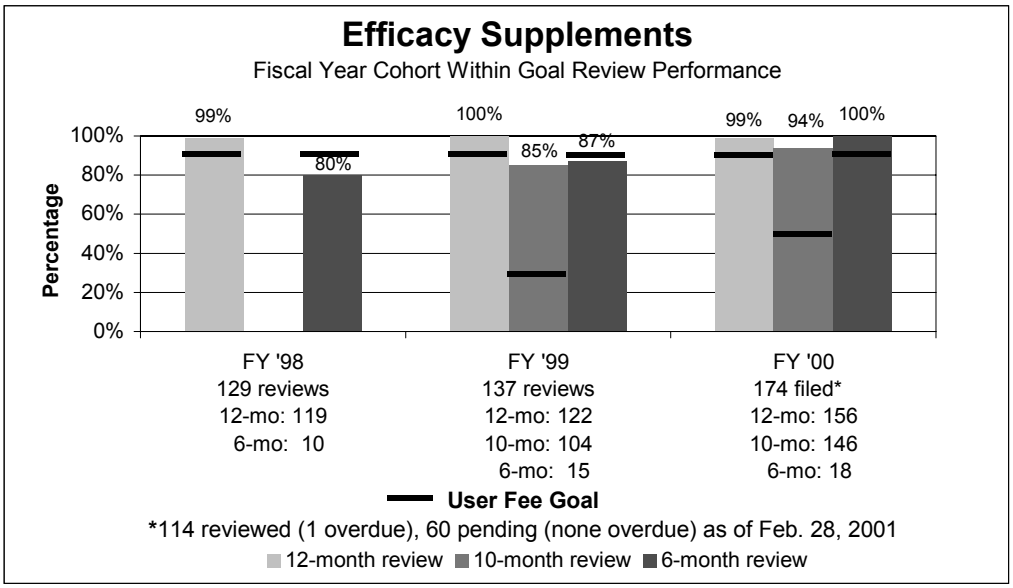
marketing applications and manufacturing supplements to already approved new drug marketing applications. We have continued to meet or exceed nearly all the progressively more stringent user fee performance goals.

With the reauthorization of user fees in 1997, we committed to goals that will help speed the time it takes for drugs to be appropriately tested and developed before submitting those results for our review. These goals include those related to meeting management, clinical holds, resolving major disputes and reaching agreement on certain protocols. There are expectations regarding electronic applications and submissions, simplification of action letters and expedited notification of deficiencies in applications.

Efficacy supplements

□ Standard efficacy supplements began a phase-in to 10-month reviews.

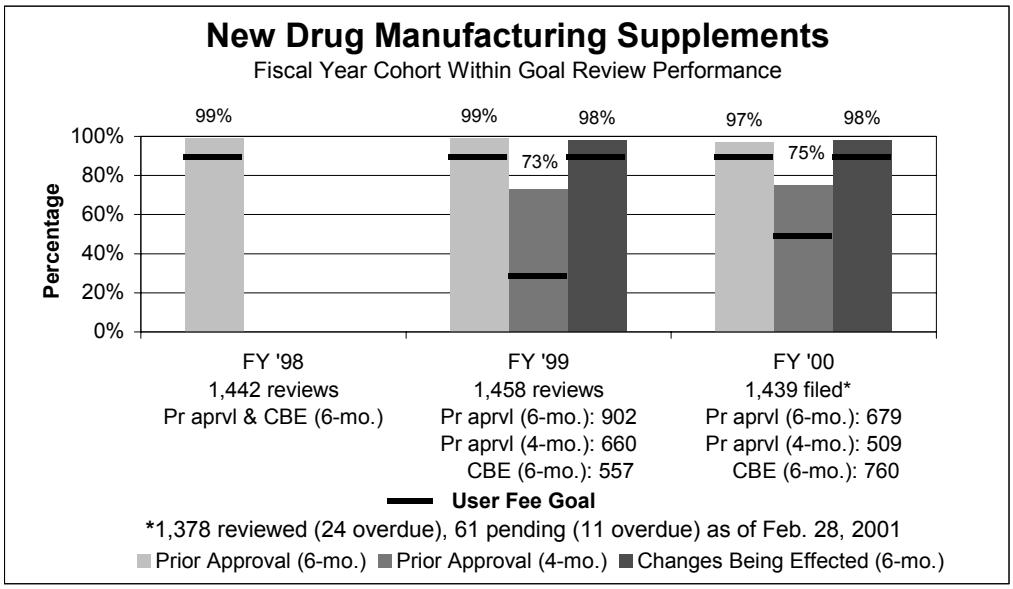
□ Priority efficacy supplements have a six-month review goal.

