Center for Drug Evaluation and Research ***2002***

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/2002/rtn2002.pdf

HTML: http://www.fda.gov/cder/reports/rtn/2002/rtn2002.htm

Slides: http://www.fda.gov/cder/reports/rtn/2002/rtn2002.ppt

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CONTENTS

Graphs and Charts

Director's Message

Last year, we at the Center for Drug Evaluation and Research worked hard to meet the challenge of promoting and protecting the public health. The dedication, creativity and expertise of our professional staff, coupled with new authorities and resources, enable us to continue to meet this challenge.

Our new Commissioner has established five strategic areas for the Agency:

- A strong FDA.
- Efficient risk management.
- Patient and consumer safety.
- Better consumer information.
- Counterterrorism.
- In 2002, we took significant steps in each of these areas.

Strong FDA

Strong and sound science means our scientists stay on the cutting edge of new technologies. Our mission depends more than ever on a solid cadre of experienced physicians, toxicologists, chemists, statisticians, mathematicians, project managers and other highly qualified and dedicated professionals. The expertise of our professional staff is essential for making our regulatory decisions balanced and fair. A committee of our scientists oversees an extensive program of training, seminars, case study rounds and guest lectures that helps keep our scientists up-to-date on the latest developments in their disciplines and current industry practices.

Quality of work life is important in retaining our professional staff, who rated CDER very high in the Secretary's 2002 survey on organizational environment.

Last year, Congress reauthorized our collection of user fees for drug reviews. The reauthorization maintains our rigorous review and drug development goals, places the program on a sound financial footing and increases our resources for surveillance of newly marketed drugs. The review function for therapeutic biological products will be transferred to our center in 2003. Consolidation will strengthen our science base, and we look forward to working with, and extend a warm welcome to, our colleagues from the Center for Biologics Evaluation and Research.

Efficient risk management

Last year, our hard work enabled us to meet nearly all of the demanding application review goals of the Prescription Drug User Fee Act. We evaluated many new drugs that offered important treatment options for Americans. For example, we approved the first non-sedating antihistamine for over-the-counter sale and the first non-stimulating treatment for attention deficit/hyperactivity disorder in children.

However, we are concerned that the approval of truly new drugs is at the lowest level in a decade. We have launched an important initiative to remove barriers to innovation in drug development.

We are leading an important FDA initiative to facilitate the modernization of American drug manufacturing. Use of cutting-edge technology will allow manufacturers to produce high-quality drug products with greater efficiency and lower cost.

Patient and consumer safety

We continued to enhance our drug safety program to help make sure that drugs are used safely once they're approved. Legislation has given us new authority and resources to conduct more rigorous safety monitoring of newly approved drugs in the first few years on the market. Last year, we evaluated more than 300,000 adverse event reports. We alerted the public to the dangers of importing or buying over the Internet 10 drugs that are marketed in this country with special safety restrictions.

Balanced and fair information is critical to the safe use of medicines. We completed surveys of physicians and consumers about direct-to-consumer advertising. About 40 percent of patients and about 45 percent of physicians feel DTC advertising encourages information seeking about potentially serious medical conditions. We are working on new guidance for direct-to-consumer advertising.

Better consumer information

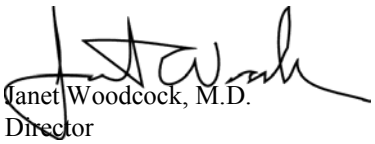
We are collaborating with a broad spectrum of groups to improve information for prescribers and consumers. Last year, we implemented a mandatory changeover to new, easy-to-understand labels for medicines sold over the counter. Industry and consumers are increasingly turning to our Internet site for important and up-to-date information on our regulatory programs and on the drugs they take to improve their health. We have 10 public education programs to promote the safe use of medicines. The program to bolster consumer confidence in generic drugs has met with particularly outstanding success and acceptance.

Counterterrorism

We continue to facilitate development of new drugs and new uses for already approved drugs that could be used as medical countermeasures. We amended our regulations so that certain human drugs and biologics intended to reduce or prevent serious or life-threatening conditions may be approved based on animal evidence of effectiveness when human efficacy studies are not ethical or feasible.

The way forward

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 to health professionals, patients and consumers.



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

What is a drug?

We regulate drugs used to treat, prevent or diagnose illnesses.

However, drugs include more than just medicines.

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

You can buy some drugs in a store without a prescription, while others require a doctor's prescription.

Some are available in less-expensive generic versions.

Prescription drugs

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

- **The disease or condition may be serious and require a doctor's management.**
- **The medicine itself may cause side effects that a doctor needs to monitor.**
- **The same symptoms 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.**

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.

2002 HIGHLIGHTS

We are pleased to present our seventh performance report. Our work last year offered many Americans new or improved choices for protecting and maintaining their health or new ways to use existing products more safely.

Drug review

Children and people with cancer, heart disease and other serious conditions have benefited from our approvals in 2002. Our workload remained very high; however, our experience last year included some concerning trends in drug development. The number of filings and approvals of new molecular entities, significant new drugs never before approved for marketing in the United States, continued to decline to their lowest point in a decade. Our statistics for priority drug reviews have also been affected by this trend.

Last year saw a steep rise in median total approval times for priority new drugs and priority new molecular entities. This resulted from the approval of drug applications received in previous years coupled with the decrease in recent priority submissions. With a smaller pool of recent priority applications with short approval times, the submissions from previous years dominated the median approval time statistics.

We met or exceeded most of our obligations to Congress for prompt and thorough review of drug applications supported by user fees.

We approved 78 new drugs, including 17 new molecular entities. We also approved 152 new or expanded uses of already approved drugs, an increase of 67 percent from the previous year.

We increased choices for self-care by approving 13 medicines for over-the-counter marketing. This included the first switch of a non-sedating antihistamine from prescription only to over-the-counter sale. A mandatory changeover to new, easy-to-understand labels for OTCs began last year.

Our reviews of generic drugs have been prompt and predictable. We approved 321 generic equivalents for prescription or over-the-counter drugs. Our generic drug education program, specially funded by Congress, has been enormously successful, with many organizations reproducing our materials at no cost to the government.

Our effort to protect our citizens and soldiers against chemical, biological and nuclear weapons was bolstered last year. We amended our regulations to permit us to approve certain countermeasures based on animal studies when human efficacy studies are infeasible or unethical.

Realignments

Last year, we adjusted our organizational structure to enhance how we use risk management principles in our operations:

□ With additional resources, our post-market drug safety experts have begun to contribute their insights to the premarket review of risk management plans for new drugs.

□ Our compliance operations have relocated and reorganized.

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

New, reauthorized legislation

Our programs will benefit from additional authorities and resources.

□ The *Bioterrorism Act of 2002* improves the nation's ability to prevent, prepare for and respond to bioterrorism and other public health emergencies.

□ The bioterrorism law also contained the third five-year reauthorization of the *Prescription Drug User Fee Act.* PDUFA III maintains our rigorous review and drug development goals, places us on a sound financial footing and increases our resources for surveillance of newly marketed drugs.

□ The *Best Pharmaceuticals for Children Act of 2002* 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 authorizes the federal government to contract for pediatric studies for drugs that lack patent protection or other marketing exclusivity.

Communications

We met almost weekly with outside experts on difficult scientific and public health issues. We received valuable input from a public hearing on risk management tools.

