Center for Drug Evaluation and Research ***2001***

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/rtn/2001/rtn2001.pdf
- HTML: http://www.fda.gov/cder/reports/rtn/2001/rtn2001.htm
- Slides: http://www.fda.gov/cder/reports/rtn/2001/rtn2001.ppt

Suggested citation: Food and Drug Administration. *CDER 2001 Report to the Nation: Improving Public Health Through Human Drugs.* Rockville, Maryland, 2002.

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DIRECTOR'S MESSAGE

Last year, we at the Center for Drug Evaluation and Research worked hard to:

- Provide rapid access to new therapies while maintaining rigorous safety and effectiveness standards.
- Listen to the voices of consumers, patients and health care professionals as well as those of regulated industry.
- Match the effort in premarket evaluation with a vigorous postmarket monitoring program.
- Make sure we support the people in CDER as well as serving the outside world.

However, routine operations were not the hallmark of a year that witnessed the terrorist attacks on and after Sept. 11. The brutal assaults challenged us to rise to the defense of the American consumers. In close cooperation with other authorities, we responded with our traditional vigor, initiative and scientific expertise.

We developed strategies to strengthen the protection of drug products against willful contamination and to improve the availability of drugs for the prevention or treatment of injuries caused by biological, chemical or nuclear agents.

For example, we took the initiative to publish a notice that the antibiotics doxycycline and penicillin G procaine are safe and effective for the post-exposure prevention of inhalational anthrax. This notice included explicit dosing based on our review of scientific literature and data from the same rhesus monkey study that had been used to support our August 2000 approval of ciprofloxacin for post-exposure prevention of inhalational anthrax. The assurance that the three drugs are safe and effective for this use eased public concerns about a potential shortage of medication for the victims of the mailed anthrax powder.

We also stepped up our work on measures to encourage the development of new drugs to counter the toxic effects of chemical, biological, radiological and nuclear weapons.

In addition to doing our part in protecting Americans against terrorism, we evaluated many new drugs that advanced the frontier of modern medicine. For example, we approved a new drug to treat a rare form of life-threatening cancer in two and one-half months. We are continuing to develop science-based data on safety and dosing regimens for drugs to treat children.

Once again, we met all of the demanding application review goals of the Prescription Drug User Fee Act, but we have encountered challenges. Our efforts to meet goals for drug development may have had an unintended impact on approval times for standard applications. These approval times have begun to increase because more applications require multiple review cycles to reach approval. We are watching trends closely.

Our generic drug program is providing a steady supply of more affordable drugs that meet our uniform and stringent standards for safety, effectiveness and quality. We are developing an education program to bolster consumer confidence in generic drugs.

We continued to enhance our drug safety program. In recent years fully 50 percent of all new drugs worldwide have been launched in the United States, and American patients have had access to 78 percent of the world's new drugs within the first year of their introduction. More rigorous safety monitoring of newly approved drugs in the first few years on the market is key to detecting unanticipated problems earlier. We have entered into several agreements that will give us access to data about the actual use of prescription drugs by children and adults. This will augment our ability to determine the significance of adverse events we receive. We will have the benefit of advice about general and product-specific safety issues from a new panel of experts in areas related to risk perception and management, pharmacology and other related disciplines.

We launched an important initiative to build the scientific data needed to modernize American drug manufacturing. While Americans have the highest quality of drugs in the world, the process used to produce them can be expensive and wasteful. We have observed an increasing trend toward manufacturing-related problems, such as recalls, disruptions of manufacturing operations and the loss of availability of essential drugs. Modern technology holds the promise of manufacturing to the same or higher quality standards while reducing the workload for industry and for us and 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. Industry and consumers are increasingly turning to our Internet site for important and up-to-date information on our regulatory programs and on the drugs they take to improve their health.

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 about 1,800 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

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.**

about suspected problems from manufacturers, health care professionals 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 consult the American public when making difficult 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 most 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.

2001 HIGHLIGHTS

We are pleased to present our sixth 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. In the wake of the terrorist attacks, our nation was prepared with an antibiotic approved to treat inhalational anthrax. We had worked on this program for several years and reported on the approval in last year's report. We were rapidly able to provide health professionals with additional guidance on using other safe and effective medicines.

Realignment

We began the new year with a revised structure aimed at aligning similar functions and creating smaller, more manageable work units.

Our organizational charts are at http://www.fda.gov/cder/cderorg.htm.

Drug review

People with cancer, heart disease, HIV, AIDS, and other serious conditions have benefited from our approvals in 2001. 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 66 new drugs, including 24 new molecular entities. New molecular entities contain an active substance never before approved for marketing in any form in the United States. We also approved 91 new or expanded uses of already approved drugs. We increased choices for self-care by approving six medicines for over-the-counter marketing and one new or expanded use for an existing over-the-counter drug. We approved 234 generic equivalents for prescription or over-the-counter 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. We augmented our risk-assessment ability by gaining access to actual use data. We will be able to consult with a new expert panel of advisors.

Last year, we processed and evaluated more than 280,000 adverse drug events. We issued nearly 900 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 three drug products be dispensed with specific consumer information that will help ensure the products are used safely and effectively. Our review of the safety profile of one approved drug resulted in its voluntary withdrawal, and the manufacturer of another drug withdrew it after reviewing safety reports.

Communications

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

We held two week-long introductory workshops for our stakeholders.

We responded to more than 52,000 individual requests for information.

Each month, our Internet information site averaged nearly 550,000 visitors and 10 million hits.

We developed public education campaigns in areas such as risk management and buying prescription drugs over the Internet.

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 began accepting the first new drug applications in the Common Technical Document format. The CTD can be used for seeking approval to market new drugs in the United States, the European Union and Japan.

We are collaborating on prioritizing issues for our harmonization efforts among the countries of North and South America. We are leading the U.S. consultations with the European Union to allow for reciprocal reliance on manufacturing plant inspections. Last year we began exchanging recall information and alerts concerning significant emerging product quality problems with the European Union.

Counterterrorism

The terrorist attacks of Sept. 11, 2001, and the subsequent anthrax contamination of the mail underscored our role in:

- Protecting the nation's drug supply from attack or deliberate contamination.
- Assuring the availability of medicines to treat victims of terrorist and bioterrorist attacks.
- Preparing ourselves to continue operations during a crisis.

The first therapy for those exposed to a terrorist attack or a biological warfare agent is often a drug. We have been taking an aggressive and proactive approach to getting antibioterrorism treatment information into the labeling of already approved drugs. We approved the first such drug, ciprofloxacin, in 2000 for treating inhalational anthrax.

The Sept. 11 terrorist attacks and the subsequent anthrax attacks have vaulted this work and other actions to protect public health and safety to our top priority.

On Sept. 11, we continued to communicate with the Centers for Disease Control and Prevention. By that night, the CDC had submitted to us a "streamlined" investigational new drug application that would allow government physicians to prescribe the antibiotic gentamicin for the treatment of pneumonic plague in the event of a bioterrorist attack.

In November, in response to concerns about a potential nuclear event, we finalized our guidance on potassium iodide, or KI, as an agent to protect the thyroid gland in radiation exposure emergencies.

The animal efficacy rule

We are preparing a final regulation to implement our 1998 proposal, commonly called "the animal efficacy rule." The rule would permit us to rely on animal evidence when a bioterrorism agent's mechanism of toxicity is well understood in humans; the efficacy endpoints in the animal trials are clearly related to benefit in humans; the drug's effect is demonstrated in a species expected to react similarly to humans; and data allow selection of an effective human dose.

Such approvals could include possible postmarketing studies when feasible and ethical, possible restrictions on distribution and a requirement that information about the basis of approval be provided to patients.

Ciprofloxacin for anthrax

We recognized several years ago that no drugs were specifically labeled for the treatment or post-exposure prevention of inhalational anthrax. We worked on ciprofloxacin first, based on expert assessment that anthrax was the most likely biological agent. We also feared that anthrax might be modified to be resistant to older antibiotics with an anthrax indication.

Ciprofloxacin has an enormous safety database. It has been used for more than 14 years with more than 100 million prescriptions in the United States and 250 million worldwide—more than 4 million of those for children.

We knew we could get similar drug levels in humans to the blood levels in the monkeys that the U.S. Army had exposed to anthrax.

We initiated the identification and collection of the data. The sponsor then submitted a supplemental application, which we approved.

Immediate response to the anthrax crisis

- Published new labeling information for doxycycline and procaine penicillin in post-exposure management to prevent the development of inhalational anthrax.
- Issued a public health advisory on the use of doxycycline for anthrax exposure.
- Coordinated with other agencies to halt the importation of unapproved ciprofloxacin.
- Posted information on antibiotic use for anthrax on the Internet.

Ongoing and long-term counterterrorism work

- Coordinating with the Department of Defense to develop an appropriate animal model to study whether available antibiotics, which aren't labeled for pneumonic plague, are effective in the treatment of this highly contagious lung disease.
- Cooperating with the National Institutes of Health, CDC, DOD and sponsors from industry to facilitate development of both investigational new drug applications and new uses for already approved drugs that could be used as medical countermeasures to a terrorist attack with agents such as smallpox and plague.
- Assisting the CDC to obtain follow-up drug safety and outcome information for patients treated with antibiotics during the anthrax post-exposure prophylaxis campaign.
- Expediting work on a final regulation that would allow us to rely on animal studies and supporting data to approve drugs for bioterrorism agents when clinical studies in humans would be unethical.
- Assisting the CDC in managing the National Pharmaceutical Stockpile.
- Coordinating with FDA's field inspectors and manufacturers to help evaluate and resolve any manufacturing concerns that might arise during emergency production.
- Expediting reviews and inspections for manufacturing supplements that may be required for expanded drug production.
- Working with CDC, DOD and the Department of Veterans Affairs to implement a shelf-life extension program for stockpiled drugs for civilian and military use.
- Gathering and maintaining information on drugs that might be effective in an attack, including data on manufacturers, bulk suppliers, inventories and lead times for production.

Internet resources

To help prepare our nation for possible bioterrorism attacks, we are working with other federal agencies to make sure adequate supplies of medicines are available to the American public.

Our Internet site provides links to the most current information on drug therapy, including information on special populations such as children and pregnant women, plus advice on purchasing and taking medication. You can find it at http://www.fda.gov/cder/drugprepare/default.htm.

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 update, page 36).**

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

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.

Scientific Research

We advance the scientific basis of regulatory practice by developing and evaluating new scientific methods and regulatory testing paradigms. We provide scientific support for reviewer training, regulatory decision making and the development of regulatory policy. We focus on creating a 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

- Identifying, evaluating and establishing improved protein biomarkers in blood in both animal models and in humans. These will help monitor the very earliest damage that can be caused by certain drugs to the heart, blood vessels, kidney, immune system and liver.
- Identifying cellular and tissue biomarkers predictive of safety and efficacy, through DNA microarrays and noninvasive imaging. The use of these novel technologies enables evaluations of their strengths and limitations for practical applications that could improve the interface between drug development and regulatory practice.
- Elucidating the molecular mechanisms operating in transgenic mice to ensure the appropriate use of more rapid and reliable tests that will detect the cancer-causing potential of drugs.
- Developing experimental models for detecting early signals of damage in liver cells. This will facilitate understanding why certain types of drugs cause liver damage.

Clinical Pharmacology

- Results from St. John's Wort interaction studies demonstrated that this herb could reduce the effectiveness of some prescription drugs. The results also provided the scientific basis for our recommendation to FDA's Center for Food Safety and Applied Nutrition and the Federal Trade Commission on the labeling of St. John's Wort products.
- Results from studies on the metabolism of hormone replacement therapy provided critical information for labeling these products and drugs that will be co-administered with them.
- We evaluated the stability and palatability of ground and dissolved antibiotic tablets for use in children in a bioterrorism emergency.
- Noninvasive imaging is an emerging technology increasingly used drug development. We are using this tool to extend our long-standing interest in the application of dose-concentration-response principles for regulatory decision-making by viewing drugs and their actions directly at the level of the drug target, rather than indirectly via plasma concentrations and/or downstream indicators of target modulation.

Studies of drugs that affect metabolic enzymes

We carefully monitor the inhibition of drug metabolism in both our research and review programs.

Clarithromycin is an example of drugs that have mechanism-based effects on metabolic enzymes.

These often cause longer-lasting drug interactions and have resulted in serious adverse events when additional drugs are prescribed.

Data on and an understanding of the effect and the time-course of mechanism-based inhibitors is critical for providing accurate dosing information when new drugs are co-administered with these agents.

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DRUG REVIEW

Drug approvals for 2001

- **66 new drugs**
- **24 new molecular entities**
- **3 orphan new drugs**
- **91 new or expanded uses for already approved drugs**
- **3 orphan new or expanded uses**
- **6 over-the-counter drugs or Rx-to OTC switches**
- **1 new or expanded use for an over-the-counter drug**
- **234 generic equivalents for prescription and over-the counter drugs**

Many Americans benefited from last year's timely reviews of new prescription medicines, over-the-counter medicines and their generic equivalents.