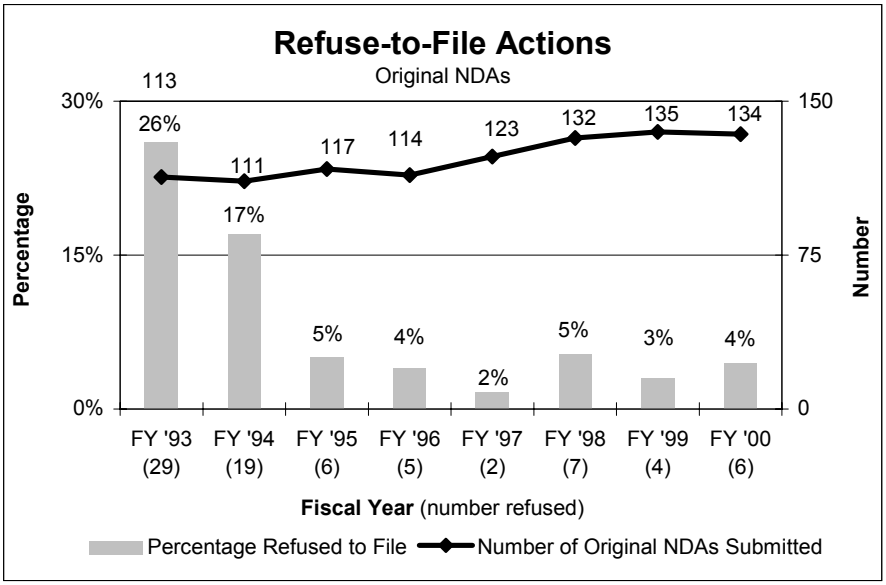


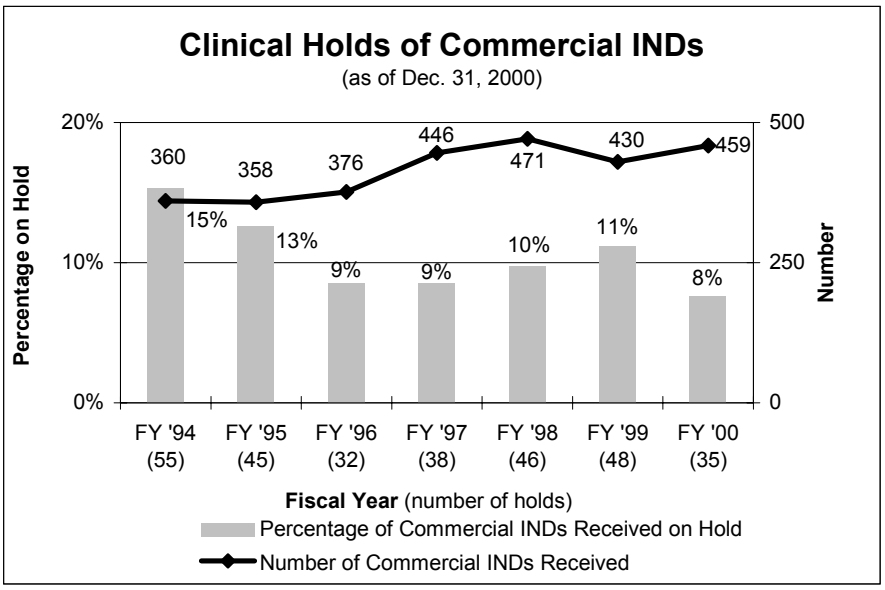
Manufacturing supplements

□ 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.







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 refuse-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.

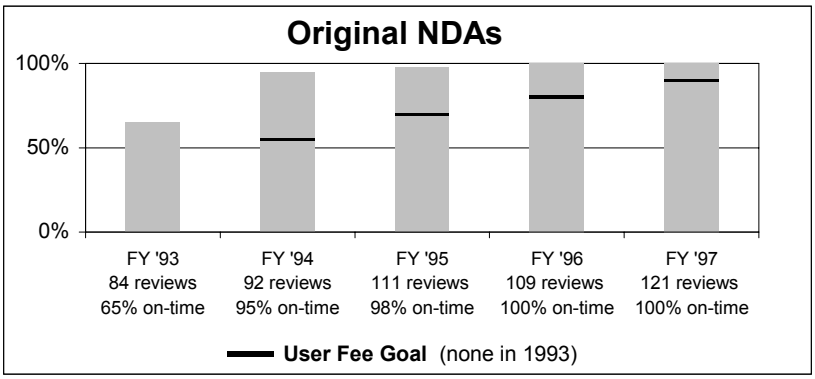
A clinical hold temporarily halts the testing of a drug in humans because of concerns about safety.

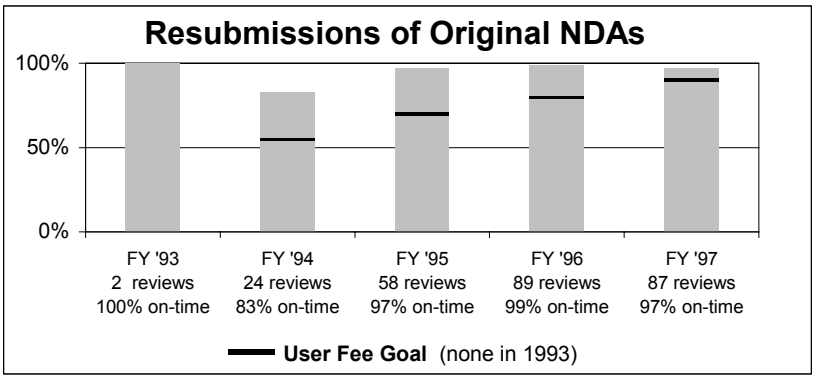
We have developed and published procedures that outline specific responsibilities and timelines for handling clinical holds imposed on investigational new drugs.

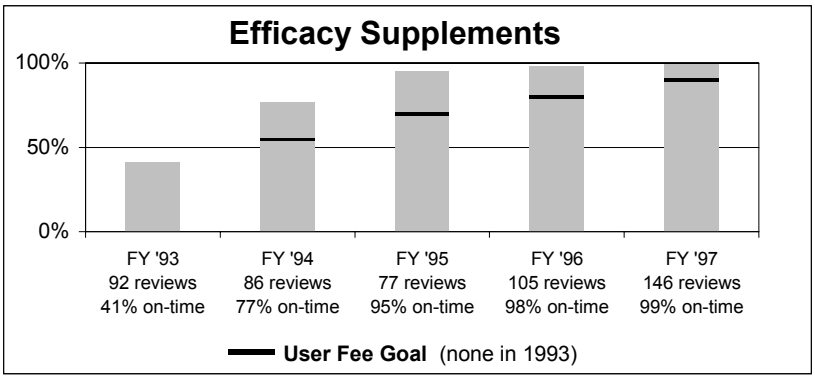
Notes:

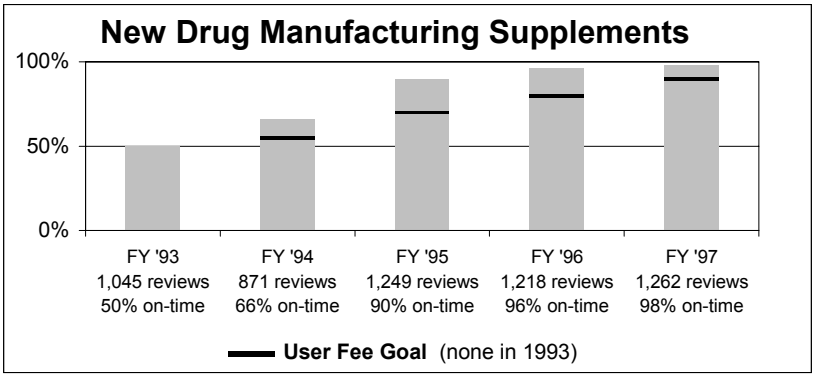
- When comparing the fiscal year user-fee performance charts with the calendar year performance charts, remember that work on one year's submission cohort is often performed in the following year or years.
- The first four charts in this section show a cumulative total and a subset. For example, the performance chart for NDAs shows performance on 12-month reviews and the subset of those that are 10-month reviews.
- This report tracks all applications, including those exempt from user fees, according to user fee goals. These numbers may differ slightly from numbers found in FDA's official reports on applications that pay user fees.