Each month, our Internet information site averaged 750,000 visitors and 13.5 million hits.

We responded to more than 70,000 individual requests for information.

We developed public education campaigns in areas such as new OTC drug labels, generic drug quality, proper drug dosing for children and pregnancy and drug use.

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 rapidly and take corrective action quickly. We improved our risk-assessment ability by gaining access to actual use data.

Last year, we processed and evaluated more than 320,000 adverse drug events. We issued nearly 700 letters to help ensure that the promotion of drug products presents a fair balance of risks and benefits and isn't false or misleading.

Improving Innovation

We believe we can help speed potentially important new drugs to the market by reducing regulatory uncertainty and increasing the predictability of product development. We are playing a key role in a broad FDA initiative called *Improving Innovation in Medical Technology: Beyond 2002.* The initiative is aimed at:

- Reducing the time and costs of medical product development.
- Facilitating the introduction of innovative new technologies.
- Maintaining our traditional high standards of consumer protection.

We are looking to achieve these goals through new actions in three major areas:

- Identifying the root causes of multiple review cycles and avoiding them when possible through early communication and other steps to improve the quality of new product applications.
- Improving the quality and efficiency of the review process by adopting a quality systems approach to medical product reviews.
- Improving the quality of submissions in new and priority product areas by providing clearer up-to-date guidance for particular diseases and for emerging technologies.

Our proposals are outlined in a detailed report at http://www.fda.gov/bbs/topics/NEWS/2003/beyond2002/report.html. The executive summary is at http://www.fda.gov/bbs/topics/NEWS/2003/beyond2002/execsumm.html.

Pharmaceutical cGMPs

Our regulatory and quality control systems for pharmaceutical products have become a gold standard for the world; however, the last comprehensive revisions to these regulations are nearly a quarter of a century old. Last year, we announced a significant new initiative, called *Pharmaceutical cGMPs for the 21st Century,* to enhance the regulation of

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 finalized the electronic version of 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.

Pharmaceutical reviews to be consolidated

The review of some new biologic products will be transferred to our center in 2003. This will enhance the efficiency and consistency of reviewing clinically similar products.

Consolidation will strengthen our science base, increase timeliness of reviews and contribute to greater uniformity of regulations, policies and practices involving all therapeutics.

Planned for transfer are cytokines, growth factors, enzymes and interferons—including recombinant versions—plus proteins for therapeutic use that are extracted from animals or microorganisms and other therapeutic immunotherapies.

pharmaceutical manufacturing and product quality and to bring a 21st century focus to this FDA responsibility.

The major goals of the initiative are to make sure that:

- Public health protection is strengthened by implementing risk-based approaches that focus both industry and FDA attention on critical areas for improving product safety and quality.
- The regulatory review program and the inspection program operate in a coordinated and synergistic manner.
- Regulation and manufacturing standards are applied consistently using state-of-the-art pharmaceutical science.
- Innovation in the pharmaceutical manufacturing sector is encouraged.
- FDA resources are used most effectively and efficiently to address the most significant health risks.

More information on the program, including the concept paper, progress reports and announcements of public meetings, is on our Web site at http://www.fda.gov/cder/gmp/index.htm.

Counterterrorism

The first therapy for those exposed to a terrorism agent is often a drug. We have been taking an aggressive and proactive approach to our role in helping prepare the nation for terrorism attacks. These steps include:

- Assuring the availability of medicines to treat victims of terrorism attacks.
- Leveraging resources with other federal agencies to answer scientific questions concerning therapies to treat conditions against terrorism agents.
- Protecting the nation's drug supply from attack or deliberate contamination.
- Preparing ourselves to continue operations during a crisis.

We continue to facilitate development of new drugs and new uses for already approved drugs that could be used as medical countermeasures. We work with other agencies to implement a shelf-life extension program for stockpiled drugs for military use. We gather information on drugs that might be used in response to an attack, including data on manufacturers, bulk suppliers, inventories and lead times for production.

Increased counterterrorism resources

We hired additional experts in medicine, science and regulatory affairs dedicated to our counterterrorism mission.

We have improved coordination and communication with other federal agencies and manufacturers.

We provide guidance and direction for the research and development of new and existing medical countermeasures.

Counterterrorism Internet resources

Our Internet site provides links to the most current information on drugs to prevent or treat disease caused by terrorism agents, including drugs for use against anthrax, plague, radiation emergencies and chemical agents; drug development of counter-terrorism products; vaccines; pediatric counter-terrorism measures; and prescribing and buying countermeasures.

You can find these links at http://www.fda.gov/cder/drugprepare/default.htm.

Shelf-life extension for drug stockpiles

Our laboratories perform shelf-life extension testing for drug products stockpiled by the U.S. military.

Draft guidance

We issued a draft guidance on developing drugs to treat inhalational anthrax.

Counterterrorism notable 2002 achievements

Animal efficacy rule. We amended our regulations so that certain human drugs and biologics intended to reduce or prevent serious or life-threatening conditions may be approved based on animal evidence of effectiveness when human efficacy studies are not ethical or feasible. The rule—also known as the Animal Efficacy Rule or Subpart I—applies when: the pathophysiology of the disease and the mechanisms of action of the drug are well understood; the efficacy endpoints in the animal trials are clearly related to human benefit; the drug effect is demonstrated in at least one well-characterized animal species expected to react with a response predictive for humans; and data allow selection of an effective human dose. We reviewed and, in February 2003, approved pyridostigmine bromide to increase survival after exposure to Soman nerve gas poisoning—the first use of the rule.

New drug approval—ATNAA. We approved ATNAA (Antidote Treatment—Nerve Agent, Autoinjector) sponsored by the U.S. Army, for use as an antidote to nerve agent exposure. Atropine and pralidoxime, the two nerve agent antidotes in this combination product, were already approved separately. Approval of the combination provided for a single injection containing both drugs, thereby allowing for more efficient and convenient administration on the battlefield.

Generic drug approval—potassium iodide. ThyroSafe Tablets, 65 mg, an over-the-counter generic drug application, was approved in September 2002 under expedited review. This thyroid blocking agent for use in radiation emergencies is half the concentration of the other approved potassium iodide tablets, making it particularly important for use in pediatric populations.

New drug review—Prussian Blue. We completed the review of the data for using Prussian Blue to treat exposure to radioactive cesium and thallium. We published our findings of safety and efficacy in February 2003 to encourage sponsors to submit applications for this indication.

New drug review—Chelators. We also reviewed all U.S. cases of radiation exposure treated with intravenous chelators. Results of this review are pending.

Grants announcement, interagency agreement. We announced the availability of grants to support clinical trials on the safety and efficacy of drug products for the treatment of human plague. We are supporting an interagency agreement with the Centers for Disease Control and Prevention to fund such studies.

Contracts. Through FDA's Office of Women's Health, we contracted for studies on therapies that may be used to treat conditions caused by terrorism agents. These studies will enroll special populations such as lactating and pregnant women and the elderly.