We met or exceeded all the performance goals we agreed to under legislation authorizing us to collect user fees for drug reviews.

We approved 24 new medicines that have never been marketed before in this country and 234 generic versions of existing drugs. We authorized seven medicines to be sold over the counter without a prescription.

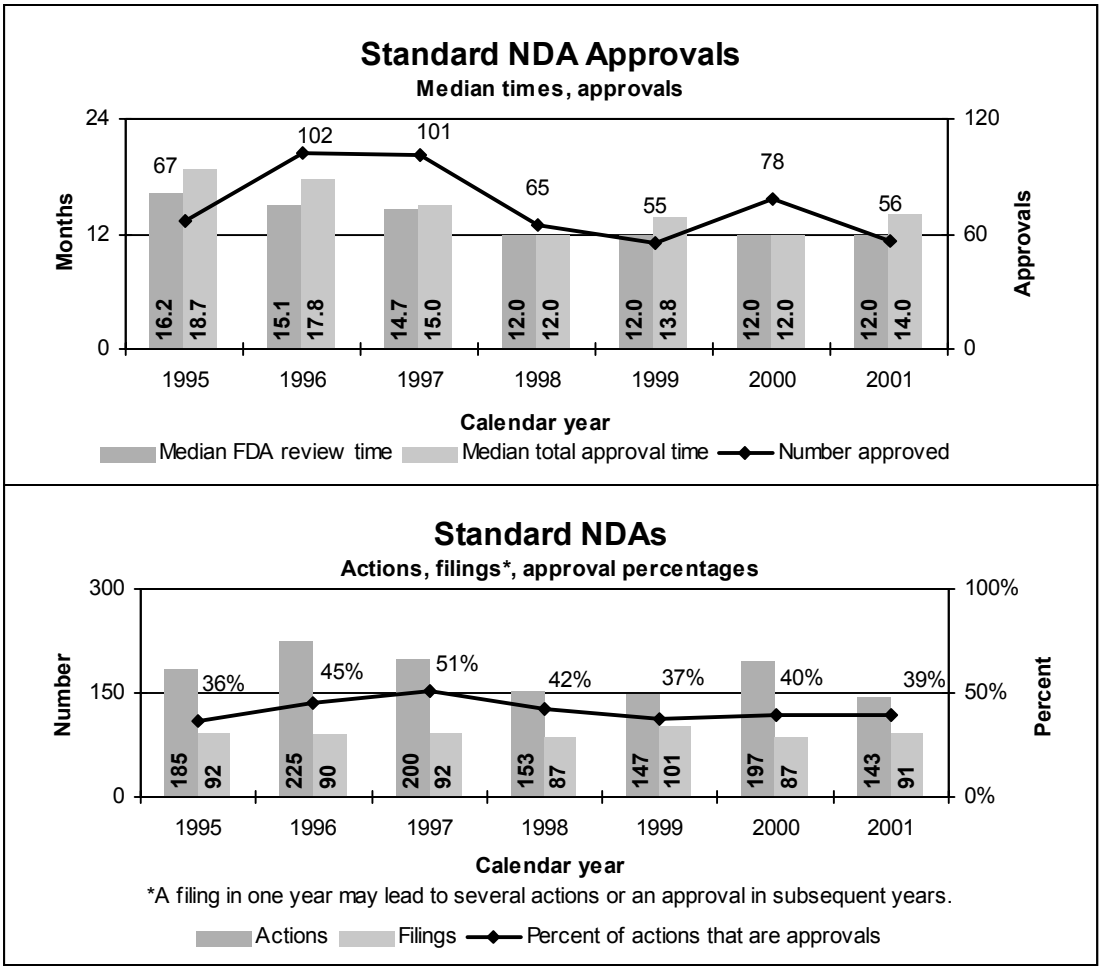
We conducted 463 foreign and domestic inspections that help protect volunteers for clinical trials from research risks and validate the quality and integrity of data submitted to us.

Highlights of new medication options for American consumers include:

- Two new drugs to treat cancer.
- Four drugs to treat heart disease and circulatory disorders.
- The first in a new class of drugs approved to treat HIV infection.
- One new drug for Alzheimer's disease.
- One new drug for schizophrenia.
- Two new prescription drugs for migraine headaches.
- One new COX-2 selective anti-inflammatory drug for arthritis and menstrual cramping.
- The first in a new class of antifungals.
- A synthetic drug to prevent blood clots that is the first in a new class.
- Two new drugs to treat glaucoma, a leading cause of blindness.
- Three new or expanded uses to treat breast cancer.
- New shorter dosing regimens of an over-the-counter treatment for vaginal yeast infections.
- A new over-the-counter use for aspirin to treat migraine.
- Three new drugs and three new or expanded uses of existing drugs for "orphan" patient populations of 200,000 or fewer.

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.



Standard new drugs

- **56 approvals**
- **Median review time: 12.0 months**
- **Median approval time: 14.0 months**
- **143 actions**
- **91 filings**

Orphan drugs

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

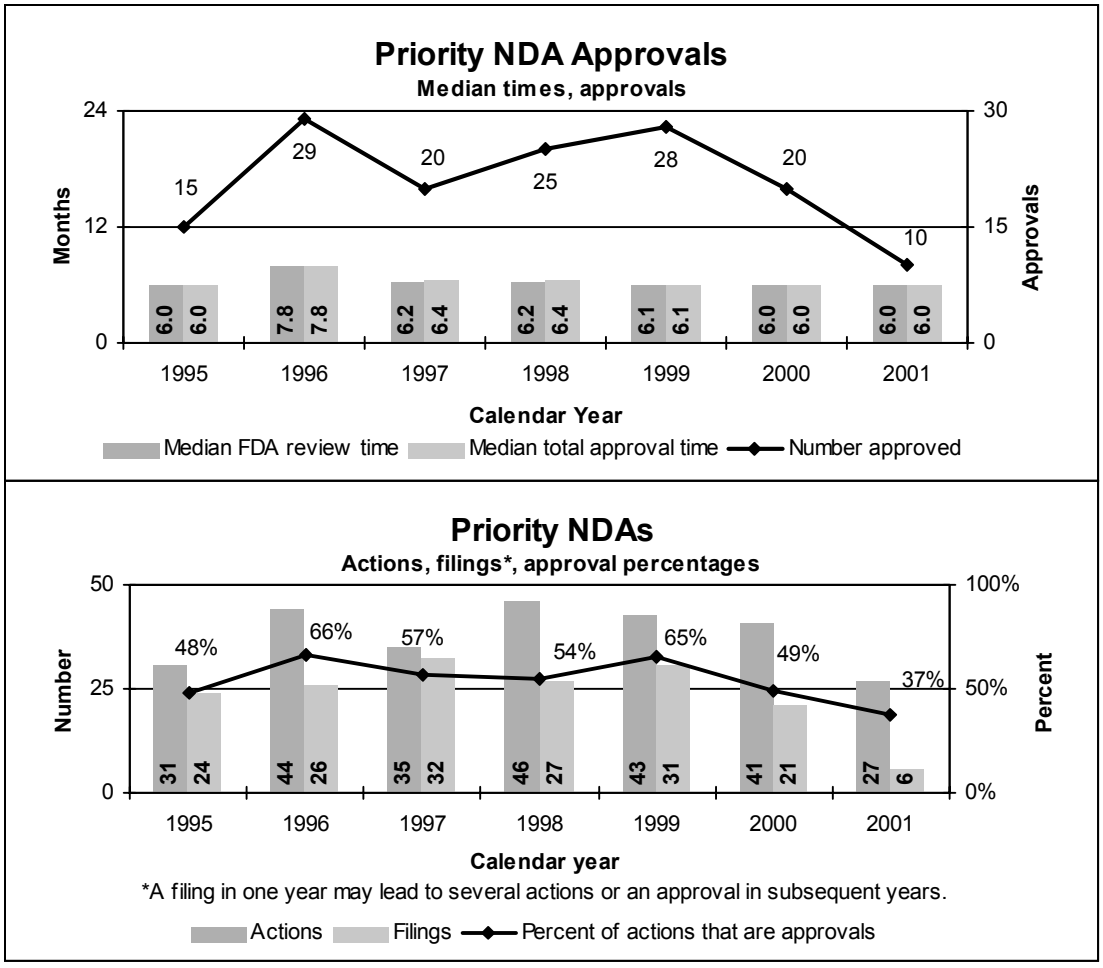
- ***Bosentan (Tracleer)*** **treats pulmonary arterial hypertension.**
- ***Imatinib mesylate (Gleevec)*** **treats chronic myeloid leukemia.**
- ***Zoledronic acid (Zometa)*** **treats excess calcium in the blood caused by tumors.**

New Drug Review

Standard new drugs. We took 143 actions on standard new drug applications, of which 56 were approvals. These drugs have therapeutic qualities similar to those of already marketed products. We have a goal of reviewing 90 percent of these applications within 10 months.

Priority new drugs. We took 27 actions on priority new drug applications, of which 10 were approvals. These drugs represent significant improvements compared with marketed products. We have a goal of reviewing 90 percent of these applications within six months.

New molecular entities. Twenty-four of the new drugs we approved were new molecular entities, and seven received priority reviews. NMEs contain an active substance that has never before been approved for marketing in any form in the United States.



Priority new drugs

- **10 approvals**
- **Median review time: 6.0 months**
- **Median approval time: 6.0 months**
- **27 actions**
- **6 filings**

Priority new drugs
(N=NME)

Bimatoprost (Lumigan) (N)

Budesonide (Entocort EC)

Caspofungin acetate (Cancidas) (N)

Fondaparinux sodium (Arixtra) (N)

Imatinib mesylate (Gleevec) (N)

Mesalamine (Canasa)

Tenofovir disoproxil fumarate (Viread) (N)

Travoprost (Travatan) (N)

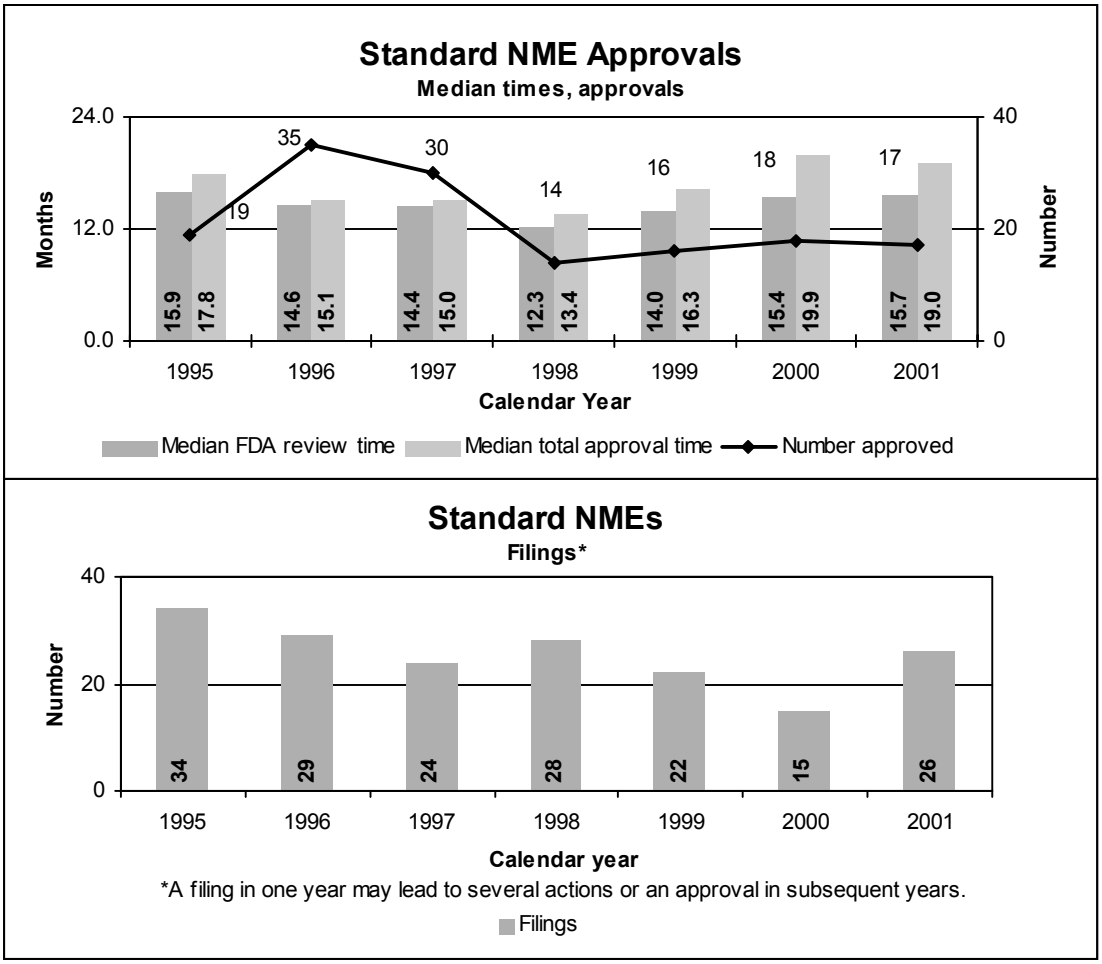
Valganciclovir hydrochloride (Valcyte)

Zoledronic acid (Zometa) (N)

Orphan drugs. Three of the approvals were for "orphan" uses in patient populations of 200,000 or fewer. Sponsors of such products receive inducements that include seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance by FDA and grants of up to $200,000 per year.