User Fee Performance: 1993-1997









User fee reforms benefit consumers

As we continue to meet and exceed our application review performance commitments, more quality products are reaching American practitioners and consumers faster.

The Prescription Drug User Fee Act has resulted in increasing numbers of applications filed, higher quality applications and quicker approvals for products with the requisite data. Our goals become more challenging each year. Nonetheless, application filings and quality remain high by historic standards and approval times continue to drop.

Increasingly, American patients are receiving the benefits of important new drugs before they are available to citizens of other countries:

- Of the new molecular entities approved in the United States from 1991 to 1995, primarily pre-PDUFA submissions, 43 percent received their approvals within a year of their first introduction on the world market.
- That percentage almost doubled to 80 percent for NMEs approved in the United States from 1996 to 1998, primarily years of user-fee submissions.

Source: Tufts University Center for the Study of Drug Development data in FDA's fiscal year 2000 user fee performance report at http://www.fda.gov/ope/pdufa/report2000/.

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 of a drug before we approve it. Therefore, a degree of uncertainty always exists about the risks of drugs. This uncertainty requires our continued vigilance, along with that of the industry, to collect and assess data during the post-marketing life of a drug.

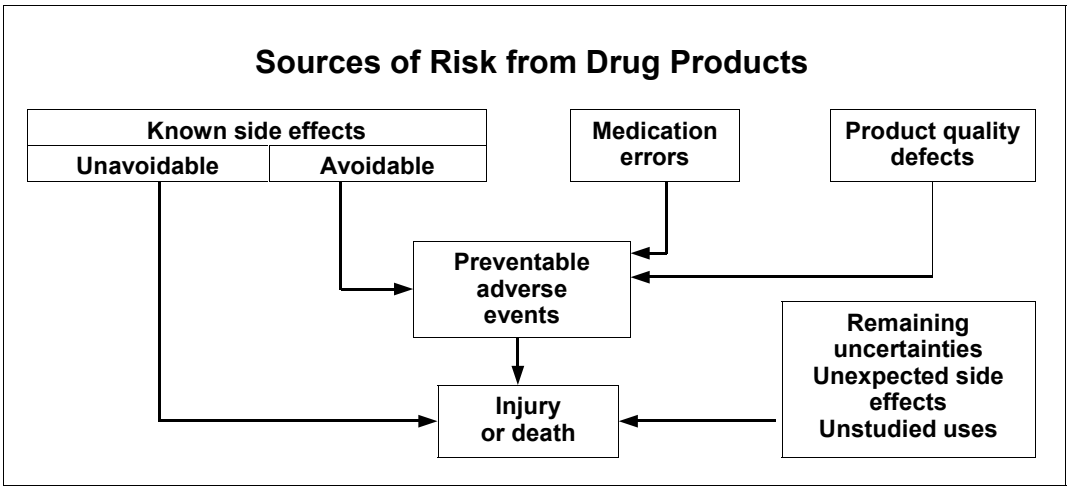
We monitor the quality of marketed drugs and their promotional materials through product testing and surveillance. As Americans are increasingly receiving the benefits of important new drugs before they are available to citizens of other countries, we must be especially vigilant in our surveillance. 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.

Highlights of drug safety and quality activities include:

- Processed and evaluated 245,750 reports of adverse drug events, including 15,374 submitted directly from individuals.
- Conducted 74 inspections to ensure adverse event reports submitted by manufacturers are accurate, timely and complete.
- Issued 1,123 letters to help ensure that the promotion of drug products presents a fair balance of risks and benefits and isn't false or misleading.
- Mandated that five drug products be dispensed with specific consumer information to help make sure them the products are used safely and effectively.
- Issued a proposed rule to revise prescription drug labeling to improve its accessibility and enhance safe and effective prescribing and use.
- Conducted reviews of the safety profile of three approved drug products that resulted in their voluntary withdrawal from the market.
- Issued a public health alert about a once widely used decongestant that has been withdrawn from the market by manufacturers.
- Evaluated results of 1,144 preapproval inspections of new drugs, 1,085 preapproval inspections of generic drugs and 1,436 postapproval inspections.
- Issued 4,197 export certificates for U.S. drug products.

Public meeting on safe drug use

We held a two-day public meeting on the safe use of drug products to inform and obtain feedback from consumer and patient groups.



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. These cause the majority of injuries and deaths from using medicines. Some are avoidable, and others are unavoidable.

- *Avoidable.* In many cases drug therapy requires an individualized treatment plan and careful monitoring. Other 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.

U.S. risk management system fails to respond to new information about a drug's risks

We cosponsored a study of contra-indicated use of cisapride. Our 1998 regulatory action involving cisapride resulted in a black-boxed warning on the labeling and a "Dear Health Care Professional" letter from the manu-facturer.

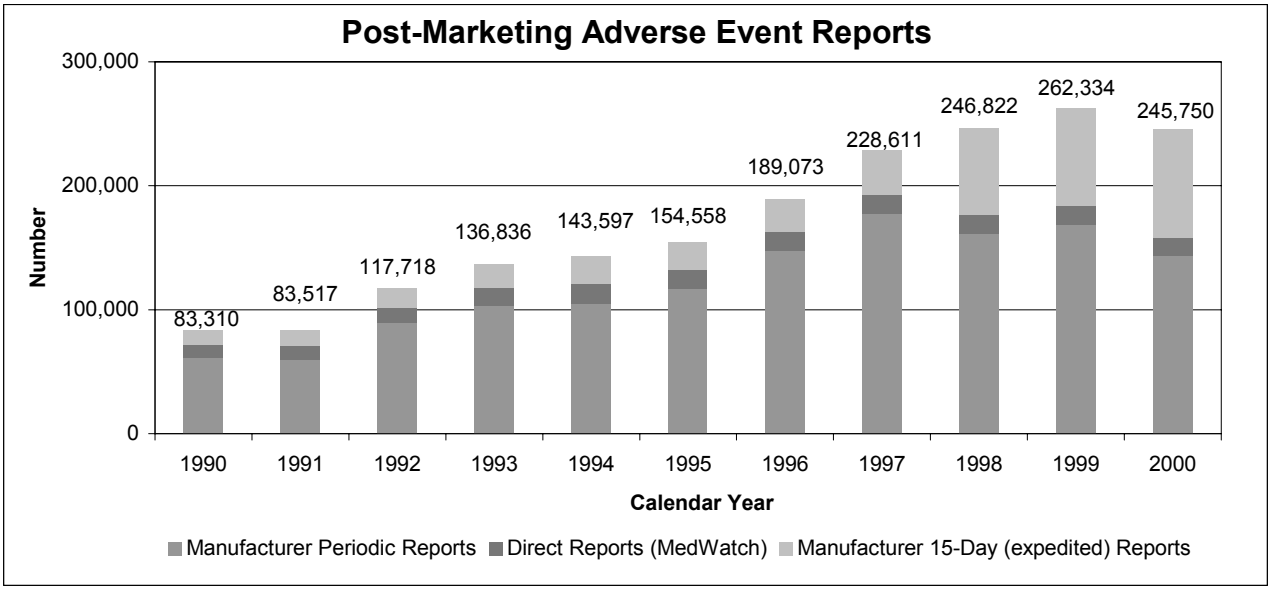
The study indicated the percentage of patients inap-propriately exposed to cisapride was unchanged after the warnings (http://jama.ama-assn.org/issues/v284n23/rfull/joc00932.html).