Public health guidance

With the results from the research on doxycycline and potassium iodide (page 7), we provided medical professionals and the public information on:

- **The palatability and stability of doxycycline tablets ground and mixed in food or drinks.**
- **Home preparation procedures for emergency administration of potassium iodide tablets to infants and children. Information on palatability and stability is also included.**

Additional information was also provided on potassium iodide:

- **Frequently asked questions about potassium iodide for use in radiation emergencies.**
- **A public announcement on protection of children and adults against thyroid cancer in case of nuclear accident.**

Counterterrorism scientific research

In collaboration with the National Institute of Allergy and Infectious Diseases and the Department of Defense, we developed a monkey model for pneumonic plague to be used to study a number of potential therapies. We are also collaborating with them on a monkey model for studies of smallpox therapies.

Some medical countermeasures are stockpiled in tablet form that may be difficult to swallow for infants, small children and others. Two examples are doxycycline, for post-exposure prophylaxis for anthrax, and potassium iodide, for use in emergencies involving radioactive iodine. We studied the stability and palata-bility of these drugs when crushed and mixed with different foods or drinks.

We developed an exposure-response model for pyridostigmine, an anti-nerve gas agent, to extrapolate animal efficacy data to a human dose regimen.

Scientific Research

We advance the scientific basis of regulatory practice by developing, evaluating or applying the best, most appropriate and contemporary scientific methods to 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 scientific linkage between non-clinical and clinical studies, enhancing 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

We are 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, kidney, immune system and liver.

To enhance safety within broad segments of patient populations and enable safe development of new drug classes, we are working on the identification and elucidation of associated serum biomarkers and mechanisms responsible for the development of vascular inflammation in specific organ systems.

We conduct targeted research on microarrays, a new technology that can identify thousands of genes or proteins rapidly and at the same time. We are evaluating how this technology could improve the interface between drug development and regulatory practice.

We confirmed reports of brain toxicity findings in neonatal rats with ketamine, an anesthetic widely used in children. Our rapid research resulted in the National Toxicology Program undertaking broad ranging non-human primate studies to assess better human relevance of these rodent findings.

Clinical pharmacology

We established scientific research capabilities in the analyses of medicinal plant and herbal products.

We continue to explore noninvasive imaging technology to extend the our long-standing interest in the application of accurate dose-concentration-response principles by viewing drugs and their actions directly at the level of the drug target, rather than indirectly via plasma concentrations.

We are developing a standardized approach for using exposure-response information for evaluating the risk and benefit of drug therapies and recommending dose adjustments in special populations.

We are developing a pediatric population pharmacokinetics study design template to facilitate implementation of sparse sample strategies in pediatric drug development.

Pharmaceutical analysis

We assure that analytical methods being developed by pharmaceutical companies are suitable for quality assurance and regulatory purposes. Last year, we assessed analytical methods for more than 20 new drugs.

We collaborate with other organizations to ensure the availability of high quality standards and calibration materials.

Other analytical methods under development last year included characterization of nasal inhalation products and complex drug substances.

We tested several analytical technologies for characterizing active pharmaceutical ingredients and guarding against counterfeit product marketing. These included isotope ratio mass spectroscopy, ion mobility spectroscopy, near infrared and Raman spectroscopies. We examined Raman imaging's ability to determine particle size distribution of the active ingredient in nasal sprays.

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 regulatory expert for the review team and as the 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.

Clinical pharmacologists and biopharmaceutists evaluate factors that influence the relationship between the body's response and the drug dose and 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 assess the clinical significance of changes in the body's response to drugs through the use of exposure-response relationships and check for interactions between drugs.

Scientific training for reviewers

Our systematic, internal training program is based on core competencies, learning pathways and individual development plans.

□ The program grew from seven activities offered in 1997 to more than 40 in science and science policy

□ We offer 44 courses in job skills, research tools, leadership and management.

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

□ Last year, we brought in 40 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.

Advanced scientific education

A committee of our scientists oversees a program of scientific training, seminars, case study rounds and guest lectures.

This multidisciplinary program helps keep our scientists up-to-date on the latest developments in their fields and current industry practices.

Quality of work life survey

In a survey conducted last year by the Department of Health and Human Services, we did better than both FDA and the entire department in 13 of 14 general areas important to organizational performance.

About three-fourths of our scientists and other employees reported positively on the effectiveness of our management practices, their feelings about the organization and the effective use of their abilities.

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DRUG REVIEW

Drug approvals for 2002

- **78 new drugs**
- **17 new molecular entities**
- **8 orphan new drugs**
- **152 new or expanded uses for already approved drugs**
- **13 over-the-counter drugs or Rx-to OTC switches**
- **321 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 the generic equivalents for both.

We approved 17 new medicines that have never been marketed before in this country, known as new molecular entities. We approved 321 generic versions of existing drugs. We authorized 13 medicines to be sold over the counter without a prescription, and 11 of them can be used by children.

We met or exceeded 12 of the 14 performance goals for the fiscal year 2001 receipt cohort, the latest year for which we have full statistics. These are goals we agreed to under legislation authorizing us to collect user fees for drug reviews. In addition to surpassing all goals for original new drug applications, we exceeded all three of the goals for new molecular entities.

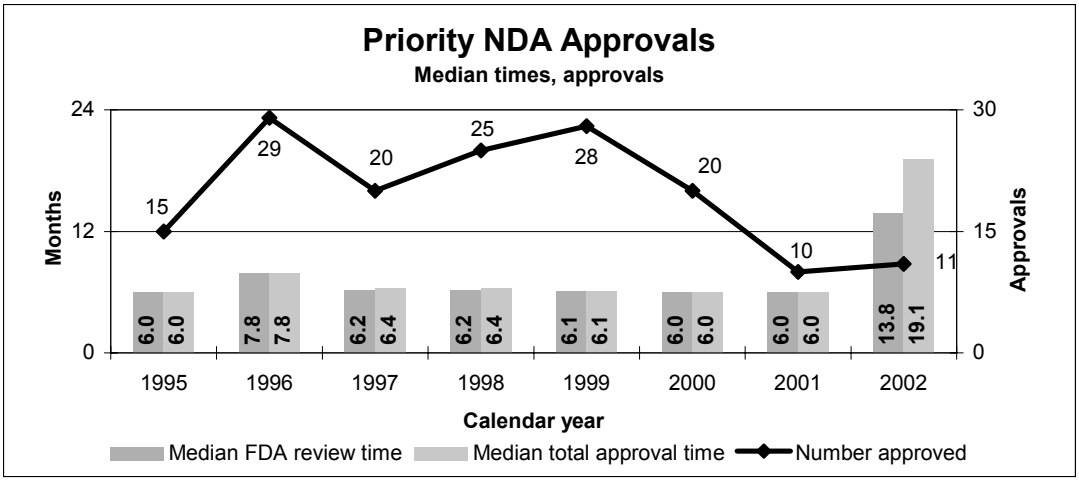
We conducted 487 foreign and domestic inspections that help protect volunteers for clinical trials from research risks and validate the quality and integrity of data submitted to us.