Review and approval times. Review time represents the time that we spend examining the application. Approval time represents our review time plus industry's response time to our requests for additional information. Our charts show these times as "medians." The value for the median time is the number that falls in the middle of the group after the numbers are ranked in order. It provides a truer picture of our performance than average time, which can be unduly influenced by a few very long or short times.

Actions and filings. An application is "filed" when we determine it is complete and accept it for review. We make a filing decision within 60 days of receiving an application. Approval is one of the actions that we can take once an application is filed. Other actions include seeking more information from the sponsor. There is no direct connection between applications filed in one year and actions in the same year. Filings provide an idea of what the workload in subsequent years will be.



Standard NME statistics

- **17 approvals**
- **Median review time: 15.7 months**
- **Median approval time: 19.0 months**
- **26 filings**

New molecular entities

Almotriptan malate (Axert)

Bimatoprost (Lumigan)

Bosentan (Tracleer)

Caspofungin acetate (Cancidas)

Cefditoren pivoxil (Spectracef)

Desloratadine (Clarinex)

Drospirenone/ethinyl estradiol (Yasmin)

Dutasteride (Dutasteride)

Ertapenem sodium (Invanz)

Etonogestrel/ethinyl estradiol (NuvaRing)

Fondaparinux sodium (Arixtra)

Formoterol fumarate (Foradil Aerolizer)

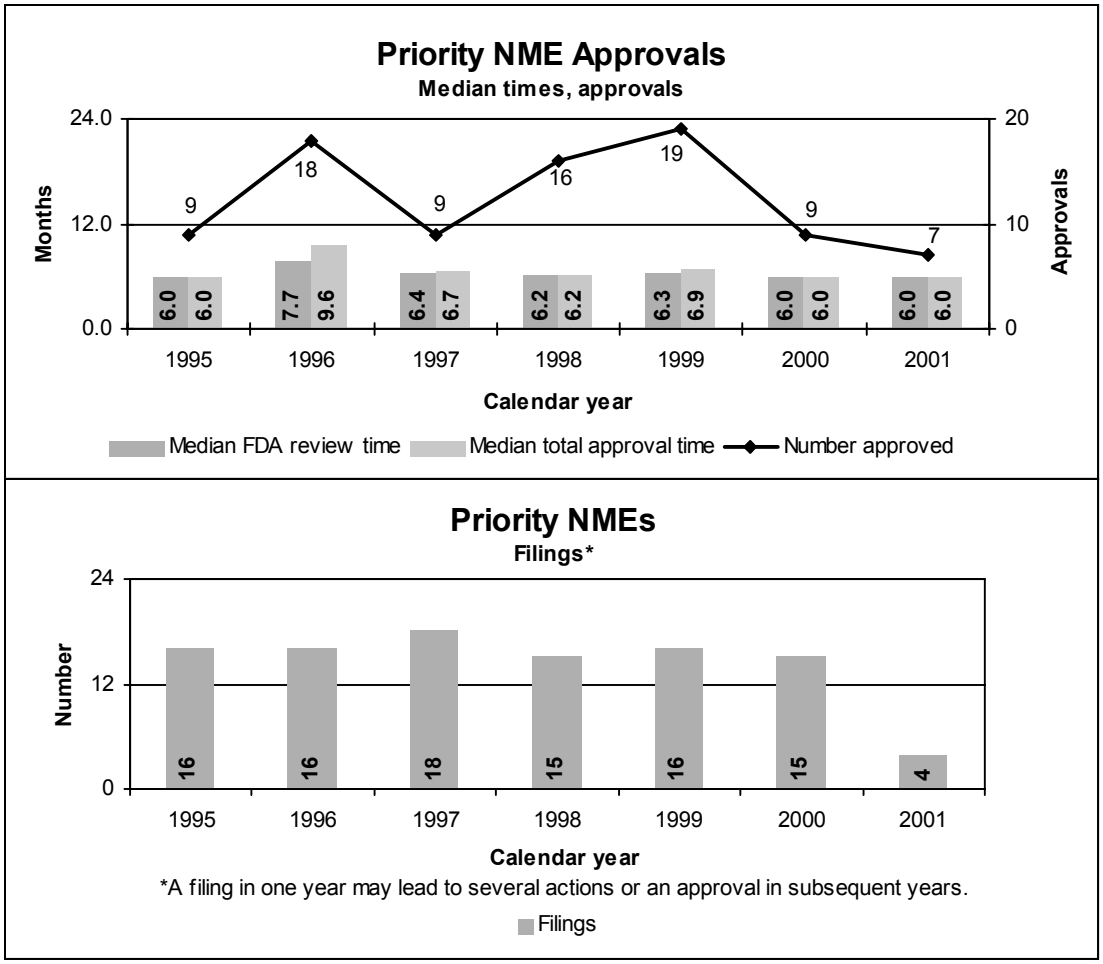
Notable 2001 new drug approvals

Last year's approvals benefited people with cancer, HIV infection, heart disease and other disorders.

People with cancer

One of our most important approvals last year was for *imatinib mesylate (Gleevec),* a new oral treatment for patients with chronic myeloid leukemia, a rare life-threatening form of cancer. We reviewed the application for the drug in two and one-half months and approved it under a special procedure that permits the marketing of important therapies on the basis of their effect on surrogate markers. The sponsor is committed to carry out additional studies demonstrating the drug's long-term safety and effectiveness. The drug was developed for use in a U.S. patient population of fewer than 200,000 and was, therefore, designated an orphan drug.

Zoledronic acid (Zometa) is an intravenous bisphonsphonate for the treatment of hypercalcemia of malignancy, the most common life-threatening metabolic complication associated with cancer. This complication, which is characterized by elevated serum calcium levels,



Priority NME statistics

- **7 approvals**
- **Median review time: 6.0 months**
- **Median approval time: 6.0 months**
- **4 filings**

New molecular entities (continued)

Frovatriptan succinate (Frova)

Galantamine hydrobromide (Reminyl)

Imatinib mesylate (Gleevec)

Nesiritide (Natrecor)

Norelgestromin/ethinyl estradiol (Ortho Evra)

Perflutren lipid microsphere (Definity)

Pimecrolimus (Elidel)

Tenofovir disoproxil fumarate (Viread)

Travoprost (Travatan)

Valdecoxib (Bextra)

Ziprasidone hydrochloride (Geodon)

Zoledronic acid (Zometa)

affects more than 10 percent of all cancer patients and generally occurs late in the course of the disease.

People with heart and circulatory disease

One new approval last year for cardiac patients is *nesiritide (Natrecor)* for the treatment of acute decompensated congestive heart failure. The drug, which was developed with the use of recombinant DNA technology, is a synthetic version of a human hormone that dilates veins and arteries.

Perflutren lipid microsphere (Definity) is an ultrasound contrast agent for use with suboptimal echocardiograms. It increases the power of heart ultrasounds and may provide earlier and more definitive diagnoses for millions of difficult-to-image patients at risk for heart disease. The drug is the first and only ultrasound contrast agent in the United States that is non-blood derived, eliminating the risks and concerns associated with the use of blood-based products.

Notable 2001 new drug approvals (continued)

Fondaparinux sodium (Arixtra) is for the prophylaxis of deep-vein thrombosis, which may lead to pulmonary embolism after orthopedic surgery for hip fracture, hip replacement and knee replacement. The drug is a synthetic compound and the first in a new class of antithrombotic agents that selectively inhibit Factor Xa.

Bosentan (Tracleer) is to improve exercise ability and decrease the rate of clinical worsening in patients with pulmonary arterial hypertension with significant limitation of physical activity. The drug is the first to be approved in a new class of drugs called endothelin receptor antagonists. The disease is a chronic, life-threatening disorder that can severely compromise the function of the lungs and heart.

People with HIV and AIDS

The first in a new class of drugs to combat HIV was approved, a once-daily medication that blocks an enzyme involved in the replication of the disease. *Tenofovir disoproxil fumarate (Viread)* is for the treatment of HIV infection when taken in combination with other antiretroviral agents. The drug is the first nucleotide analogue reverse transcriptase inhibitor approved for the treatment of HIV. The drug works by blocking reverse transcriptase, an enzyme involved in the replication of HIV. As a nucleotide, the drug remains in cells longer than many other antiretroviral drugs, allowing for once-daily dosing.

Valganciclovir hydrochloride (Valcyte) treats the eye infection cytomegalovirus retinitis in patients with AIDS.

People with arthritis

Valdecoxib (Bextra), a COX-2 specific inhibitor, is for treating the signs and symptoms of osteoarthritis, adult rheumatoid arthritis and the pain associated with menstrual cramping.

People with glaucoma

We approved two ophthalmic solutions for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Bimatoprost (Lumigan) and *travoprost (Travatan)* treat patients who are intolerant of, insufficiently responsive or inadequately controlled using other intraocular pressure-lowering medications. Glaucoma is a leading cause of preventable blindness.

People with mental and neurological disorders

Ziprasidone hydrochloride (Geodon) is for the treatment of schizophrenia, a life-long illness that strikes men and women in their late adolescence or early 20s, often with multiple relapses and impaired daily functioning.

Galantamine hydrobromide (Reminyl) is for the treatment of mild to moderate Alzheimer's disease.

Men

***Dutasteride (Dutasteride)* treats benign prostatic hyperplasia, a non-cancerous enlargement of the prostate gland, which can lead to the manifestation of lower urinary tract symptoms. The pathological changes of this disorder are found in about 50 percent of men in their 50s and up to 90 percent of men in their 90s.**

Women

We approved three contraceptives, including two that deliver continuous doses of the hormones progestin and estrogen in new ways to prevent pregnancy:

□ ***Etonogestrel/ethinyl estradiol (NuvaRing),*** **the first monthly vaginal ring for birth control, delivers the hormones through a flexible, transparent polymer ring inserted in the vagina.**

□ ***Norelgestromin/ ethinyl estradiol (Ortho Evra),*** **the first skin patch approved for birth control, releases the hormones through the skin into the blood stream and has to be changed each week.**

Both the ring and the patch have to be removed one week each month when the woman menstruates.

We also approved a new low-dose oral contraceptive, *drospirenone/ethinyl estradiol (Yasmin).*

Notable 2001 new drug approvals (continued)

We approved two drugs for the acute treatment of migraine with or without aura in adults: *almotriptan malate (Axert)* and *frovatriptan succinate (Frova).*

Infectious diseases

Caspofungin acetate (Cancidas) is for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies. The drug is the first in a new class of antifungals and works by attacking the fungal cell wall. Aspergillosis is a life-threatening fungal infection in high-risk patients, especially cancer patients, organ and bone-marrow transplant recipients, and patients with HIV/AIDS.

Cefditoren pivoxil (Spectracef) is a cephalosporin antibiotic for the treatment of acute exacerbations of chronic bronchitis, pharyngitis/ tonsillitis and uncomplicated skin and skin structure infections in adults and children 12 years and older.

Ertapenem sodium (Invanz) is a long-acting injectable antibiotic for treatment of adults with moderate to severe bacterial infections, including complicated intra-abdominal infections, complicated skin and skin structure infections, community-acquired pneumonia, complicated urinary tract infections and acute pelvic infections.

People with respiratory diseases and allergies

Formoterol fumarate (Foradil) is a fast-acting, long-lasting bronchodilator for the maintenance treatment of asthma and the prevention of bronchospasm in reversible obstructive airways disease. The drug provides both long-lasting symptom control and rapid bronchodilation from a single product.

Desloratadine (Clarinex) treats nasal and non-nasal symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older. The drug is a once-daily, nonsedating antihistamine.

People with skin disease

Pimecrolimus (Elidel) is the first non-steroid cream for mild to moderate atopic dermatitis in patients 2 years and older. Commonly known as eczema, atopic dermatitis is an itchy skin condition that primarily affects children and may last until the late teen-age years or even for life.

People with gastrointestinal disorders

Mesalamine (Canasa) is a suppository for the treatment of active ulcerative proctitis, an inflammation of the rectum.

Budesonide (Entocort EC) treats mild to moderate active Crohn's disease, an inflammatory disease, involving the ileum and/or ascending colon.

New drug statistics on Internet

Other statistics are available on our Web site at http://www.fda.gov/cder/rdmt/default.htm.

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. When studying approved drugs in children (page 15), sponsors often learn new information about the drug's safety and the doses that should be used. An efficacy supplement changes the labeling information to reflect the new discoveries, even if there is not a new or expanded use.