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.

In 2000, we reviewed about 300 proprietary names and developed standard operating procedures on the review process.

We developed a comprehensive Web site on medication errors at http://www.fda.gov/cder/drug/MedErrors/default.htm.



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.

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.

Information technology

A powerful tool for detecting signals is the computerized spontaneous reporting evaluation system. We use 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 submission options, international compatibility and pharmacovigilance screening.

Adverse event reporting

In 2000, we received 245,750 reports of suspected drug-related adverse events:

- **87,160 manufacturer 15-day (expedited) reports.**
- **15,254 MedWatch reports directly from individuals.**
- **143,336 manufacturer periodic reports and other follow-up reports.**

AERS on Internet

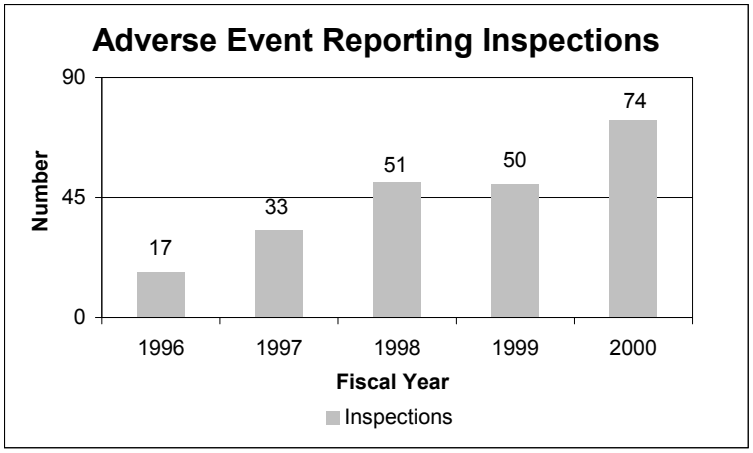
You can learn more about the Adverse Event Reporting System at http://www.fda.gov/cder/aers/index.htm.

Report types

- ***15-day (expedited) reports.*** **These report serious and unexpected adverse events to us as soon as possible within 15 days of discovering the problem.**
- ***Direct reports from MedWatch.*** **An individual, usually a health care practitioner, notifies us directly of a suspected serious adverse event.**
- ***Manufacturer periodic reports.*** **These report all other adverse events, such as those that are less than serious or described in the labeling. This type of report is submitted quarterly for the first three years of marketing and annually after that.**

Postmarketing adverse drug event reporting inspections in fiscal year 2000:

- **52 U.S. inspections**
- **22 foreign inspections**



Adverse event reporting enforcement

We enforce regulations on postmarketing adverse event reporting to ensure that reports are accurate, timely and complete. During fiscal year 2000, we accomplished 74 inspections to ensure industry compliance. There were 52 domestic and 22 foreign inspections.

Drug safety research

We sponsored research that identified the mechanisms for drug interactions between St. John's Wort, an unregulated dietary supplement, and prescription drugs.

Drug-induced liver injury

Drug-induced liver injury is the most common cause for removing approved drugs from the market, limiting a drug to second-line use or requiring special monitoring or restricted use.

We have been working with manufacturers to address clinical studies in patients with impaired liver function. Data from these studies will provide information on dose adjustment and help prevent drug-induced liver injury.

MedWatch Outreach and Reporting

We administer the MedWatch program that helps promote the safe use of drugs by:

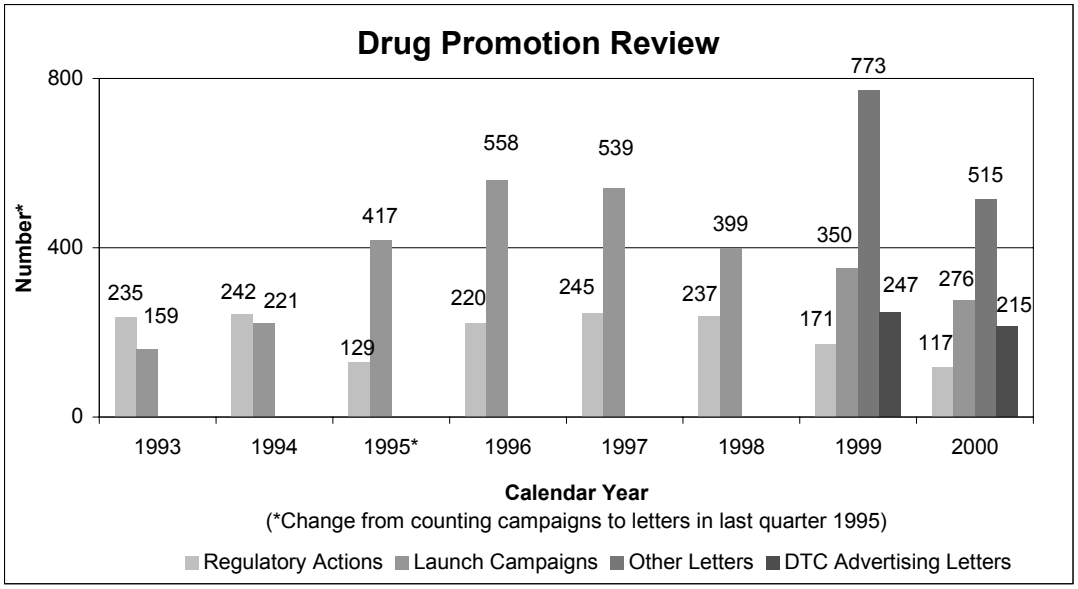
- Rapidly disseminating new safety information on the Internet and by providing e-mail notification to health professionals, institutions, the public and our MedWatch partners consisting of professional societies, health agencies and patient and consumer groups.
- Providing a mechanism for health professionals and the public to voluntarily report serious adverse events and problems with all FDA-regulated medical products. Reports can be filed by mail, fax, telephone or the Internet.
- Educating health professionals and consumers about the importance of recognizing and reporting serious adverse events and product problems, including medication errors. Our education program includes Internet outreach, speeches, articles and exhibits.