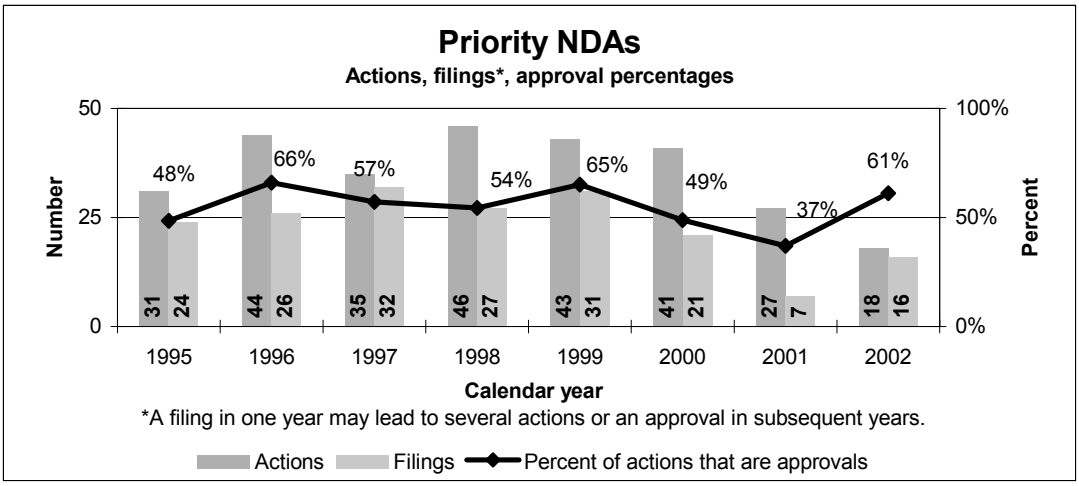
Highlights of new medication options for American consumers include:

- Three new drugs to treat childhood diseases.
- 19 labels with new information for treating children.
- The first two drugs to treat opiate dependence that can be prescribed in an office setting under the Drug Addiction Treatment Act of 2000.
- Two new drugs to treat cancer.
- Three new drugs to treat heart disease.
- Three new drugs to treat infectious diseases.
- Eight drugs to treat "orphan" patient populations of 200,000 or fewer.
- The first active ingredient in a nonsedating antihistamine switched from prescription only to over-the-counter sale.
- One new antidote for chemical warfare nerve agents.

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.





Priority new drugs

- **11 approvals**
- **Median review time: 13.8 months**
- **Median approval time: 19.1 months**
- **18 actions**
- **16 filings**

New Drug Review

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. Our guide to understanding median approval time statistics is available at http://www.fda.gov/cder/present/MedianAPtime/index.htm.

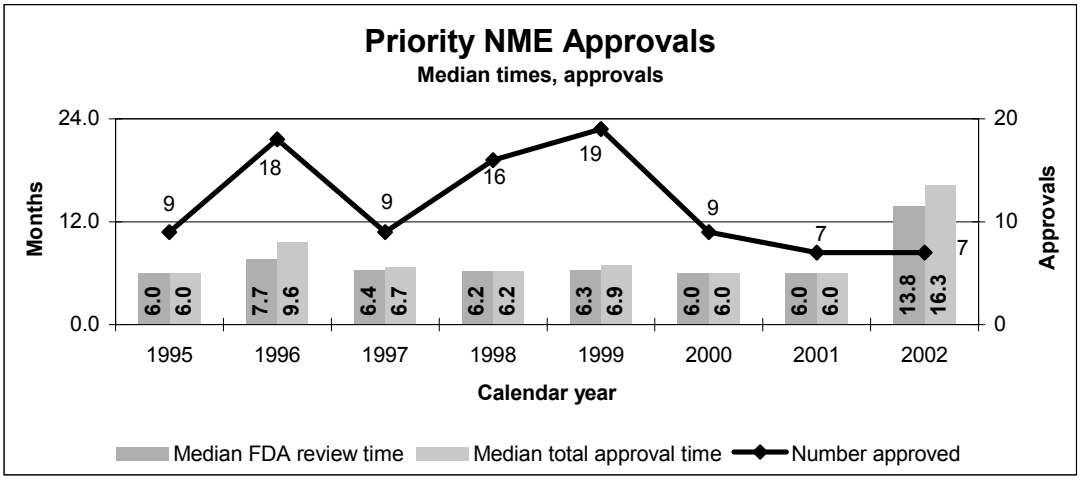
Actions and filings. An application is "filed" when we determine it is complete and accept it for review. We make a filing decision within 60 days of receiving an application. Approval is one of the actions that we can take once an application is filed. Other actions include seeking more information 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.

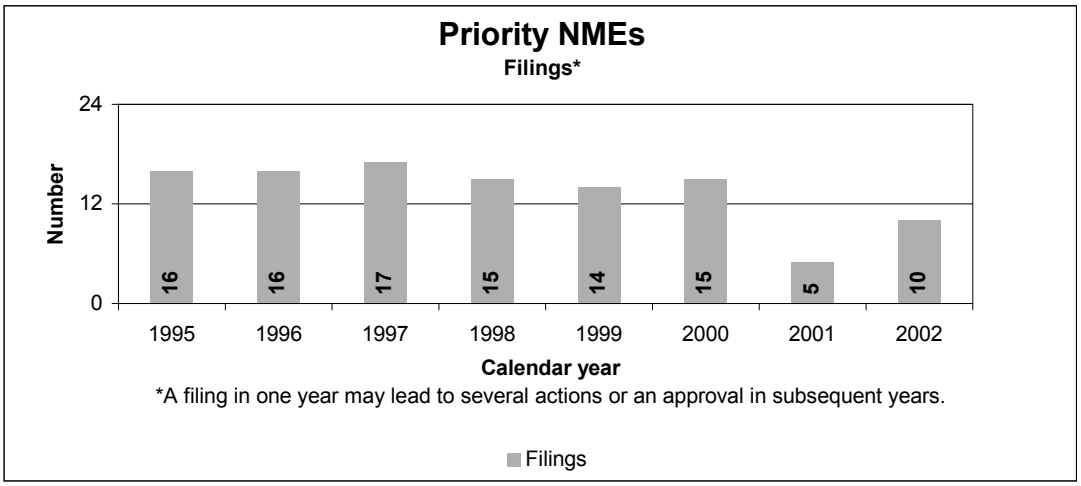
Orphan drugs
(N=NME)

- **Buprenorphine hydrochloride (Subutex)**
- **Buprenorphine hydrochloride and naloxone hydrochloride dihydrate (Suboxone)**
- **Icodextrin (Extraneal) (N)**
- **Nitazoxanide (Alinia)**
- **Nitisinone (Orfadin)**
- **Secretin (SecreFlo)**
- **Sodium oxybate (Xyrem) (N)**
- **Treprostinil sodium (Remodulin) (N)**

Priority new drugs
(N=NME)

- **Adefovir dipivoxil (Hepsera) (N)**
- **Atropine and pralidoxime chloride (ATNAA)**
- **Cyclosporine (Restasis)**
- **Oxaliplatin (Eloxatin) (N)**
- **Ribavirin (Copegus)**
- **Tegaserod maleate (Zelnorm) (N)**
- **Buprenorphine hydrochloride and naloxone hydrochloride dihydrate (Suboxone)**





Older applications dominate statistics for priority reviews

Last year saw a steep rise in median total approval times for priority NDAs and NMEs.

This was a statistical artifact caused by the approval of a number of older applications remaining from the 1999 and 2000 receipt cohort coupled with a significant decrease in the number of priority applications received in 2001 and 2002.

With a smaller pool of recent priority applications with short approval times, the remaining "tail" of submissions for earlier years dominated the median approval time statistic.

New molecular entities. Seventeen 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. We took 18 actions on priority new drug applications, of which 11 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.