Last year we took action on 213 applications for new or expanded uses of already approved drugs. We approved 91, including six that were given priority reviews of six months or less. Three of the approvals were for orphan uses in patient populations of 200,000 or fewer.

Notable 2001 new or expanded use approvals

We approved *capecitabine (Xeloda)* when used with docetaxel for the treatment of locally advanced or metastatic breast cancer after failure to respond to anthracycline-containing cancer therapy. The drug was also approved for first-line treatment of metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred.

Letrozole (Femara) is for first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

Verteporfin (Visudyne) is for the treatment of patients with eye disease affecting the central, clearest portion of vision, specifically for those with predominantly classic subfoveal choroidal neovascularization due to macular degeneration, presumed ocular histoplasmosis or pathologic myopia.

Pantoprazole sodium (Protonix I.V.) is an injection for the treatment of the pathological hypersecretion of stomach acid associated with Zollinger-Ellison Syndrome.

Orphan new or expanded uses

***Somatropin [rDNA] (Genotropin)* is for long-term treatment of growth failure in children born small for their gestational age and who fail to manifest catch-up growth by the time they are 2 years old.**

***Topiramate (Topamax)* treats Lennox-Gastaut syndrome, a severe seizure disorder that occurs in children (two approvals).**

Priority new or expanded uses

Capecitabine

Letrozole

Pantoprazole sodium

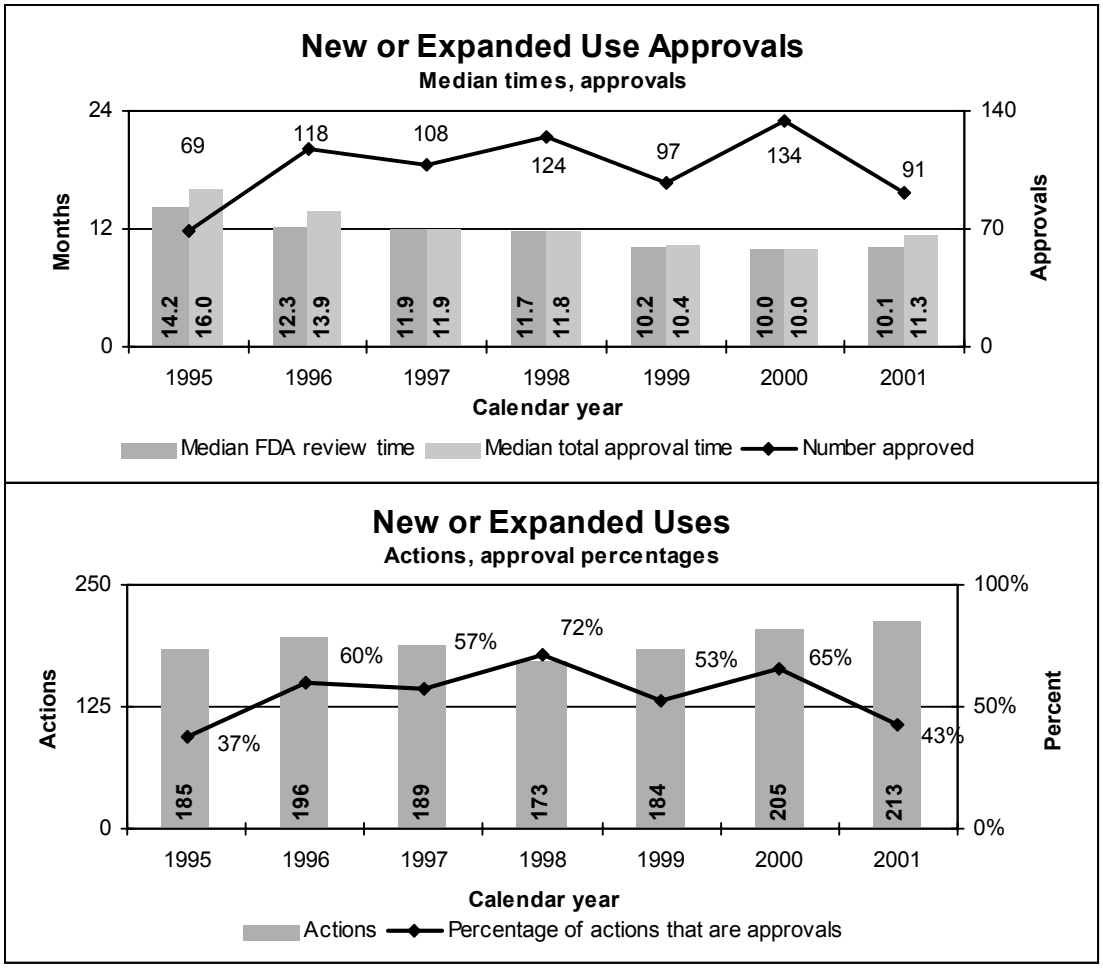
Sodium ferric gluconate

Somatropin [rDNA origin] for injection

Verteporfin

New or expanded uses (efficacy supplements)

- **91 approvals**
- **Median review time: 10.1 months**
- **Median approval time: 11.3 months**
- **6 priority reviews**
- **3 orphan uses**
- **213 actions**



Pediatric Exclusivity

The 2002 Best Pharmaceuticals for Children Act renewed our authority to grant six months of marketing exclusivity to manufacturers who conduct and submit pediatric studies in response to our written requests. It also allows us to collect user fees for reviewing these pediatric supplements and requires they be reviewed as priority supplements. The law also authorizes the federal government to contract for pediatric studies for drugs that lack patent protection or other marketing exclusivity.

Pediatric exclusivity has helped us uncover important new dosing and safety information that will help pediatricians and other prescribers use drugs to treat children more confidently. As of March 2002, we had received 300 proposed pediatric study requests from manufacturers and had issued 241 written requests. These studies could potentially involve more than 32,000 children. Pediatric studies have already been conducted on more than 65 drugs. Reports from these studies have been submitted, exclusivity granted to 56 drugs, and new pediatric labeling in 31 as of March 2002.

Internet resource

Our pediatric medicine page is at http://www.fda.gov/cder/pediatric/index.htm.

Pediatric exclusivity cumulative statistics

- **300 proposed pediatric study requests received**
- **241 written requests issued**
- **31 labeling changes**

Pediatric conditions with approved labeling

Drugs with newly developed approved pediatric use information in their labeling are used to treat conditions such as:

- **Abnormal heart rhythms**
- **Allergies**
- **Anesthesia and sedation**
- **Diabetes mellitus**
- **Heartburn**
- **High blood pressure**
- **High cholesterol**
- **High eye pressure**
- **HIV infection**
- **Inflammation**
- **Juvenile rheumatoid arthritis**
- **Low levels of calcium associated with severe kidney disease**
- **Obsessive compulsive disorder**
- **Pain**
- **Seizures**
- **Skin disorders**

Approved information to treat children's illnesses

Of the 31 drugs with newly approved pediatric information in their labels, nine had significant changes for dosing, safety or use, and one drug available in several different products was not recommended for pediatric use. The nine with significant changes were:

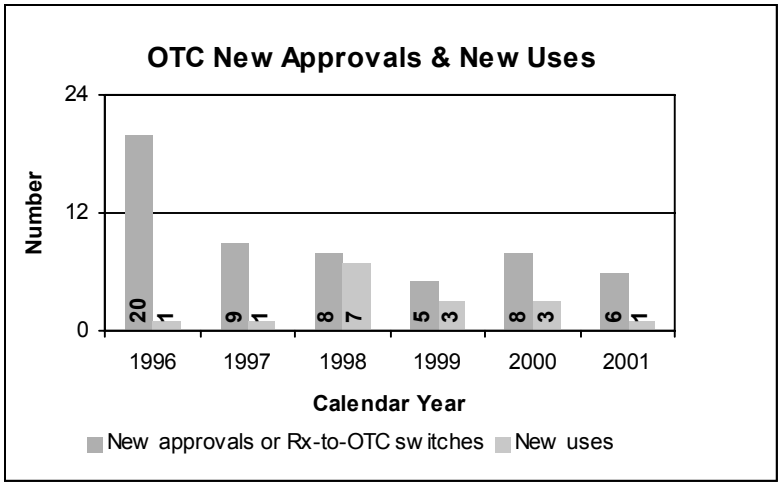
- *Gabapentin (Neurontin),* a seizure drug, requires higher doses in children younger than 5 years in order to control seizures, and new adverse events such as hostility and aggression were identified in children younger than 12.
- *Propofol (Diprivan),* an anesthesia drug, showed higher death rates when used for sedation in pediatric intensive care units compared with standard sedative agents (9 percent vs. 4 percent); serious slowing of the heart rate can occur when the drug is coadministered with fentanyl, a pain drug.
- *Sevoflurane (Ultane),* used for anesthesia, had rare cases of seizures reported in children without a previous seizure history.
- *Ribavirin/Intron A (Rebetron),* a treatment for chronic hepatitis C, showed increased suicidal ideation or attempts among pediatric patients compared with adults (2.4 percent vs. 1 percent) and decreased the rate of linear growth and weight gain during therapy, with general reversal in the post-treatment period.
- *Pimecrolimus (Elidel)* is for short-term and intermittent long-term therapy in mild to moderate eczema in non-immunocompromised patients older than 2 years, but it is **not recommended** in patients younger than 2 for safety concerns including infections, fever and diarrhea.
- *Midazolam (Versed),* used for sedation and to reduce anxiety, showed higher risk of serious life-threatening situations in children with congenital heart disease and pulmonary hypertension. Studies identified the need to begin therapy at the lower end of the dosing range in these patients to prevent respiratory compromise.
- *Etodolac (Lodine),* when used in the management of the signs and symptoms of juvenile rheumatoid arthritis for children 6 to 16 years old, requires higher weight-adjusted doses in younger children that is about twice the lower dose recommended in adults for effective treatment.
- *Fluvoxamine (Luvox),* when used to treat obsessive compulsive disorder, requires higher doses in adolescents than previously recommended; however, girls ages 8 to 11 may require lower doses.
- Studies of *buspirone (Buspar)* failed to establish safety and effectiveness in patients 6 to 17 years old for treatment of general anxiety disorder at doses recommended for adults.

Approved information recommends against pediatric use

Newly approved labeling shows that several products with a specific topical steroid are not recommended for pediatric use. They are:

***Betamethasone (Diprolene AF, Diprosone Cream, Ointment, Lotion),* used to treat corticosteroid-responsive skin disorders, is not recommended in patients younger than 12 because it suppressed adrenal axis activity and caused local adverse reactions, including signs of skin atrophy.**

***Betamethasone/ clotrimazole (Lotrisone),* a treatment for ringworm infections, is not recommended in patients younger than 17 because it suppressed adrenal axis activity.**



Over-the-counter drug statistics

□ 6 new drugs or Rx-to-OTC switch approvals

□ 1 new or expanded use approval for an OTC drug

Over-the-Counter Drug Review

In 2000, we approved six new drugs and one new use for over-the-counter marketing.

New OTC medicines and new uses

Miconazole nitrate (Monistat 3) is to treat vaginal yeast infections and external itching associated with a vaginal yeast infection. This is not the first OTC approval for this compound.

Miconazole nitrate (Monistat 1). This is a one-day treatment regimen vs. a three-day treatment regimen under Monistat 3 (above) and a seven-day treatment regimen under Monistat 7.

The combination *clemastine fumarate, pseudoephedrine hydrochloride and acetaminophen (Tavist A/S/H)* treats symptoms of hay fever and other seasonal allergies. This is the first approval for this combination but not the first time for any of these compounds on the OTC market.

Chlorhexidine gluconate and ethyl alcohol (Avagard-CHG) is for use as a surgical hand scrub or hand wash for healthcare personnel. This is not the only chlorhexidine product available OTC.

Aspirin, 500 mg, (Bayer Extra Strength Aspirin for Migraine Pain) is for the treatment of migraine headaches. This represents a new OTC use for aspirin.

A cream with *1 percent butenafine hydrochloride (Lotrimin Ultra)* is an Rx-to-OTC switch for the use of this drug product to treat jock itch, athlete's foot and ringworm.

A nasal spray containing *cromolyn sodium (Nasalcrom*) is now approved for OTC use down to 2 years of age.

Public meeting airs OTC antihistamine issues

A citizen's petition submitted in 1997 asked us to consider switching the antihistamines loratadine, fexofenadine and cetirizine to OTC marketing status.

Last year, our advisory panel of outside experts concluded that these drugs would be a reasonably safe alternative for consumers to treat nasal symptoms of seasonal and nonseasonal allergies.

We and the manufacturers are considering their recommendation.

Improved labels for OTC medicines

American consumers are benefiting from easy-to-understand labels on drugs they buy without a prescription.

Titled "Drug Facts," the new labels become mandatory in May 2002.

These new labels 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.

Generic Drug Review

We received 320 submissions and approved 234 generic drug products in 2001, including 40 separate molecules in 55 products that represent the first time a generic drug was available for the brand-name product. The median approval time for generic drugs was 18.1 months.