Currently, we have 8,000 subscribers to our e-mail notification service and 190 MedWatch partners.

MedWatch drug safety Internet resources

The latest medical product safety information can be found on the MedWatch Web site 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.



Drug promotion review statistics for FY 2000

We issued a total of 1,123 drug promotion letters last year.

- **117 regulatory action letters**
- **276 launch campaigns**
- **515 advisory acknowledgement or closure letters**
- **215 direct-to-consumer advertising advisory and regulatory action letters**

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. We operate a comprehensive program of education, surveillance and enforcement about drug advertising and promotion.

Launches and advisories

When requested, we review advertisements and other promotional materials before drug companies launch marketing campaigns that introduce new drugs or campaigns that introduce new indications or dosages for approved drugs. In fiscal year 2000, we issued 276 advisory letters to companies regarding their promotional materials for launch campaigns.

We also issued 306 other advisory letters to the industry regarding proposed promotional pieces, both professional and consumer directed. In addition, we issued 209 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

Regulatory actions

We issued 117 regulatory action letters to companies for prescription drug promotions determined to be false, misleading, lacking in fair balance of risks and benefits or that promoted a product or indication before approval. These were either "untitled" letters for violations or "warning" letters for more serious or repeat violations. Examples of specific types of violative promotions include "homemade" promotional pieces (seven letters), Internet Web sites (six letters), promotional exhibit hall displays (three letters), oral representations (two letters), plus traditional materials such as journal advertisements and sales brochures.

Direct-to-consumer promotion

We issued 215 letters regarding direct-to-consumer promotion, including 47 letters for launch campaigns, 147 for non-launch advisories, and 20 regulatory letters. Of the regulatory letters, 13 were for advertisements broadcast on television or radio and 7 were for print advertisements.

We posted on our Web site the results from a national telephone survey of patient attitudes and behaviors associated with direct-to-consumer advertisements and obtained funding for a follow-up survey of patients and a new survey of physicians.

Improved patient information for prescription drugs

We held a two-day public workshop to discuss the findings of an interim study of the degree to which useful written information about prescription drugs was given to patients in eight states. The study examined if the information was consistent with the criteria specified in a 1997 action plan agreed to by the government and the private sector.

The meeting presented the study methodology and results. It provided us feedback before we developed an assessment of the year 2000 goals specified in the action plan. More information is at http://www.fda.gov/cder/calendar/meeting/rx2000.

We obtained funding for the assessment and used feedback from the public meeting and written comments from the public to further develop the assessment methodology.

Medication Guides

We may require specific written patient information for selected prescription drugs that pose a serious and significant public health concern. These are called Medication Guides. They must be distributed to patients with each prescription dispensed. We determine if a drug requires a Medication Guide because information is necessary for patients to use the product safely and effectively or to decide to use or continue to use the product. Last year we issued Medication Guides for five products.

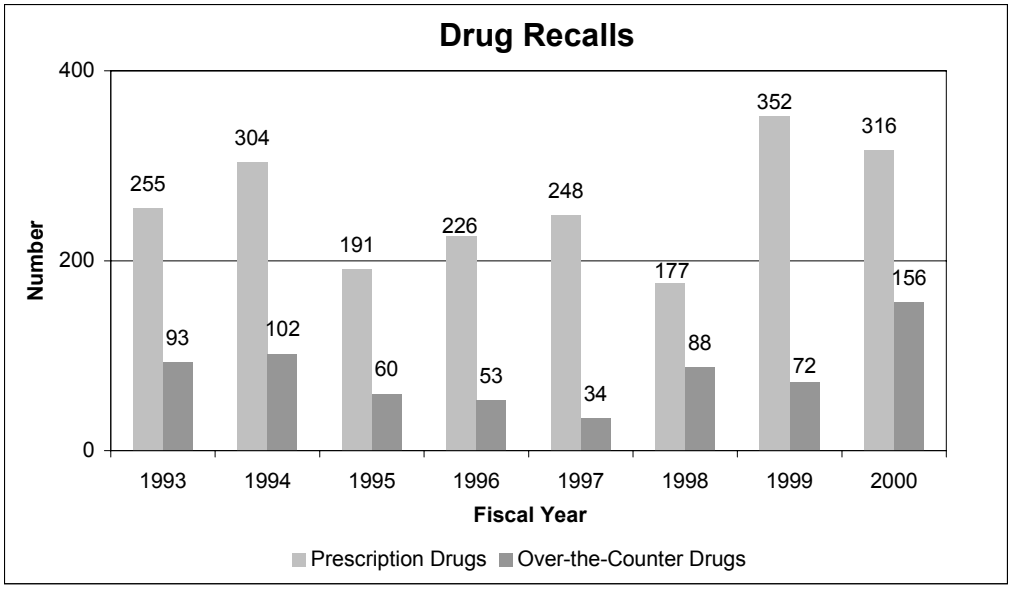
Proposed rule to revise prescription drug labeling

We published a proposed rule that would revise the content and format of prescription drug labeling. The main purpose of labeling is to communicate essential information about prescription drugs to health care providers.

The proposal would add a highlights section of critical prescribing information and an index. It would reorganize and reorder labeling to make the information easier for practitioners to find, read and use. We expect the proposed changes to contribute to our risk communication efforts by improving the accessibility of labeling information and consequently enhancing the safe and effective use of prescription drugs.

Medication Guides issued in 2000:

- **Abacavir (Ziagen)**
- **Abacavir, lamivudine and zidovudine combination (Trizivir)**
- **Alosetron (Lotronex)**
- **Isotretinoin (Accutane)**
- **Mifepristone (Mifeprex)**



Top 10 reasons for drug recalls in fiscal year 2000:

- **Lack of assurance of sterility in production or testing of sterile drug products**
- **Deviations from current good manufacturing practices**
- **Subpotency**
- **Microbial contamination of nonsterile products**
- **Chemical contamination**
- **Penicillin cross-contamination of other products**
- **Failure of or inability to validate manufacturing processes**
- **Drug product marketed without an approved new or generic application**
- **Failure of drug to dissolve properly**
- **Product found to exceed limits set for impurities or degradation**

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.