Standard new drugs. We took 154 actions on standard new drug applications, of which 67 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.

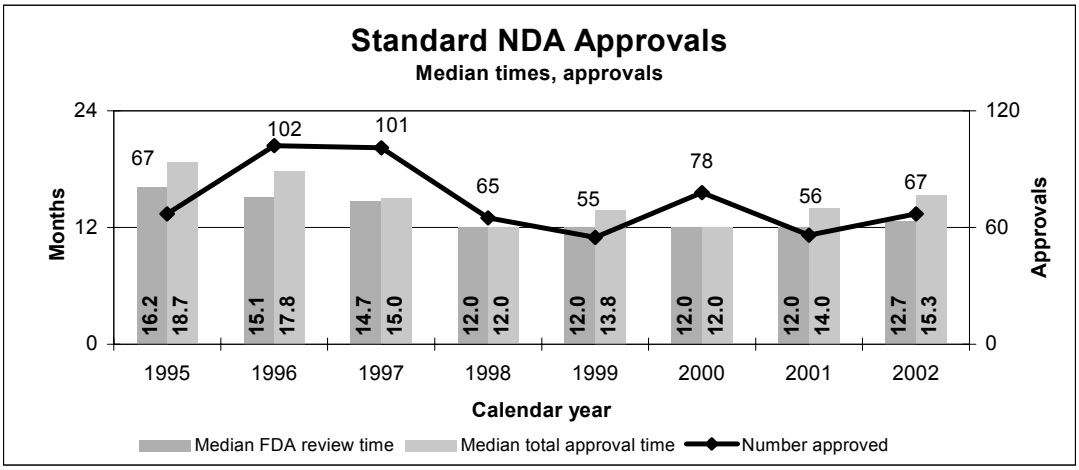
Orphan drugs. Eight of the approvals were for "orphan" uses in patient populations of 200,000 or fewer. Sponsors of such products receive inducements that include seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance by FDA and grants of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

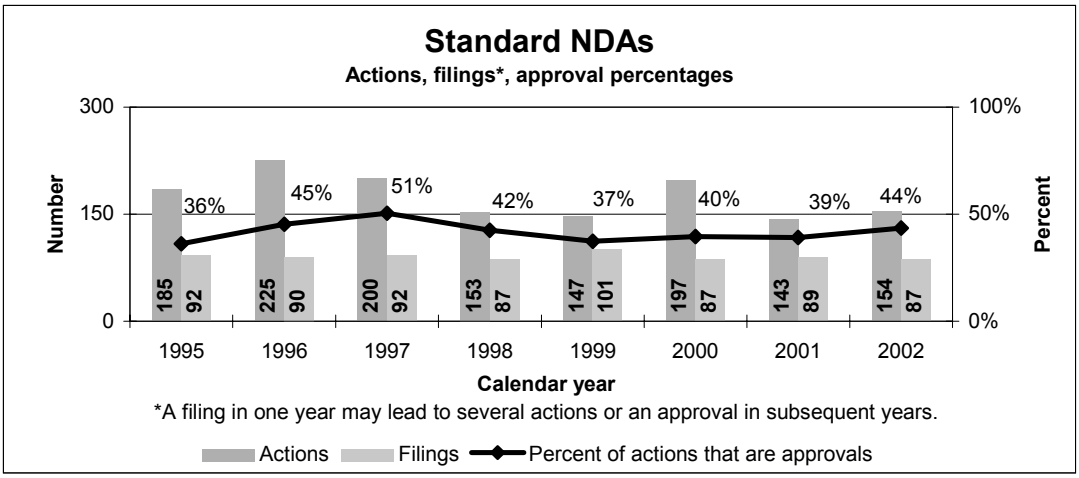
Priority new drugs
(continued; N=NME)

- **Nitazoxanide (Alinia) (N)**
- **Nitisinone (Orfadin) (N)**
- **Sodium oxybate (Xyrem) (N)**
- **Treprostinil sodium (Remodulin) (N)**

Priority new molecular entities

- **7 approvals**
- **Median review time: 13.8 months**
- **Median approval time: 16.3 months**
- **10 filings**





Standard new drugs

- **67 approvals**
- **Median review time: 12.7 months**
- **Median approval time: 15.3 months**
- **154 actions**
- **87 filings**

Notable 2002 new drug approvals

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

People with cancer

Oxaliplatin for injection (Eloxatin) is used with infusional 5-FU/LV to treat cancer of the colon or rectum in patients whose disease has recurred or progressed during or within six months of completion of first-line therapy.

Fulvestrant (Faslodex) is for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

People with gastrointestinal disorders

Tegaserod maleate (Zelnorm) is the first drug approved for the short-term treatment of women with irritable bowel syndrome whose primary bowel symptom is constipation. The medicine is the first agent in a new class of drugs called serotonin-4 receptor agonists (5HT4 agonist) developed to target the gastrointestinal tract.

Reasons for approval delays studied

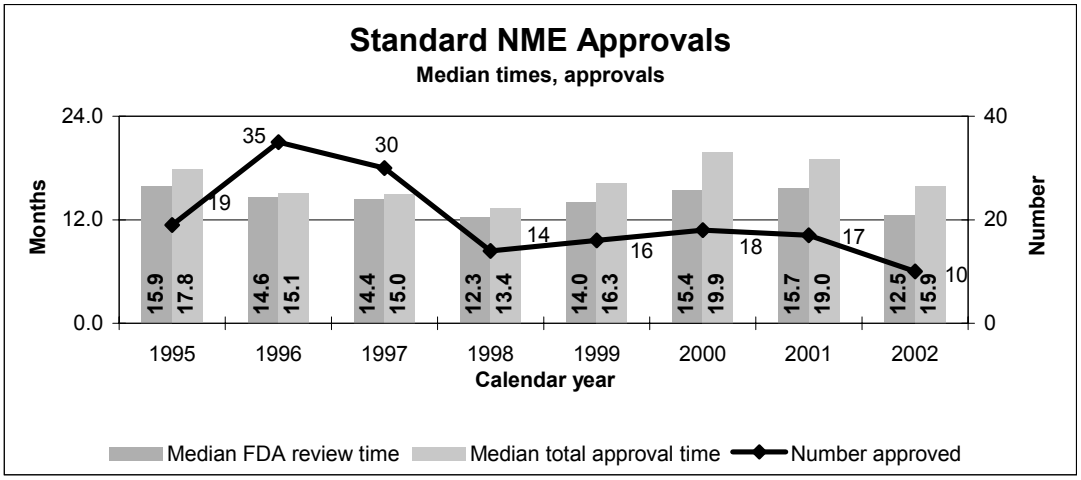
We examined reasons for approval delays on first cycle reviews for standard and priority new molecular entities in 2000 and 2001.