We are making changes to decrease the overall time to approval of applications. The median statistic for total approval time has hovered at about 18 to 19 months for five years. Planned changes include several efficiencies in the review process and hiring of additional chemistry reviewers.

Notable 2001 generic drug approvals

Examples of first-time approvals for the brand-name equivalent are:

- *Fluoxetine* (Prozac) used to treat depression.
- *Buspirone* (BuSpar) used to treat anxiety disorders.
- *Famotidine* (Pepcid) used to treat ulcers.
- *Lovastatin* (Mevacor) used to control lipid profiles.
- *Omeprazole* (Prilosec) used to treat ulcers.

Our approval of generic versions of these drugs last year could save American consumers and the federal government hundreds of millions of dollars each year.

We also issued 73 tentative approvals and 13 approvables last year:

- *Tentative approvals.* 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 drug product. These and other legal issues continue to be a challenge to the generic drug review program. While tentative approvals represent a full workload for us, they are only displayed in the chart on the next page once they are converted to full approvals. For example, some of the 234 approvals in 2001 represent conversions of tentative approvals granted in 2001 or previous years.
- *Approvables.* Approvable applications are reviewed and ready for full approval except for a pending labeling issue, generally related to legal matters such as exclusivity. These also represent full workload but are only displayed once they are converted to full approval.

Generic drug Web site

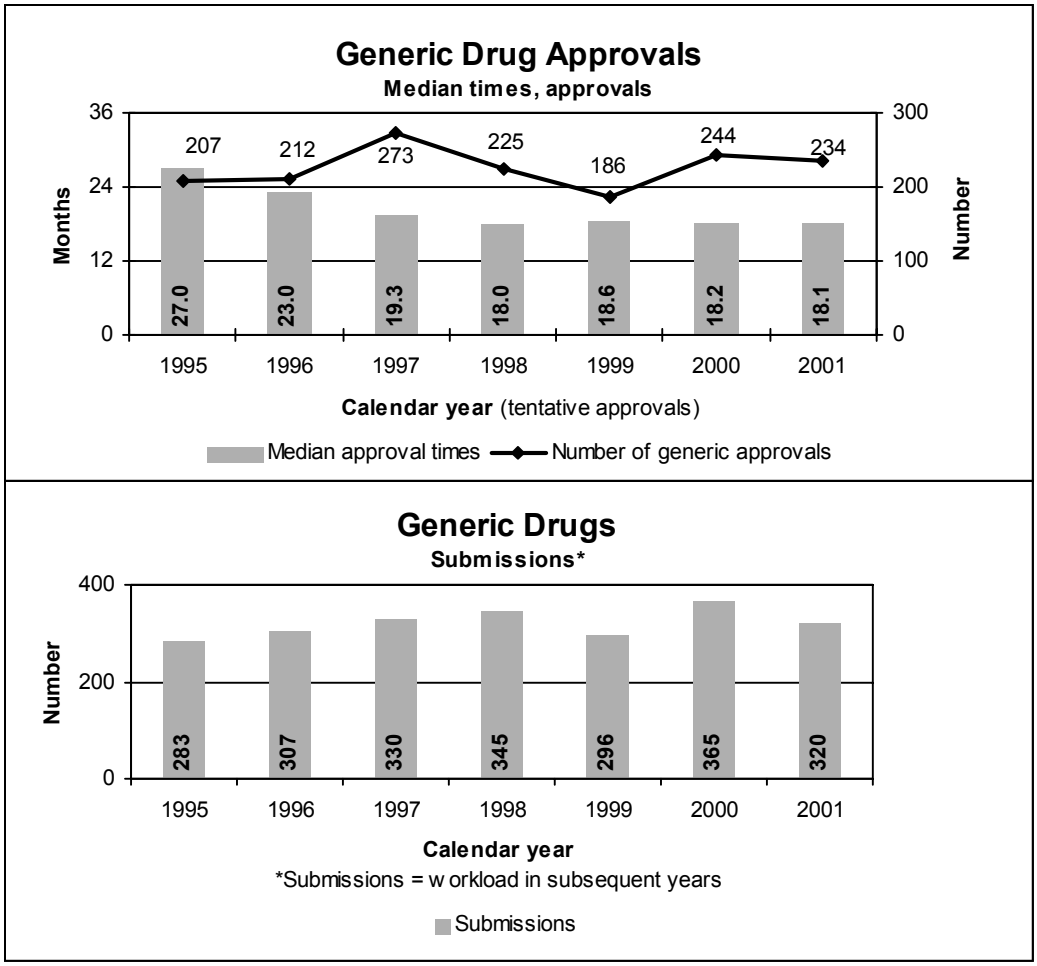
You can find more information about our generic drug program at http://internet-dev.fda.gov/cder/ogd/index.htm.

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.



Generic drug statistics

- **234 generic drug approvals**
- **Median approval time: 18.1 months**
- **320 submissions**
- **73 tentative approvals**
- **13 approvables**

Tentative approvals

- **1995: 15**
- **1996: 25**
- **1997: 40**
- **1998: 40**
- **1999: 56**
- **2000: 61**
- **2001: 73**

Building consumer confidence in generic drugs

To promote consumer confidence in the safety and effectiveness of generic drugs, we are developing a multimedia education program. The goal will be to educate health care practitioners and consumers about the rigorous review and approval process that generic products undergo before we approve them for sale in this country. We are creating partnerships and a network with other government agencies. The efforts will include:

- Focus groups to determine what information is needed.
- Print media public service announcements.
- Radio public service announcements.
- Presentations at organizational meetings for health-care professionals.

Electronic submissions

The electronic submissions initiative is a continuing priority. We developed and issued a draft guidance on a standardized format for application submission that will be compatible for both new drug and generic applications. This should promote industry participation in the program.

User fee review goals

Under PDUFA II, our review goals continued to shorten. By fiscal year 2002, the goals called for us to review and act on 90 percent of:

□ Priority new drug applications and efficacy supplements (those for products providing significant therapeutic gains) within six months.

□ Standard new drug applications and efficacy supplements within 10 months.

□ Manufacturing supplements not requiring prior approval within six months, and those requiring prior approval within four months.

□ Class 1 resubmissions of original applications (those involving minor changes) within two months, and Class 2 resubmissions of original applications (those involving changes not specifically identified in the user fee goals document) within 6 months.

User Fee Program

We met all of the demanding review goals of the Prescription Drug User Fee Act for applications submitted in fiscal year 2000, the latest year for which there are meaningful review statistics. We are on track for meeting them in fiscal year 2001.

The law, first enacted in 1992, was renewed for an additional five years in 1997. 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. As a result, we are able to respond more rapidly to new drug applications without compromising review quality. That means more quality drug products are reaching American practitioners and consumers more quickly.

We agreed in 1992 to specific performance goals for the prompt review of four categories of submissions: original new drug applications, resubmissions of original NDAs, efficacy supplements to already approved marketing applications and manufacturing supplements to already approved new drug marketing applications.

With the 1997 reauthorization, known as PDUFA II, we committed to additional goals intended to improve our responsiveness to and communication with industry sponsors during the early years of drug development. These goals specify timeframes for activities such as scheduling meetings and responding to various sponsor requests. While the intent of the 1992 law was to speed up the review process, the intent of PDUFA II is to speed up the entire drug development process.

We have encountered challenges in trying to meet the PDUFA II goals. The fees we collected have been significantly less than expected due to a reduced number of new drug applications and an increased proportion of submissions whose fees were exempted or waived. At the same time, the number of goal-driven tasks for which we collect no fees increased substantially under PDUFA II. So far we have been able to meet most of our performance goals.

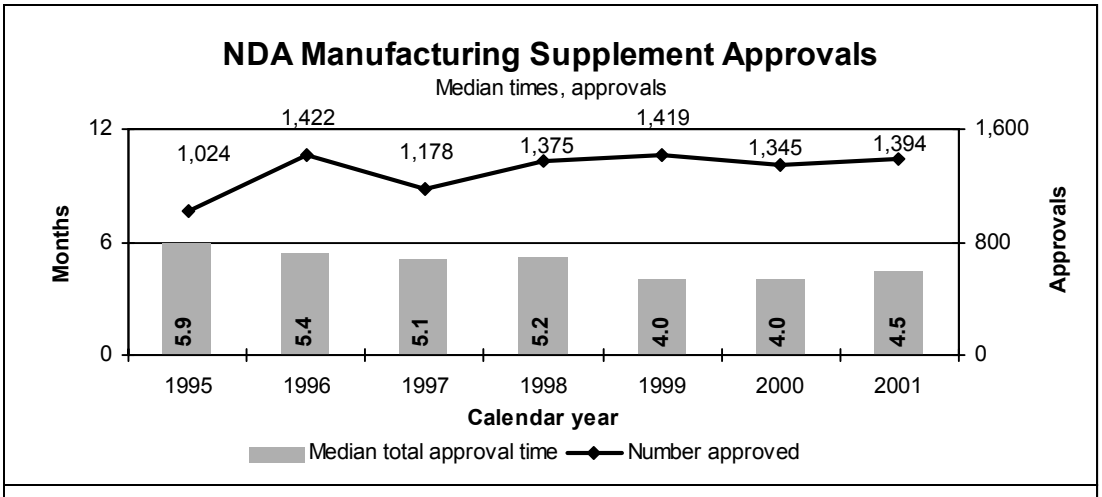
Our efforts to meet the PDUFA II goals may have had an unintended impact on approval times of standard new drug applications. These approval times have begun to increase because more applications require multiple review cycles to reach approval. This may be due to the fact that reviewers have been pressed to meet the additional PDUFA II goals for drug development, such as meeting management, special protocol assessments and responses to clinical holds. Reviewers have had less time for resolving last-minute problems with these standard applications before the action goal date. Such applications must undergo an additional review cycle with its attendant timeframes and goals. Statistics on this trend are preliminary, and we are watching it closely.

User fee report

Our full report to Congress on our user fee performance is at http://www.fda.gov/oc/pdufa/report2001/pdufareport.html.

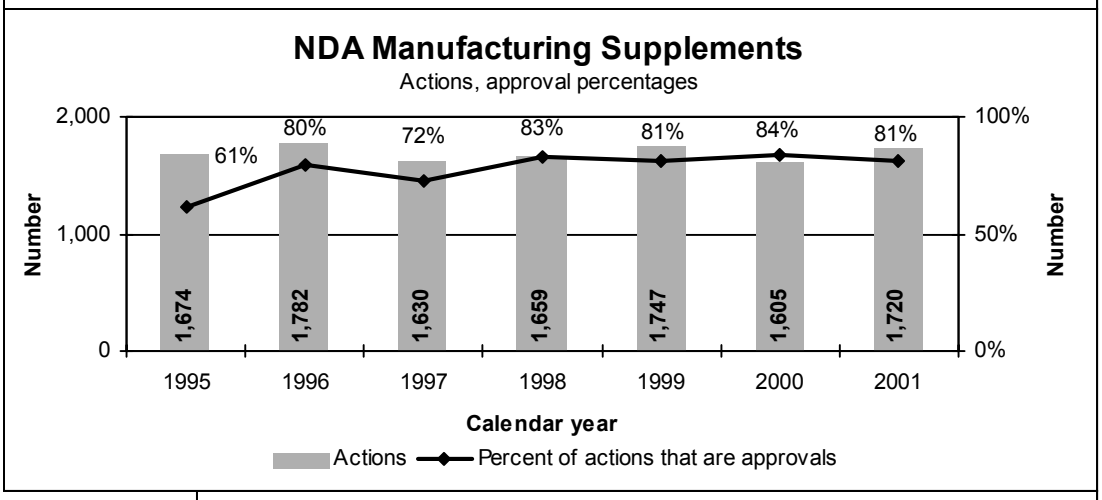
New drug manufacturing supplements

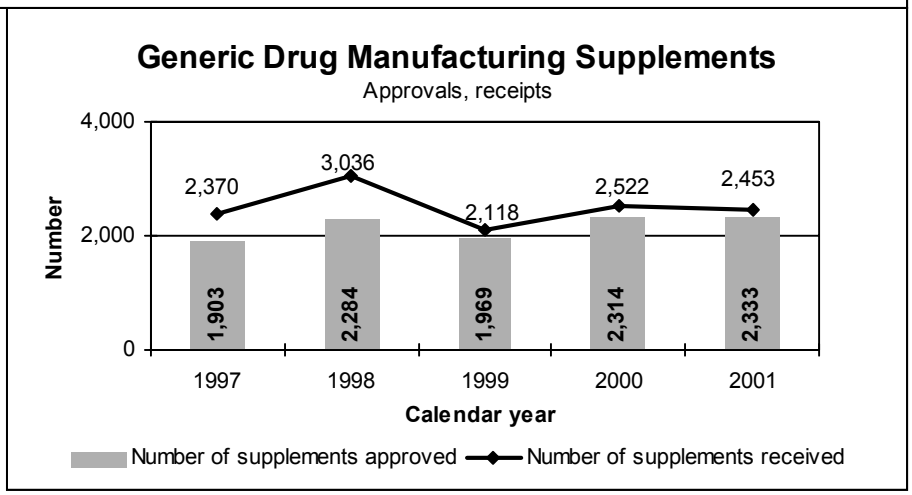
- **1,394 approvals**
- **Median FDA review time: 4.4 months**
- **Median total approval time: 4.5 months**



Generic drug manufacturing supplements

- **2,333 approvals**
- **2,453 receipts**





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.