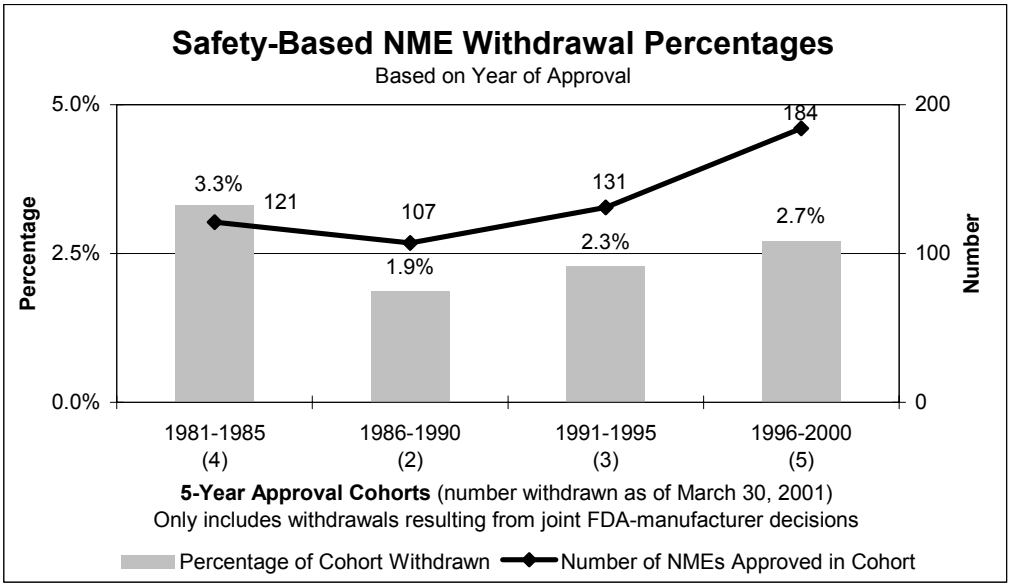
Voluntary recalls

A voluntary recall is taken by a manufacturer or distributor to carry out their responsibilities 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 withdrawals in 2000

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:

- *Alosetron (Lotrenox),* a treatment for irritable bowel syndrome in women, was voluntarily withdrawn after analysis of adverse event reports (http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm).
- *Cisapride (Propulsid),* a treatment for severe nighttime heartburn, is no longer marketed in the United States. We and the manufacturer determined that many preventable adverse events were occurring in patients who should never have been prescribed cisapride.
- *Phenylpropanolamine,* a decongestant ingredient used in many prescription and over-the-counter cough and cold medications, was



1981-2000 NME withdrawals resulting from joint FDA-manufacturer reanalysis of risks vs. benefits

- **543 NMEs approved**
- **14 withdrawn**
- **2.6 percent withdrawn**

Recent safety-based drug withdrawals

Drug name (year approved/ year withdrawn)

- **Fenfluramine (1973/1997)**
- **Ticrinafen (1979/1980)**
- **Zomepirac (1980/1983)**
- **Benoxaprofen (1982/1982)**
- **Nomifensine (1984/1986)**
- **Suprofen (1985/1987)**
- **Terfenadine (1985/1998)**
- **Encainide (1986/1991)**
- **Astemizole (1988/1999)**
- **Flosequinan (1992/1993)**
- **Temafloxacin (1992/1992)**

voluntarily removed from the U.S. market by manufacturers after FDA issued a public health advisory that it might cause strokes and announced it was taking steps that might lead to its withdrawal. Phenylpropanolamine was never formally approved for safety and efficacy (http://www.fda.gov/cder/drug/infopage/ppa/default.htm).

- *Troglitazone, (Rezulin),* a treatment for type 2 diabetes, was voluntarily withdrawn by after review of safety data showed that the drug is more toxic to the liver than two other more recently approved drugs that offer a similar benefit.

Record of safety-based market withdrawals

During the period 1981 to 2000, we approved 543 new molecular entities. Fourteen of these, or 2.6 percent, were withdrawn for safety reasons after joint FDA-manufacturer review. The record of withdrawal of drugs approved in recent years is similar 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.

Recent safety-based drug withdrawals (cont.)

- **Cisapride (1993/2000)**
- **Dexfenfluramine (1996/1997)** (not an NME)
- **Bromfenac (1997/1998)**
- **Grepafloxin (1997/1999)**
- **Mibefradil (1997/1998)**
- **Troglitazone (1999/2000)**
- **Rapacuronium (1999/2001)** (manufacturer only decision)
- **Alosetron (2000/2000)**
- **Phenylpro-panolamine (—/2000)** (never approved by FDA)

Drug Product Quality

We provide comprehensive regulatory coverage of the production and distribution of drug products. We manage inspection programs designed to minimize consumer exposure to defective drug products. We have two basic strategies to meet this goal:

- Evaluating the findings of factory inspections of the conditions and practices in plants 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 in deficiencies. 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.

New drug preapproval plant evaluations

- **FY 2000: 1,144**
- **FY 1999: 773**

Generic drug preapproval plant evaluations

- **FY 2000: 1,085**
- **FY 1999: 1,775**

Good manufacturing practice inspections

- **FY 2000: 1,436**
- **FY 1999: 1,844**

Manufacturing plant inspections

FDA field offices conduct inspections of domestic and foreign plants that manufacture, test, package and label drugs. 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 2000, FDA evaluated 1,144 domestic plants in support of new drug applications. One user fee goal was missed. Also, FDA evaluated 1,085 domestic firms in support of generic drug applications.
- *Good manufacturing practice inspections.* There were 1,436 good manufacturing practice inspections in fiscal year 2000. Of the warning letters that resulted from these inspections, we reviewed 34 policy consistency. We also reviewed 48 field recommendations for regulatory action and approved 28. These included two injunctions, 14 seizures and seven warning letters. We reviewed 248 foreign establishment inspection reports. These reviews resulted in 11 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.
- *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.

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.

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.