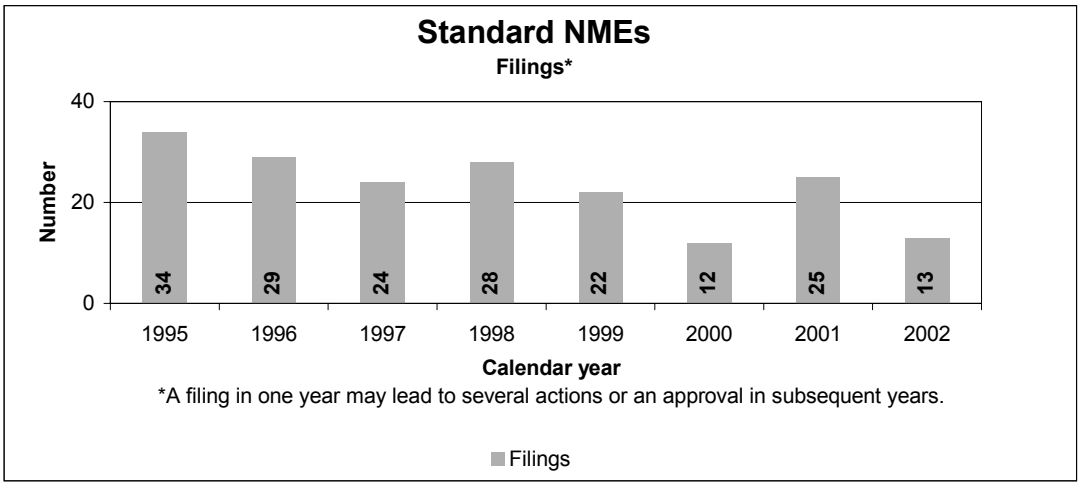
Standard NMEs:

- **Safety issues (38 percent)**
- **Efficacy issues (21 percent)**
- **Manufacturing facility issues (14 percent)**
- **Labeling issues (14 percent)**
- **Chemistry, manufacturing, and controls issues (10 percent)**
- **Submission quality (3 percent)**

Priority NMEs:

- **Chemistry, manufacturing and controls issues (46 percent)**
- **Safety issues (27 percent)**
- **Efficacy issues (18 percent)**
- **Manufacturing facilities issues (9 percent)**





New molecular entities

- **Adefovir dipivoxil (Hepsera)**
- **Aripiprazole (Abilify)**
- **Atomoxetine hydrochloride (Strattera)**
- **Dimyristoylphosphatidylcholine and perflexane (Imagent Kit for the Preparation of Perflexane Lipid Microspheres)**
- **Eletriptan hydrobromide (Relpax)**
- **Eplerenone (Inspra)**
- **Ezetimibe (Zetia)**
- **Fulvestrant (Faslodex)**
- **Icodextrin (Extraneal)**
- **Nitazoxanide (Alinia)**
- **Nitisinone (Orfadin)**
- **Olmesartan medoxomil (Benicar)**
- **Oxaliplatin (Eloxatin)**
- **Sodium oxybate (Xyrem)**
- **Tegaserod maleate (Zelnorm)**
- **Treprostinil sodium (Remodulin)**
- **Voriconazole (Vfend)**

People with heart disease

Eplerenone (Inspra) treats high blood pressure both alone and in combination with other antihypertensive therapies. The drug works by selectively blocking aldosterone, a hormone that plays a role in regulating electrolyte and water balance.

An imaging agent, *dimyristoylphosphatidylcholine and perflexane (Imagent Kit for the Preparation of Perflexane Lipid Microspheres),* can help in the diagnosis of heart disease. It is intended for use in patients with suboptimal ultrasound images of the heart. It helps distinguish between normal and abnormal heart structure and motion, two primary indicators of cardiac health.

Olmesartan medoxomil (Benicar) treats high blood pressure.

People with pulmonary hypertension

Treprostinil sodium (Remodulin) is a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension, a disease in which blood pressure in pulmonary arteries rises to life-threatening levels. The orphan priority drug received accelerated approval.

Standard new molecular entities

- **10 approvals**
- **Median review time: 12.5 months**
- **Median approval time: 15.9 months**
- **13 filings**

Notable 2002 new drug approvals (continued)

People needing dialysis

Icodextrin (Extraneal) is a peritoneal dialysis solution that expands patients' options for effective fluid management in home-based peritoneal dialysis, a form of kidney dialysis.

Infectious diseases

Adefovir dipivoxil (Hepsera) is the first nucleotide analogue to be approved for the treatment of chronic hepatitis B.

Voriconazole (Vfend) is a triazole antifungal agent indicated as the primary treatment for acute invasive aspergillosis and as a salvage treatment for rare but serious fungal infections. It is available in both oral and intravenous formulations.

Ribavirin (Copegus), in a new formulation, received a priority review for treatment of hepatitis C.

People with mental illness

Aripiprazole (Abilify), which is administered as a once-daily oral tablet, was shown in clinical studies to provide significant improvements in both the positive and negative symptoms of schizophrenia.

People with neurological disorders

Sodium oxybate (Xyrem), an oral solution, is the first drug approved for the treatment of cataplexy, a sudden loss of muscle tone associated with narcolepsy. The medicine is a Schedule III controlled substance.

Eletriptan hydrobromide (Relpax) acts on blood vessels and sensory nerve endings to relieve the symptoms of migraine attacks.

Pediatric uses

Atomoxetine sodium (Strattera) is the first major new treatment for attention-deficit/hyperactivity disorder in three decades. The drug works to prolong the presence in the brain of the chemical norepinephrine, which is involved in regulating attention and impulsivity levels. It provides full-day relief of symptoms without causing insomnia in most children and adults. It is the first drug approved to treat the condition in adults.

Nitazoxanide (Alinia), a priority orphan approval, is the first oral suspension medicine specifically approved for the treatment of diarrhea caused by two parasitic infections, cryptosporidiosis and giardiasis in children 1 to 11 years old. In compromised children, these infections have been associated with malnutrition and impaired growth.

Nitisinone (Orfadin), a priority orphan approval, is used to treat hereditary tyrosinemia type I, a life-threatening metabolic disorder that affects fewer than 100 children the United States. The disease, which results from the lack of an enzyme to break down the amino acid tyrosine, usually results in progressive liver disease and liver cancer.

Office-based addiction treatment

***Buprenorphine hydrochloride (Subutex)* and the combination of *buprenorphine and naloxone (Suboxone)* treat opiate addiction by preventing symptoms of withdrawal from heroin and other opiates.**

These orphan drugs are the first treatments of opiate dependence that can be prescribed in an office setting under the Drug Addiction Treatment Act of 2000.

Internet resources for drug review statistics

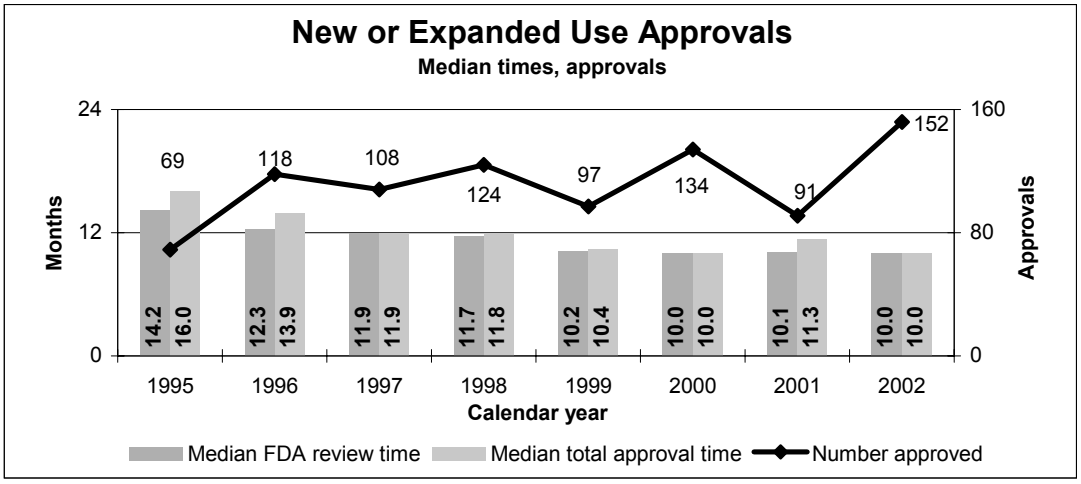
Other drug review statistics are available on our Web site at http://www.fda.gov/cder/rdmt/default.htm.