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.

Electronic Submissions

Currently, the entire archival copy of the new drug application, postmarketing safety reports and advertising and promotional material can be submitted in electronic format without paper. We find submissions provided electronically as described in our guidance documents both easier to process and more efficient to review.

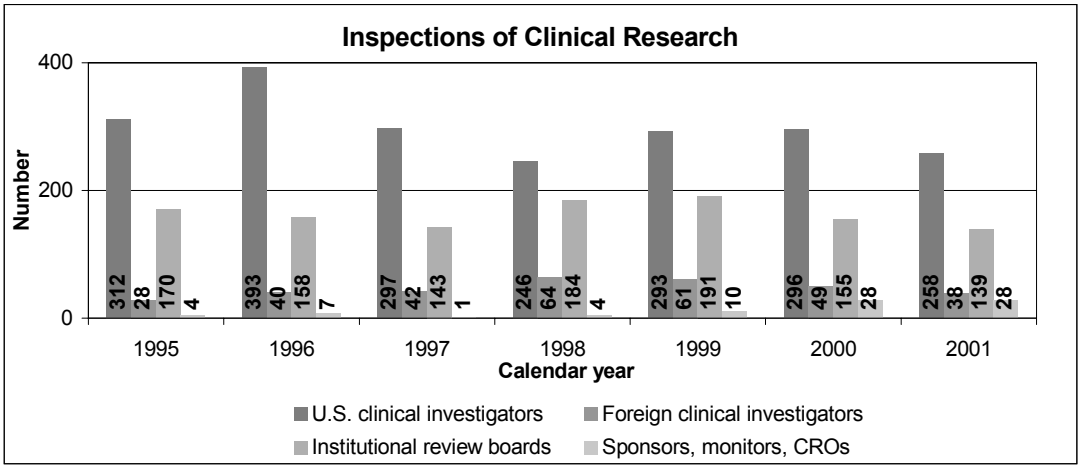
While the number of electronic submissions continues to increase each year, only 15 percent of supplements and amendments are submitted in electronic format. Over the next year, we look to industry to increase the number of electronic-only submissions.

Over the past year, we have worked on and begun evaluating electronic submission projects that will:

- Provide a Web-based tool for companies to register establishments and list products.
- Make use of standardized study data submissions to improve the review process.
- Improve the way we process and review labeling changes.

We also are working on the ability to accept the following documents in electronic format:

- Abbreviated new drug applications for generic drugs.
- Annual reports for marketing applications.
- Investigational new drug applications for premarket clinical studies.
- Individual case safety reports for marketed drugs (page 27).



Inspections of clinical research in 2001

We conducted a total of 463 inspections of clinical research:

- **258 U.S. clinical investigators**
- **38 foreign clinical investigators**
- **139 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.

Top 5 deficiency categories for clinical investigator inspections

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

International inspections of clinical research

We have conducted 457 inspections of clinical research in 47 countries from 1980 to 2001.

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 38)** **and the Declaration of Helsinki.**

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, internal training program in science, policy and job-related skills for reviewers 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.

□ Last year, we brought in 44 visiting professors to talk directly to individual review divisions about critical, new drug-related research and techniques.

□ We collaborate with five local universities to present special courses. Last year we examined the effects of drug therapy on the heart.

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.

Actual use data now available

We awarded three contracts that give us access to commercial databases that contain non-patient-identifiable information on the actual use of marketed prescription drugs in adults and children.

This information will significantly augment our ability to determine the public health significance of reports we receive through AERs and other sources.

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.

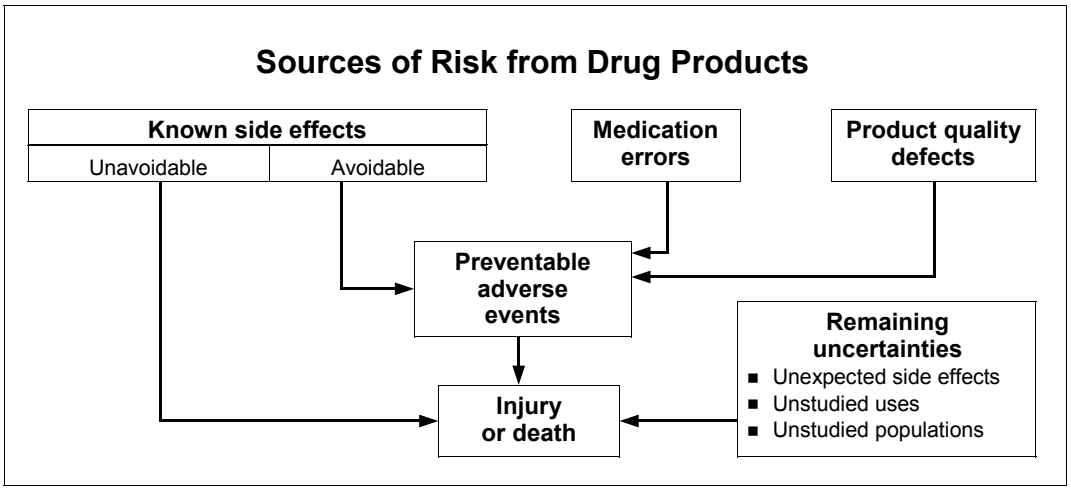
Highlights of drug safety and quality activities include:

- Processing and evaluating 286,755 reports of adverse drug events, including 19,324 submitted directly from individuals.
- Accepting 15 percent of expedited adverse event reports electronically.
- Issuing "cyber letters" and warnings to 11 Internet sites selling unapproved foreign ciprofloxacin in the wake of the anthrax-contaminated mail.
- Issuing 880 letters to help ensure that the promotion of drug products presents a fair balance of risks and benefits and isn't false or misleading.
- Mandating that three drug products be dispensed with specific consumer information to help make sure that they are used safely and effectively.
- Evaluating results of 822 preapproval inspections of new drugs, 1,268 preapproval inspections of generic drugs and 1,497 postapproval inspections.
- Issuing 4,542 export certificates for U.S. drug products.
- Launching a major initiative to assist industry in improving the capability and efficiency of drug manufacturing while maintaining or improving quality for consumers.
- Evaluating the first scientific recommendations from the Product Quality Research Institute.

New expert panel

We will be able to consult with a new Drug Safety and Risk Management Subcommittee to the Advisory Committee for Pharmaceutical Science.

The new panel is composed of nationally recognized experts in the areas of risk perception, risk management, pharmacoepidemiology, clinical pharmacology, clinical research and medication errors who will advise us on general and product-specific safety issues.



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. For example, 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.

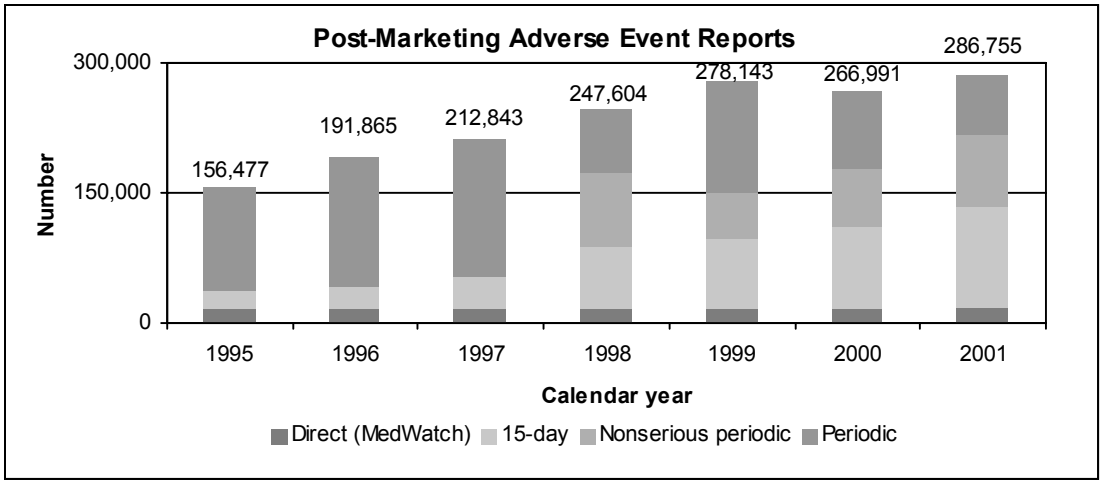
Medication errors

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.

Our comprehensive Web site on medication errors is 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.



Adverse event reporting

In 2001, we received 286,755 reports of suspected drug-related adverse events:

- **19,324 MedWatch reports directly from individuals.**
- **115,012 manufacturer 15-day (expedited) reports.**
- **152,419 manufacturer periodic reports (70,306 serious and 82,113 nonserious)**

AERS on Internet

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

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 drug safety tool is the Adverse Event Reporting System. This computerized system combines the voluntary adverse drug reaction reports from MedWatch and the required reports from manufacturers. These reports often form the basis of "signals" that there may be a potential for serious, unrecognized, drug-associated events. When a signal is detected, further testing of the hypothesis is undertaken using various epidemiological and analytic databases, studies and other instruments and resources. AERS offers paper and electronic submission options, international compatibility and pharmacovigilance screening.

Electronic submissions

AERS was designed and implemented so that the majority of the reports would be entered electronically. We are in the process of migrating the reporting format from paper to electronic. In a pilot program, we are accepting electronic individual case safety reports from five major drug firms. In 2001, electronic submissions into AERS represented 15 percent of the total expedited reports we received. We estimate the cost of receiving a report is cut from $18 per report to $5 per report for those submitted electronically.

Report types

- ***Direct reports from MedWatch.*** **An individual, usually a health care practitioner, notifies us directly of a suspected serious adverse event.**
- ***15-day (expedited) reports.*** **Manufacturers report these serious and unexpected adverse events to us as soon as possible within 15 days of discovering the problem.**
- ***Manufacturer periodic reports.*** **These report all other adverse events, such as those less than serious or described in the labeling. These are submitted quarterly for the first three years of marketing and annually after that. Nonserious reports are displayed separately starting with 1998.**

Adverse event reporting enforcement

We enforce regulations on postmarketing adverse event reporting to ensure that reports are accurate, timely and complete. We develop regulatory strategies and initiate inspections to determine industry compliance with the regulations. We use a risk-based approach to identify firms for inspection. We focus on firms with:

- Reporting deficiencies.
- Drug products that pose a significant health risk.
- Other priority issues that impact the public health.

We evaluate the inspection findings and determine if enforcement action is appropriate.

Risk management case study

We have learned in recent years that our traditional methods for informing prescribers of changes in a drug's risks and benefits have little effect once prescribing patterns have been well established.

One example is the new risk management program for isotretinoin.

The drug is very effective in treating the most serious form of acne, but its use carries significant potential risks, including birth defects and even fetal death.

In recent years, as more women receive prescriptions for isotretinoin, the risk that pregnant women may be inappropriately using the drug has increased.

On advice from our expert panel and in consultation with us, the manufacturer made significant changes to isotretinoin's risk management program for pregnancy prevention.

MedWatch drug safety Internet resources

The latest medical product safety information can be found 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.

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.

Last year, subscribers to our e-mail notification service more than doubled to about 20,000.

We issued about 40 safety alerts for drugs. Notifications were posted on the Internet and e-mailed to individuals and our 190 MedWatch partner organizations.

Each month, our subscribers and partners received 25 to 45 safety-related labeling changes for 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 cosponsored a two-day conference and workshop to help foster consensus on principles and areas for research and further work. Conference materials are available at http://www.fda.gov/cder/livertox/default.htm.

We have been working with manufacturers to address how to carry out studies in patients with impaired liver function to provide information on dose adjustment in such patients.

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 shortage program aids counterterrorism effort

Utilizing data obtained from manufacturers and distributors, our drug shortage program provides supply and production information in response to federal government requests in relation to counterterrorism efforts.

Cyber Letters for Foreign Ciprofloxacin

In the wake of the public health crisis surrounding anthrax-contaminated mail, we issued "cyber letters" to 11 Web sites selling unapproved foreign ciprofloxacin (page 5). We issued warnings to Internet vendors abroad who were offering ciprofloxacin to American consumers. We informed consumers that they should be aware of these risks associated with obtaining a prescription drug over the Internet:

- The product could be contaminated and harmful.
- The product could be a counterfeit and not contain the drug's active ingredient.
- The product could contain the wrong dose of the drug.
- Without adequate screening by a health care professional, the product may not be safe and appropriate for the user.
- The consumer may not have access to a health care professional if a serious side effect occurs after taking the product.
- The consumer may receive no product at all after sending payment.

Buying medicines online

Many consumers find it saves time and money to buy their medicines online. We have information to help consumers determine whether a Web site is a licensed pharmacy in good standing. You can find out more about buying medicines online at http://www.fda.gov/oc/buyonline/default.htm.