Unsubstantiated claims; fraudulent, 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 effective 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 Product Quality Research

We conduct scientific research on drug product quality issues. Last year our efforts included:

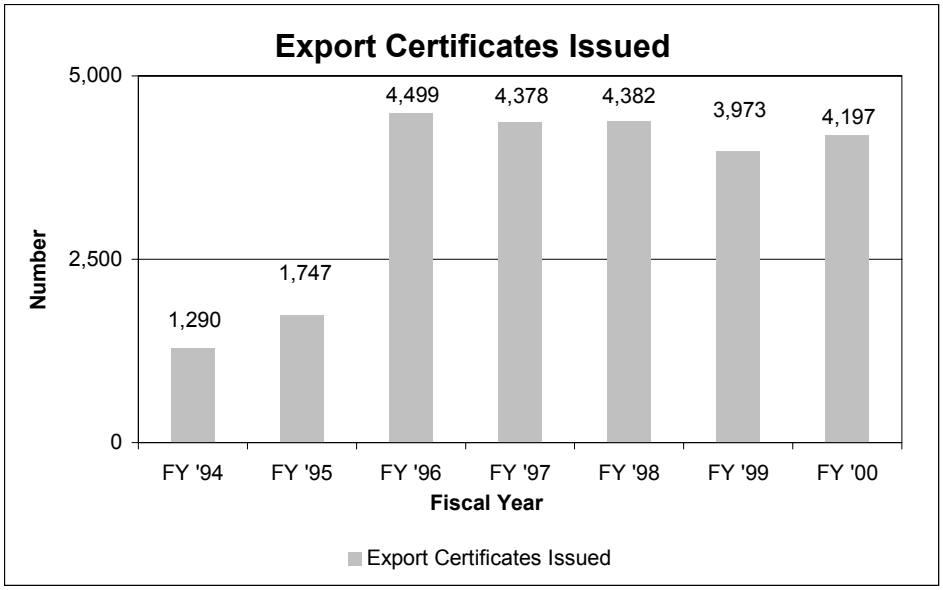
- Developing *in vitro,* or test tube, methods for studying the impact of excipients and diluting agents on the absorption of orally administered drugs. Excipients are commonly known as "inactive ingredients."
- Identifying genetic markers that will authenticate cultivated St. John's Wort and detect contamination by related species.
- Developing and validating numerous methods for testing the quality of pharmaceutical products. For example, near-infrared spectroscopy can detect and quantify different hydrated forms of an active ingredient in commercial drug products.

PQRI 2000 update

The Product Quality Research Institute (page 4) marked its first year by initiating seven working groups to address:

- Blend uniformity.
- Oral biopharmaceutics.
- Packaging changes.
- Bulk drug post-approval changes.
- Drug substance impurity testing.
- Drug substance particle size analysis.

PQRI is expected to make recommendations in 2001 aimed at ensuring thorough mixing of a drug within the blend and dosage unit.



Export certificates issued in FY 2000:

- **4,197**

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 remains 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. Export certificates verify that 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.

Drug Shortages

We work to help prevent or alleviate shortages of medically necessary drug products. Drug shortages occur for a variety of reasons including manufacturing difficulties, bulk supplier problems and corporate decisions to discontinue drugs.

Because drug shortages can have significant public health consequences, we work with all parties involved to make sure all medically necessary products are available within the United States.

Drug shortages on Internet

We developed a Web site that lists current drug shortages, describes efforts to resolve them and explains how to report them. The site is at http://www.fda.gov/cder/drug/shortages/.

3

INTERNATIONAL ACTIVITIES

Highlights from 2000 include:

- Finalization of the Common Technical Document that can be used for seeking approval to market new drugs in the United States, the European Union and Japan.
- Initiation of harmonization efforts among the countries of North and South America.
- Leadership of the U.S. consultations with the European Union to allow for reciprocal reliance on manufacturing plant inspections.

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 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. Before ICH, many time-consuming and expensive technical tests 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.

Second ICH phase launched

ICH embarked on a second phase of activities and agreed to broaden representation to other parties. This effort will have implications for already marketed drugs, over-the-counter drugs and generic equivalents.

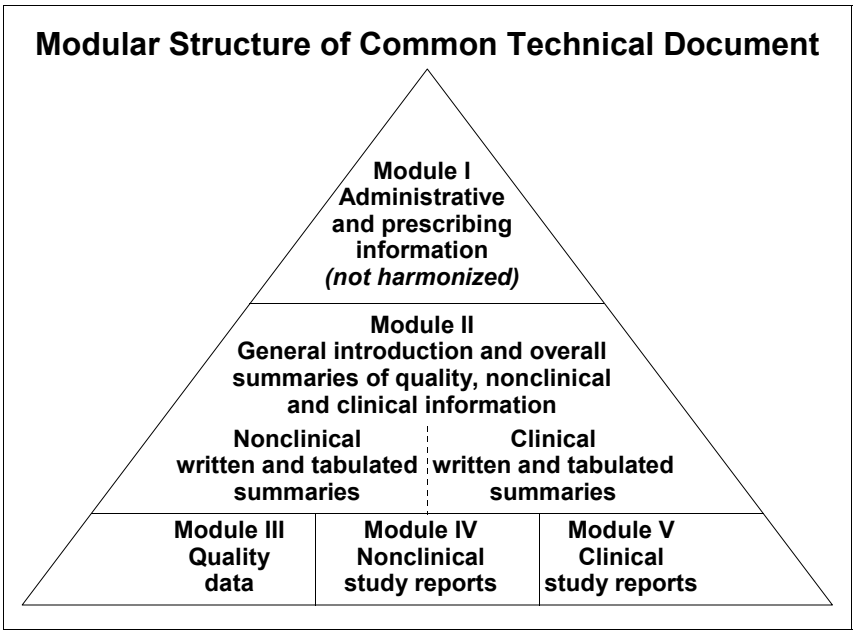
Internet sources

We have published ICH documents as guidances to industry. These are on our Web site at http://www.fda.gov/cder/guidance/index.htm.

More information about ICH activities is at http://www.fda.gov/cder/audiences/iact/iachome.htm.

PAHO information is at http://www.paho.org Information on PANDRH is at http://www.paho.org/english/gov/cd/cd42_13-e.pdf.

The Mutual Recognition Agreement is at http://www.iep.doc.gov/mra/mra.htm and on the European Union's Web site at http://dg3.eudra.org/.



Common Technical Document finalized

The ICH partners reached agreement on an information package of technical data, in the same format and with the same content, that can be submitted to drug review authorities in all three ICH regions.

We expect to be able to accept new drug applications conforming to the new format by mid-2001.

Work on making the document suitable for electronic submission is nearing completion.

Harmonization initiative in the Americas

We are working with the Pan American Health Organization to promote regulatory harmonization within the Americas. PAHO is part of the United Nations system, serving as the World Health Organization's regional office for the Americas. The initiative, called the Pan American Network for Drug Regulatory Harmonization or PANDRH, will search for common ground on various topics in a prioritized work plan.

We are the lead for two topics of high priority—good manufacturing practices and bioavailability/bioequivalence. We are working with the countries of Latin America to provide training on these two important issues. Training to the same standards should help lead to harmonization.