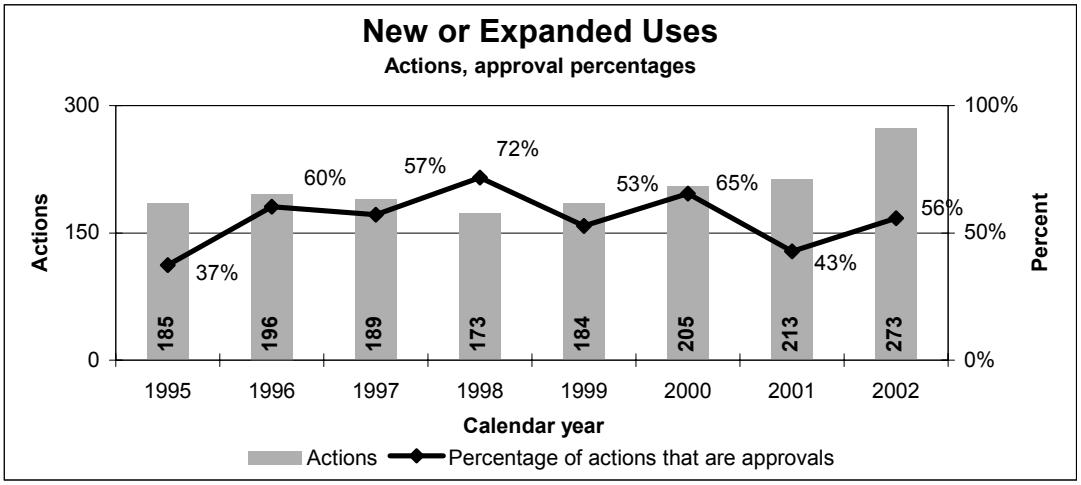
Chemical warfare antidote

***Atropine and pralidoxime chloride (ATNAA),* sponsored by the U.S. Army, is for use as an antidote to nerve agent exposure** **(page 6).**

People with eye disease

***Cyclosporine (Restasis),* in a new ophthalmic emulsion formulation, received a priority review for treatment of moderate to severe inflammation of the eye's cornea and to restore and maintain normal tear secretion and surface integrity of the eye.**





Priority efficacy supplement reviews

- ☐ **Alosetron hydrochloride**
- ☐ **Anastrozole**
- ☐ **Argatroban**
- ☐ **Clopidogrel bisulfate**
- ☐ **Clozapine**
- ☐ **Imatinib mesylate**
- ☐ **Irbesartan**
- ☐ **Lansoprazole**
- ☐ **Latanoprost ophthalmic solution**
- ☐ **Linezolid (3 approvals)**
- ☐ **Losartan potassium**
- ☐ **Pravastatin**
- ☐ **Secretin (2 approvals)**
- ☐ **Tamoxifen citrate**
- ☐ **Vinorelbine tartrate**
- ☐ **Zoledronic acid**

Orphan new or expanded uses

- ☐ **Imatinib mesylate**
- ☐ **Secretin**

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.

We have a goal of reviewing standard supplements in 10 months and priority supplements in six months. The new and expanded use review statistics on this page include figures for both priority and standard applications. Priority and standard application review performance will be reported separately in the future to reflect better their different review goals.

Notable 2002 new or expanded use approvals

Anastrozole (Arimidex Tablets) is for adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Argatroban (Argatroban Injection), an anticoagulant, is for use in patients undergoing heart catherizations and have or are at risk for developing heparin-induced decreases in the number of blood platelets.

New or expanded uses (efficacy supplements)

- ☐ **152 approvals**
- ☐ **Median review time: 10.0 months**
- ☐ **Median approval time: 10.0 months**
- ☐ **19 priority reviews**
- ☐ **2 orphan uses**
- ☐ **273 actions**

Clopidogrel bisulfate (Plavix), a blood thinner, is now approved to treat acute coronary syndrome.

Clozapine (Clozaril) can be used to treat patients with schizophrenia or schizoaffective disorder who are at risk for emergent suicidal behavior.

Imatinib mesylate (Gleevec) is for treatment of gastrointestinal stromal tumor, which affects about 5,000 people in the United States each year. It is a tumor that generally arises within the stomach or intestinal tract and metastasizes within the abdomen or the pelvis. The drug was first approved in May 2001 for treatment of Philadelphia chromosome positive chronic myeloid leukemia.

Irbesartan (Avapro) and *losartan potassium (Cozaar)* can be used to treat kidney damage in people with Type 2 diabetes. Both belong to a class of high blood pressure drugs known as angiotensin II receptor blockers.

Latanoprost ophthalmic solution (Xalatan) is for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Secretin (SecreFlo for Injection), used for secretin stimulation testing, received two approvals for identification of pancreatic disorders.

Zoledronic acid (Zometa) is for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard therapy.

Irritable bowel syndrome treatment reintroduced

***Alosetron hydrochloride (Lotronex),* a treatment for diarrhea-predominant irritable bowel syndrome in women that had been withdrawn for safety reasons in 2000, was reintroduced with limited distribution and a risk management plan (page 31). The regulatory mechanism for reintroduction was a priority efficacy supplement.**

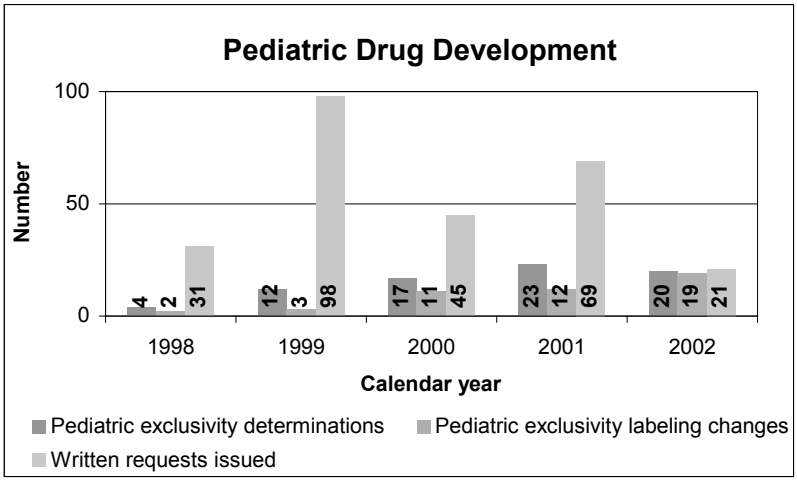
Priority pediatric labeling changes

When studying approved drugs in children, 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. Consistent with the mandate in the Best Pharmaceuticals for Children Act, these pediatric supplements received priority reviews last year:

- *Lansoprazole (Prevacid),* a treatment for gastric reflux disease, has updated labeling for children 1 to 11 years old.
- *Linezolid (Zyvox),* first in a new class of antibiotics, is for treating infections in children, including those caused by some antibiotic resistant organisms.
- *Pravastatin (Pravachol)* is for the treatment of an inherited form of high cholesterol in children 8 years old and older.
- *Tamoxifen citrate (Nolvadex)* labeling contains new information on pediatric studies for girls 2 to 10 years old with McCune-Albright syndrome.