Drug shortages on the Internet

We have 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.**
- **We have an e-mail address to provide the public a communication tool for drug shortage information at DrugShortages@cder.fda.gov.**

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 2001, we issued 178 advisory letters to companies regarding their promotional materials for launch campaigns.

We issued 313 other advisory letters to the industry regarding proposed promotional pieces, both professional and consumer directed. In addition, we issued 284 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

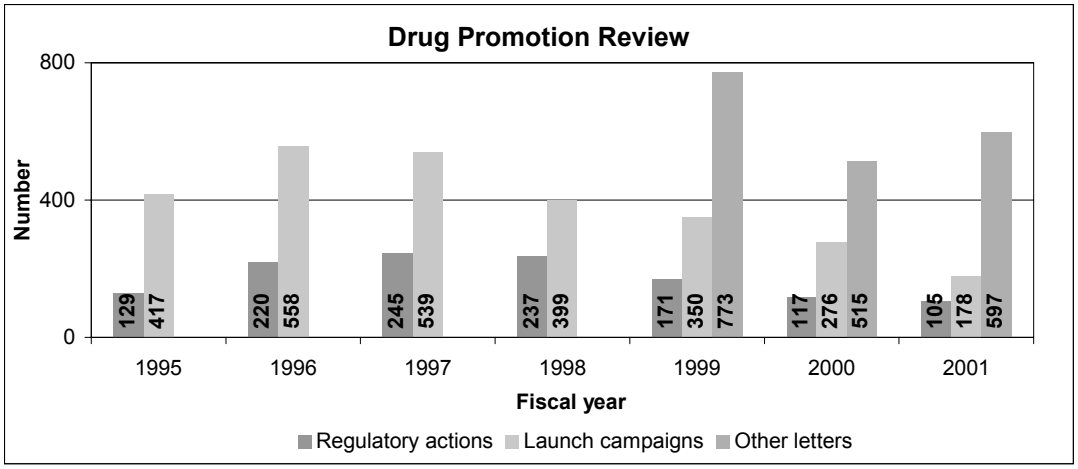
Regulatory actions

We issued 105 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 promotional exhibit hall displays (20 letters), oral representations (11 letters), Internet Web sites (10 letters), plus traditional materials such as journal advertisements and sales brochures.

Direct-to-consumer promotion

Included in our letters were 190 regarding direct-to-consumer promotion. This compares with 215 letters in 2000. Of last year's letters, 50 were for launch campaigns, 123 for non-launch advisories, and 16 were regulatory letters. Of the regulatory letters, seven were for advertisements broadcast on television or radio, five for print advertisements, three for a combination of broadcast and print advertisements, and one for a Web site.

We initiated two national telephone surveys. One is a follow-up to our 1999 survey of patients' attitudes and behaviors associated with direct-to-consumer advertisements. The other is a new survey of physicians' attitudes and behaviors associated with direct-to-consumer advertisements.



Drug promotion review statistics

We issued a total of 880 drug promotion letters last year.

□ 105 regulatory action letters

□ 178 launch campaigns

□ 597 advisory acknowledgement or closure letters

Patient information for prescription drugs

We continued our research activities in support of the private plan to provide patients with useful information about their prescription drugs. The target goal is for 75 percent of patients to receive useful information with new prescriptions. This past year we worked on evaluating the written patient medication information materials received.

Additionally, we carried out a telephone survey of U.S. consumers about where they get their information about prescription drugs.

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 three products.

Medication Guides issued in 2001:

□ Bosentan (Tracleer)

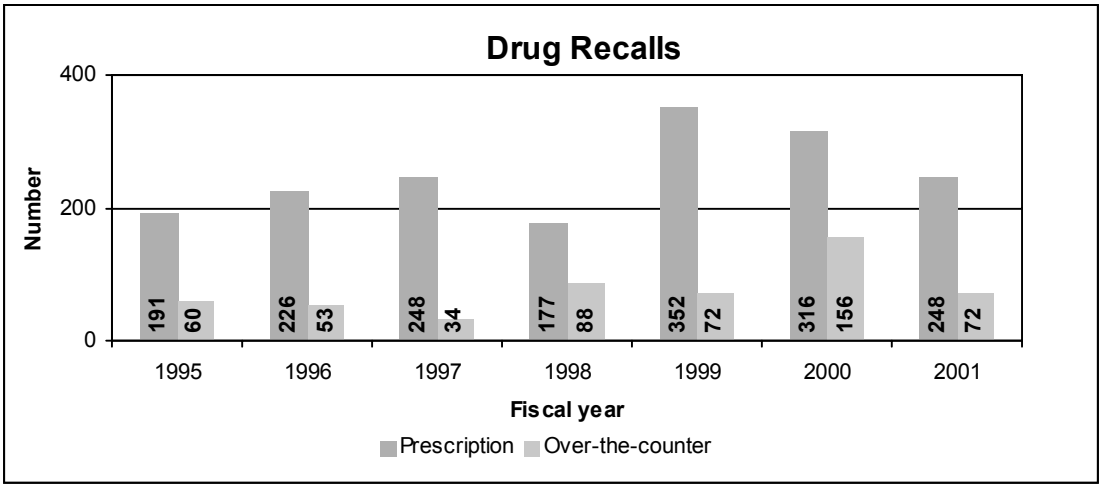
□ Ribavirin (Rebetol)

□ Ribavirin and interferon alfa-2b (Rebetron), a combination drug and biologic product

Proposed rule to revise prescription drug labeling

We received more than 100 comments on our December 2000 proposal to revise the content and format of prescription drug labeling. Companies, associations, academicians and individuals commented, and we will respond when we publish the final regulation.

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.



Drug Recalls and Withdrawals

In some cases, a drug product must be recalled due to a problem occurring in the manufacture or distribution of the product that may present a significant risk to public health. These problems usually, but not always, occur in one or a small number of batches of the drug. The most common reasons for drug recalls include those listed in the column at the right. In other cases, a drug is determined to be unsafe for continued marketing and must be withdrawn completely.

Recalls

Manufacturers or distributors usually implement voluntary recalls in order to carry out their responsibilities to protect the public health when they need to remove a marketed drug product that presents a risk of injury to consumers or to correct a defective drug product. A voluntary recall of a drug product is more efficient and effective in assuring timely consumer protection than an FDA-initiated court action or seizure of the product.

Safety-based withdrawals in 2001

In some cases, there is an intrinsic property of the drug that makes it necessary to withdraw the drug from the market for safety reasons. For example, these drugs were withdrawn from the U.S. market last year for safety reasons:

- *Cerivastatin (Baycol),* a cholesterol lowering drug, was voluntarily withdrawn because of reports of sometimes fatal rhabdomyolysis, a severe muscle adverse reaction.
- *Rapacuronium (Raplon),* an injectable anesthesia drug, was voluntarily withdrawn from the market after its manufacturer received reports indicating that the drug might have been associated with bronchospasm, a mild to severe inability to breathe normally that can lead to permanent injury or death.

How we coordinate drug recalls

We coordinate drug recall information, assist manufacturers or distributors in developing recall plans and prepare health hazard evaluations to determine the risk posed to the public by products being recalled.

We classify recall actions in accordance to the level of risk. We participate in determining recall strategies based upon the health hazard posed by the product and other factors including the extent of distribution of the product to be recalled.

We determine the need for public warnings and assist the recalling firm with public notification about the recall.

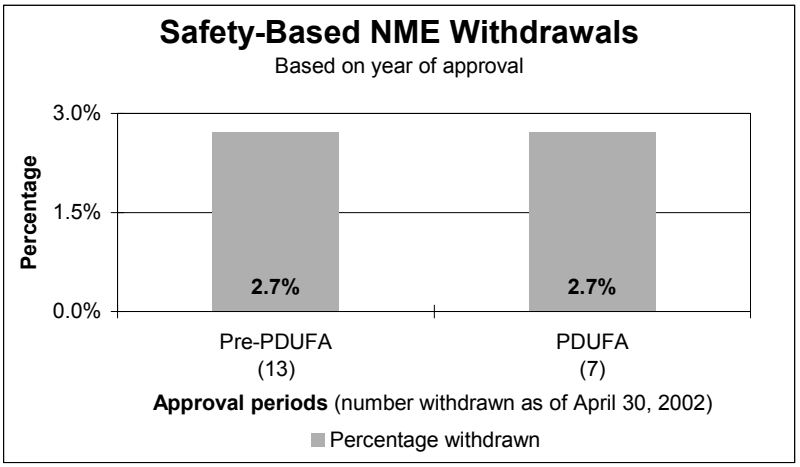
Top 10 reasons for drug recalls in fiscal year 2001:

- **Deviations from current good manufacturing practices**
- **Subpotency**
- **Stability data fail to support expiration date**
- **Failure of drug to dissolve properly**
- **Correctly labeled product in the wrong carton or package**
- **Strength of product incorrectly labeled**
- **Microbial contamination of nonsterile products**
- **Drug product marketed without an approved new or generic application**
- **Lack of assurance of sterility in production or testing of sterile drug products**
- **Discoloration**
- **Counterfeit dosage form**

Recent safety-based drug withdrawals

Drug name (year approved/ year withdrawn)

- **Phenylpropanolamine (—/2000)** (never approved by FDA)
- **Fenfluramine (1973/1997)**
- **Azaribine (1975/1976)**
- **Ticrynafen (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)**
- **Cisapride (1993/2000)**



Record of safety-based market withdrawals

When drug withdrawals are compared based on year of approval, the recent period when we applied user-fee review goals is similar to the previous period.

- *Pre-PDUFA period.* Between Jan. 1, 1971, and Dec. 31, 1993, we approved 477 new molecular entities, and 13 (2.7 percent) were eventually withdrawn. Nearly all the drugs we approved in this period were received before we implemented PDUFA review goals.
- *PDUFA period.* Between Jan. 1, 1994, and Dec. 31, 2001, we approved 258 NMEs, and 7 (2.7 percent) have been withdrawn. Nearly all drugs we approved in this period were reviewed under PDUFA goals.

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 inspections that examine the conditions and practices in plants where 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.

Recent safety-based drug withdrawals (cont.)

- **Dexfenfluramine (1996/1997)** (not an NME)
- **Bromfenac (1997/1998)**
- **Cerivastatin (1997/2001)**
- **Grepafloxin (1997/1999)**
- **Mibefradil (1997/1998)**
- **Troglitazone (1997/2000)**
- **Rapacuronium (1999/2001)**
- **Alosetron (2000/2000)**

Reporting systems for drug quality problems

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

- *Drug Quality Reporting System.* Through MedWatch (page 28), we receive reports of observed or suspected defects and quality problems associated with marketed drugs. We evaluate and prioritize the reports to determine potential health hazards and industry trends and to develop special programs and surveys. We identify significant health hazards associated with drug manufacturing, packaging and labeling and initiate field inspections assignments. We review inspection reports and recommend appropriate corrective action. We maintain a central reporting system to detect problem areas and trends.
- *Field Alert Reports.* Firms are required to notify FDA promptly of any significant problems that may represent safety hazards for their marketed drug products. FDA's district offices evaluate these reports and conduct follow-up inspections. We review and evaluate the inspection findings to determine if firms are complying with reporting requirements. We review and approve enforcement recommendations for failure to meet these requirements.

Risk-based surveillance sampling of drugs

We monitor the quality of the nation's drug supply through surveillance and sampling of foreign and domestic finished dosage forms and bulk shipments of active ingredients. The drug products surveyed are selected according to a risk-based strategy that targets products with the greatest potential to harm the public health. FDA district offices conduct follow-up inspections to determine the cause of sample failures and to assure corrective action by the firms.

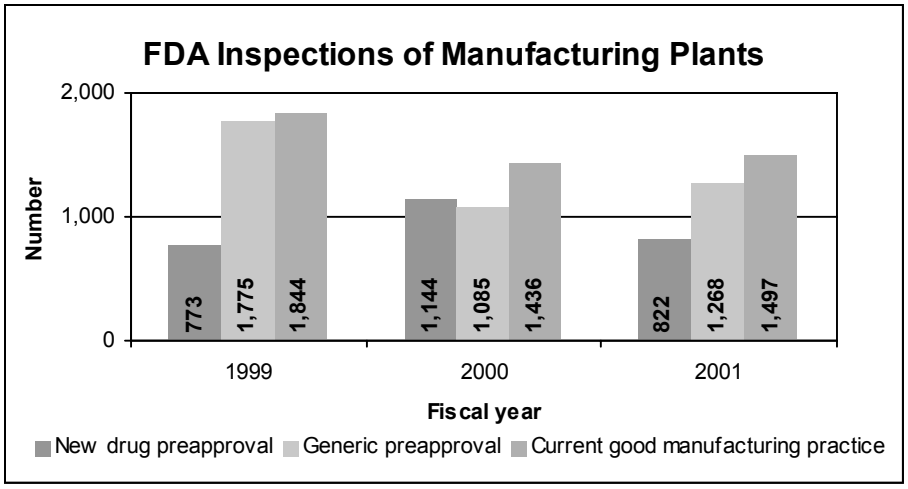
Sampling criteria

Criteria for our risk-based surveillance sampling of drugs include:

- □ **High-volume/high-risk products**
- □ **Therapeutic importance**
- □ **Emerging problems**
- □ **Dissolution issues**
- □ **New molecular entities**
- □ **Method validation issues**
- □ **Counterfeit drugs**
- □ **History of violations**

Prescription drugs sold without approved applications

We identify drugs that are marketed without an approved new or generic drug application. We assess unapproved drugs to maximize protection of the public health and make best use of FDA's limited resources. We prioritize drugs that may be subject to compliance actions into risk-based categories. These begin with those posing the most saftey considerations and effect on public heatlh.