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 with regulatory systems for good manufacturing practices that we have assessed and determined will achieve a comparable level of public health protection.

While the agreement will allow us to use an inspection report from one of our European counterparts as though it were our own, the actual regulatory decision will be up to us. Our experts in good manufacturing practices are leading the FDA team that is working with a team from the European Union to implement this agreement.

MRA update

Last year marked the second year of a three-year transition to implementation.

Implementation has not proceeded as smoothly as planned, but both parties remain optimistic and continue to strive toward a mutually beneficial outcome.

4

COMMUNICATIONS

Highlights from 2000 include:

- Meeting almost weekly with outside experts on difficult scientific and public health issues.
- Responding to more than 58,000 individual requests for information.
- Receiving nearly 5 million visitors and about 80 million hits on our Internet information site, which has 30,000 pages and documents.

Public participation

We confer with panels of outside experts in science, medicine and public health in meetings open to the public. We assure that patient representatives are included on advisory committees considering medicines for HIV, AIDS, cancer and other serious disorders. We analyzed public comments on proposed new rules, and we sought and received comments on our guidances to industry.

In special public meetings, we received valuable input from consumer and patient groups, professional and scientific societies, industry and trade associations about:

- Ways to include consumer input in our evaluation of the usefulness of written information currently dispensed with prescription drugs.
- Reexamining a number of issues about over-the-counter drugs including prescription-to-OTC switches and classes of drugs available over the counter.
- Strengths and weaknesses of the Prescription Drug User Fee Act.

We cosponsored two public workshops on how consumers can make sure they use drug products safely and understand their role in improving the drug quality control system.

Consumer and industry outreach

We use a number of modern communication methods to reach our stakeholders. Highlights include:

- Responding to more than 1,680 telephone and e-mail requests from the specialized media that focus on the pharmaceutical industry. This compares with 1,250 in 1999 and about 1,000 in 1998.
- Completing successful showings of our exhibit and information program at 19 national health care conferences and meetings, reaching an estimated audience of over 100,000 health care professionals.

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.

Internet updates

We have 33,000 subscribers to our service that provides daily and weekly e-mail updates of new content on our Web site.

To subscribe, visit http://www.fda.gov/cder/cdernew/listserv.html.

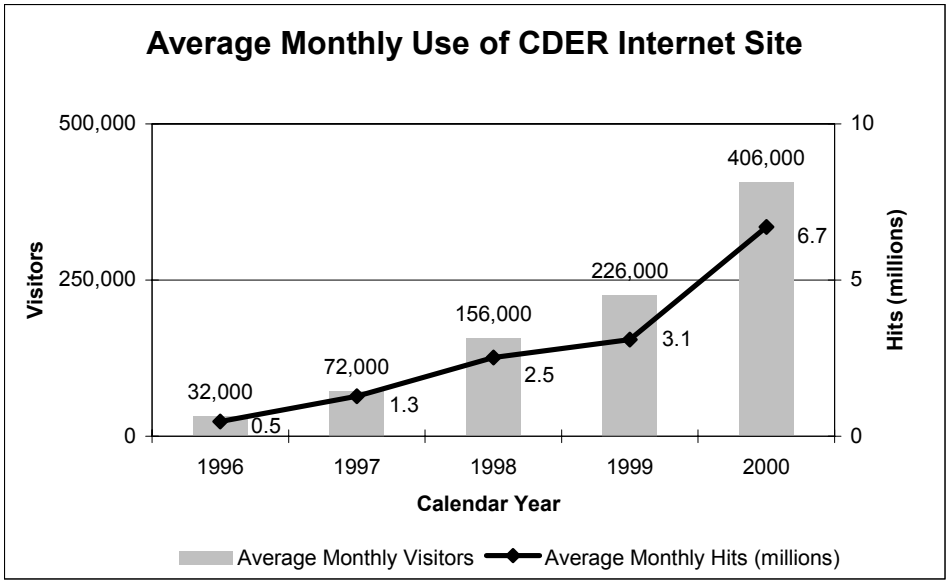
Stakeholders in drug review, drug quality and safety

We work closely with many organizations on issues of public health and safety, including:

- **Consumers, patients and their organizations**
- **Scientific and professional societies**
- **Industry and trade associations**
- **Universities, hospitals and health care professionals**
- **Federal, state and local government agencies**
- **Foreign governments**

Reorganization of information activities

Our Office of Training and Communication created the Division of Drug Information and the Division of Public Affairs to improve information dissemination to our stakeholders and enhance consumer outreach and education.



Workshop on postapproval changes in analytical methods and packaging

We cosponsored a workshop to discuss scientific issues related to changes in analytical methodologies and packaging for pharmaceuticals.

Participants explored viable scientific approaches for predicting the potential impact of changes on drug substance and quality.

- Conducting about 70 domestic and foreign videoconferences for academia, industry and associations.

Educational campaigns

In response to the expressed need for additional information from the public and health care professionals, we developed public education campaigns about:

- Benefits vs. risks of medication use.
- Buying prescription medical products over the Internet.
- Aspirin therapy to reduce the risk of heart attacks and strokes.
- Pharmacy compounding.
- The new over-the-counter medicine labels.

Dissemination activities

- *CDER Live!* We conducted two satellite television broadcasts for industry in which our scientific and regulatory experts engaged in panel discussions about minimizing medical errors and direct-to-consumer advertising. About 5,000 industry executives, scientists and managers viewed the programs live, with additional viewers by webcast.
- *E-mail information requests.* We responded to more than 16,400 e-mail requests from industry, consumers, patients and health care professionals.
- *Other communication.* We answered more than 27,000 telephone inquiries, 4,000 faxes and nearly 7,000 written requests. We responded to more than 9,500 requests for documents and guidance publications.

Packaging training

We cosponsored a training session for members of the pharmaceutical industry to discuss and clarify our guidance on container closure systems.

Ombudsman's activity

In its fifth year of operation, our ombudsman helped settle issues between the Center and industry, health professionals and consumers.

The ombudsman handled about 100 complaints. He answered more than 1,000 e-mails, approximately 1,000 telephone calls and 20 letters.

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

Where to Find More Information

We support multiple ways to obtain information about drug products and the laws, regulations and guidances concerning them.

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
- *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
- CDER organizational charts: http://www.fda.gov/cder/cderorg.htm
- CDER key officials: http://www.fda.gov/cder/directories/keyoffic.pdf

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

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Drug Information Division
HFD-240, Room 12B-31
5600 Fishers Lane
Rockville, MD 20857