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 2001, FDA evaluated 822 plants in support of new drug applications. Also, FDA evaluated 1,268 domestic firms in support of generic drug applications.
- *Good manufacturing practice inspections.* There were 1,497 good manufacturing practice inspections in fiscal year 2001. We reviewed 48 field recommendations for regulatory action and approved 18. These included two injunctions, eight seizures and four warning letters. We reviewed 249 foreign establishment inspection reports. These reviews resulted in 10 warning letters.

Unsubstantiated claims; fraudulent, hazardous products

We often encounter products marketed to U.S. consumers that make illegal and unsubstantiated medical claims. These may include claims to treat serious diseases that have proven effective treatments. Products making unproven claims may, therefore, pose a significant health risk. Consumers may use a fraudulent product in place of an effective treatment or may delay the use of effective treatment. On occasion, fraudulent products are found to contain toxic components that are likely to cause serious illness or injury.

In addition, the marketing of products making unsubstantiated claims threatens to undermine the U.S. drug development and approval process by interfering with the incentive for new drug development.

Protecting consumers from fraudulent drugs

We protect U.S. consumers from fraudulent or hazardous drug products by:

□ Issuing enforcement letters to firms or individuals marketing fraudulent products. Last year, more than 50 such letters were issued based on unsubstantiated claims found in product labeling and on Internet sites.

□ Pursuing enforcement actions. These include seizures of violative products and injunctions against firms or individuals who continue to market violative products.

Drug Product Quality Science

PQRI update

We are evaluating the first scientific recommendations from the Product Quality Research Institute (page 6). These are aimed at ensuring thorough mixing of a drug within the blend and dosage unit.

PQRI has a number of working groups addressing the issues such as:

- **Methods for determining physical attributes of drug substances starting with particle size**
- **Impurities and how best to detect, identify and quantify them**
- **Reliance on product specifications**
- **Qualifying changes to container/closure systems - solid oral dosage forms**
- **Leachables and extractables in orally inhaled and nasal drug products**
- **Particles size distribution comparisons**

Research

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

- Developing and validating methods for testing the quality of drug products and rapid identification of counterfeit products. This included work on near-infrared spectroscopy and near-infrared imaging.
- Approving shelf-life extensions for drug products on the joint FDA and Department of Defense Shelf Life Extension Program. We assess stability profiles of stockpiled drugs for risk management.

Process analytical technologies initiative

We launched an initiative to assist manufacturers in improving the capability and efficiency of the pharmaceutical process while maintaining or improving product quality. Known as process analytical technologies, these are systems for continuous analysis and control of manufacturing processes based on real-time or rapid measurements during processing.

To assist in this effort, we are bringing together experts in the areas of analytical chemistry, physical chemistry, pharmaceutical technology, regulatory compliance, chemical engineering and international pharmaceutical manufacturing. These include experts from industry and academia along with our own and those from other FDA components.

Product quality scientific workshops

We cosponsored two scientific workshops to bring together our scientists with those from academia and industry to discuss our approaches and industry's experiences and perspective.

The workshops were:

- *Assuring Quality and Performance of Sustained and Controlled Release Parenterals*. This workshop covered dispersed systems (microspheres, liposomes, gels and suspensions) as well as implants of small molecule and peptide therapeutics for human and animal use.
- *Streamlining the Chemistry, Manufacturing and Controls Regulatory Process for New and Generic Drugs.* This workshop discussed scientific criteria for establishing a class of drugs considered to be low risk with respect to product quality.

Microbiology

We assess product sterility, maintenance of product safety and the microbiological controls used by firms for drug development and manufacturing.

Our microbiology review assures the safety of sterile and non-sterile products through scientific evaluation and communication with the industry and assures consistency through guidance documents.

We promote the development of uniform and practical test methods and criteria for our own use and through the U.S. Pharmacopoeia and the International Conference on Harmonization (page 38).

We initiated a new program to advance rapid microbiology test methods. This included advisory committee meetings and a proposed sub-committee to resolve administrative and technical hurdles.

Export certificates issued in fiscal year 2001:

- **4,542**

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.

3

INTERNATIONAL ACTIVITIES

Highlights from 2001 include:

- Accepting the first new drug applications in the Common Technical Document format. The CTD can be used for seeking approval to market new drugs in the United States, the European Union and Japan.
- Nearing completion of the electronic CTD.
- Prioritizing issues for our 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.
- Exchanging recall information and alerts concerning significant emerging product quality problems with the European Union.

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.

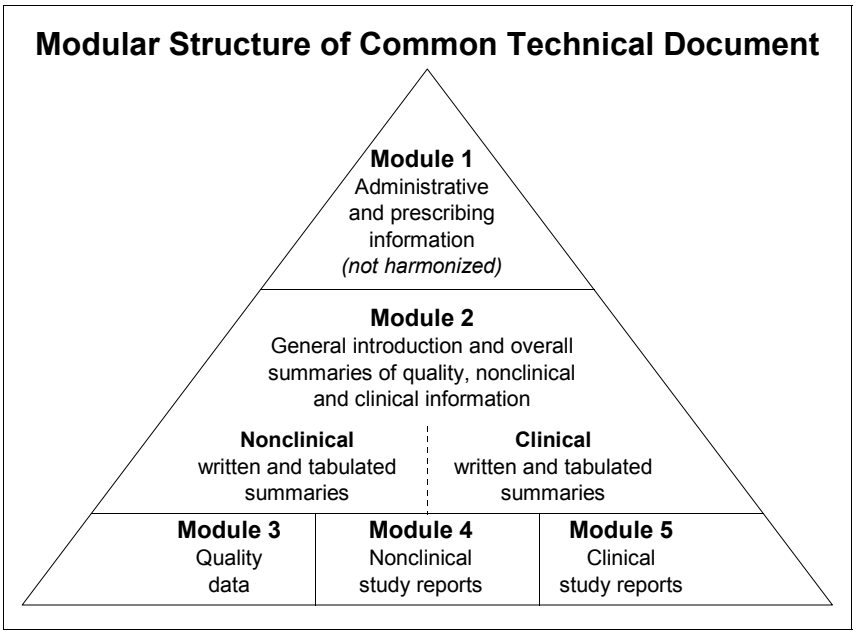
Internet sources

□ More information about our international activities, including Spanish language materials, is at http://www.fda.gov/cder/audiences/iact/iachome.htm.

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



Common Technical Document update

The ICH Common Technical Document allows data in the same format to be submitted to drug review authorities in all three ICH regions.

□ We have received five new drug submissions in CTD format, several for new dosage forms. Some submissions use paper for some sections and electronic media for others.

□ 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 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. Other urgent issues are good clinical practices and counterfeit drugs.

U.S.-European Union Mutual Recognition Agreement

This agreement provides for reciprocal reliance on inspection systems in the United States and each of 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

A planned three-year transition to full implementation has not proceeded as smoothly as anticipated, but both parties remain optimistic

□ Last year, we began exchanging recall information and alerts concerning significant emerging product quality problems.

□ We proposed exchanging inspection reports on a pilot basis and audited the first E.U. member state.

□ A team of E.U. officials audited our regulatory system for good manufacturing practices with a positive outcome.

4

COMMUNICATIONS

Highlights from 2001 include:

- Meeting almost weekly with outside experts on difficult scientific and public health issues.
- Responding to more than 52,000 individual requests for information.
- Launching twice-yearly, week-long introductory workshops for our stakeholders.
- Receiving nearly 6.6 million visitors and about 111 million hits on our Internet information site, which has 40,000 pages and documents, five databases and 175,000 hyperlinks.

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 outside scientists, consumer and patient groups, professional and scientific societies, industry and trade associations about:

- Converting certain prescription antihistamines to over the counter sales (page 17).
- The effects of medication on vehicle operators. This was our first joint meeting with the National Transportation Safety Board. It was held in response to the board's request for warning labels on medicines that may impair a person's ability to drive, fly, sail or operate vehicles.

Workshops

- *CDER 101.* We inaugurated a workshop for external stakeholders including foreign regulators. Our cosponsors were two non-profit organizations and an academic institution. The workshop features many of our experts in a week-long introduction to our mission, organization and regulatory processes. We held two workshops in 2001 and will continue to offer them twice a year.
- *Scientific workshops.* We cosponsored one workshop addressing drug-induced liver damage (page 30) and two addressing product quality issues in manufacturing (page 36).

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

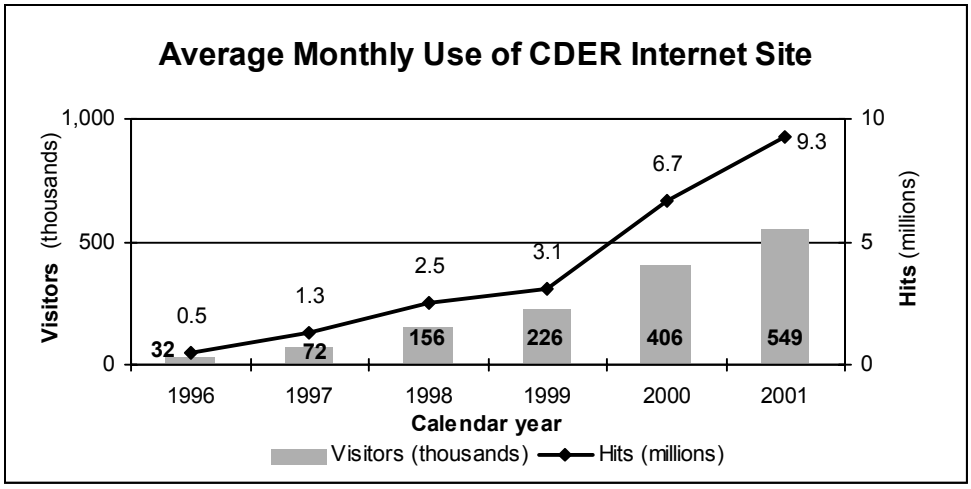
We have 40,000 subscribers to our service that provides daily and weekly e-mail updates of new content on our Web site.

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**



Consumer and industry outreach

- *Regulations.* We published seven regulations, and we sought public comment on another five proposed regulations.
- *Guidances.* We published 15 guidances for industry that explain our position on best practices in scientific and technical areas. We published another 16 in draft form seeking public comment.
- *Manual of Policies and Procedures.* To foster transparency of our operations, we publish our internal operating policies and procedures on the Internet. We added 20 documents last year.
- *Trade press.* We responded to more than 2,340 telephone and e-mail requests from the specialized press covering the pharmaceutical industry.
- *Exhibits*. We exhibited at 23 conferences, reaching an estimated audience of over 100,000 consumers, educators and health care professionals.
- *Videoconferencing.* We held about 100 domestic and foreign videoconferences for academia, industry and associations.
- *CDER Live!* We conducted a satellite television broadcast and webcast for more than 5,000 industry employees in which we discussed our proposal to improve the format and content of the prescription drug label.
- *Drug reviews on Internet.* We posted on our Internet site our reviews of more than 200 approved new drugs or new uses for approved drugs.
- *Information requests.* We responded to 6,000 requests under the Freedom of Information Act and more than 16,500 e-mail requests from industry, consumers, patients and health care professionals.
- *Other communications.* We answered more than 34,000 telephone inquiries, 1,100 faxes and 8,800 written requests. We responded to nearly 6,000 requests for documents and guidance publications.

Partnering to reduce medical gas mix-ups

We developed an outreach plan to eliminate deaths and injuries occurring when incorrect medical gas tanks are connected to oxygen lines in hospitals and nursing homes. This involved more than two dozen health care organizations and several accreditation organizations.

Ombudsman's activity

In its sixth year of operation, our ombudsman helped settle issues between us and industry, health professionals and consumers.

□ The ombudsman handled about 100 disputes.

□ He answered more than 1,300 e-mails, approximately 1,000 telephone calls and 20 letters.

□ In addition, the ombudsman held about 20 meetings with external parties.

Public education campaigns

In response to expressed need for information from the public and health care professionals, we developed 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

□ The new over-the-counter medicine labels

□ Misuse of prescription pain relievers

□ Drug interactions

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-05
5600 Fishers Lane
Rockville, MD 20857

Organizational Structure of the Center for Drug Evaluation and Research

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