Other pediatric exclusivity priority reviews

***Vinorelbine tartrate (Navelbine)* is a cancer treatment, and pediatric clinical trials are now described in the labeling.**



2002 pediatric drug statistics

- **20 exclusivity determinations made**
- **19 exclusivity labeling changes**
- **21 written requests issued**

Pediatric Rule thrown out; clearer authority sought

In October 2002, the U.S. District Court for the District of Columbia ruled that we lacked legislative authority to issue our Pediatric Rule and has barred us from enforcing it.

The government decided not to pursue an appeal and will work with Congress to pursue legislation requiring drug manufacturers to conduct appropriate pediatric clinical trials.

Internet resources

Our Web site for up-to-date pediatric labeling changes is at http://www.fda.gov/cder/pediatric/index.htm.

Pediatric Drug Development

Last year, we approved 19 labeling changes for pediatric uses. Also, we approved three new molecular entities (page 14).

As of April 1, 2003, we had received 328 proposed pediatric study requests from manufacturers, issued 272 written requests, made 84 exclusivity determinations and added pediatric use information to 50 labels.

The *Best Pharmaceuticals for Children Act of 2002* renewed our authority to grant six months of additional 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 mandates a six-month priority review for a pediatric supplement submitted in response to a written request.

The law also authorizes the National Institutes of Health to contract for pediatric studies for drugs that lack patent protection or other marketing exclusivity, referred to as "off-patent" drugs. In consultation with us, the NIH obtained input from outside pediatric experts to identify the priority off-patent drugs for which pediatric studies are needed. A list of 12 of these drugs was published in January 2003, and contracts for testing them will publish later in 2003.

Pediatric exclusivity has helped us uncover important dosing and safety information, such as drug effects on growth, to help healthcare providers use drugs to treat children more confidently. The absence of pediatric testing and labeling poses significant risks for children. Children may be exposed to ineffective treatment through underdosing. Inadequate dosing information exposes children to the risk of adverse reactions without the benefit of efficacy; however, overdosing may pose greater risk of adverse reactions. Young patients may not benefit from therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication. The failure to produce drugs in dosage forms that can be used by young children such as liquids or chewable tablets can also deny them access to important medications.

Conditions with approved pediatric labeling

- **Abnormal heart rhythms**
- **Allergies**
- **Anesthesia and sedation**
- **Asthma**
- **Atopic dermatitis**
- **Attention deficit/ hyperactivity disorder**
- **Diabetes mellitus (Type 1 and Type 2)**
- **Gastroesophageal reflux**
- **High blood pressure**
- **High cholesterol**
- **High eye pressure**
- **HIV infection**
- **Infectious diseases**
- **Juvenile rheumatoid arthritis**
- **Low levels of calcium associated with severe kidney disease**
- **Obsessive compulsive disorder**
- **Pain**
- **Seizures**
- **Severe recalcitrant nodular acne**

Electronic Submissions

The number of new drug applications submitted electronically continues to grow. Last year's electronic submissions were double the number submitted in the previous year. Overall, we had more electronic submissions last year than in the previous four years combined.

The number of participating companies and the number of applications with electronic components continues to grow. About 70 percent of newly filed new drug applications have an electronic component, and two-thirds are completely electronic. About 17 percent of new or expanded use applications have an electronic component with 85 percent being completely electronic.

Last year, we began receiving generic drug applications in electronic format. We continue to receive electronic drug advertising material in electronic format.

Reviewers continue to find that electronic submissions provided as described in our guidance documents allow them to be more efficient. Our training programs include hands on classroom training as well as on-site training to teams receiving electronic applications. This training improves the ability to use the submissions effectively.

We have been working with other regulatory agencies and pharmaceutical groups in the International Conference on Harmonization (page 38) to complete the electronic common technical document. In 2003, we expect to begin receiving investigational new drug applications, annual reports and Drug Master Files in e-CTD format.

In addition to receiving electronic applications, we have received over 22,000 electronic individual case safety reports from manufacturers. These reports are transmitted electronically and automatically entered into the Adverse Event Report System (page 27). This allows the reviewers to evaluate the reports sooner and reduces our resources for entering information into the system.

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.

Last year, we began seeking public comment on a draft guidance that will provide sponsors with advice on how to establish pregnancy exposure registries. Registries that prospectively monitor the outcomes of pregnancies in women exposed to a specific drug can provide clinically relevant human data for treating or counseling patients who are pregnant or anticipating pregnancy.

Internet resources

More information on our electronic submissions program is at http://www.fda.gov/cder/regulatory/ersr/.

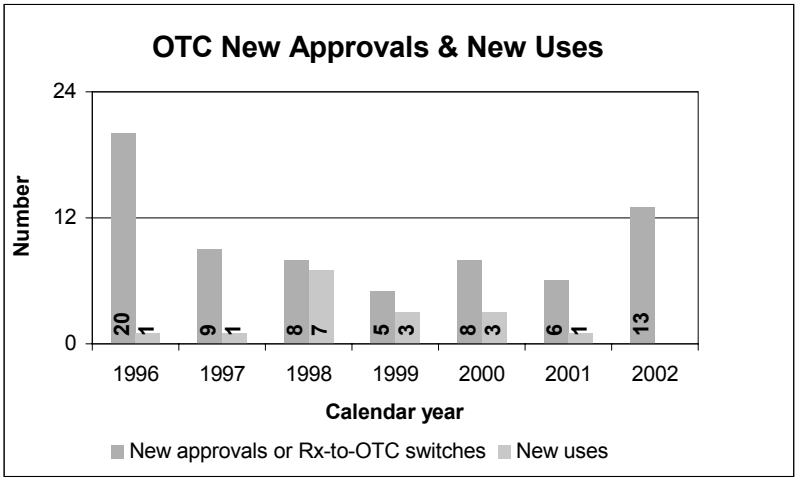
Antimicrobial resistance

The emergence of drug-resistant bacteria is considered to be a major threat to the public health. We developed a regulation outlining new labeling designed to help reduce the development of drug-resistant bacterial strains. This rule became final in February 2003 and aims at reducing the inappropriate prescription of antibiotics to children and adults for common ailments such as ear infections and chronic coughs.

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

Public meeting on antimicrobial drug development

We along with industry and academia cosponsored a two-day public meeting to explore the scientific and regulatory issues in developing drugs to treat highly resistant pathogens.



Improved labels for OTC medicines

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

A mandatory changeover to the new labels, titled "Drug Facts," began in 2002.

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.

Over-the-Counter Drug Review

We approved 13 new drugs or Rx-to-OTC switches, 11 of which can be used by children. Among the approvals are:

- *Guiafenesin extended release 600 mg tablets (Mucinex)* helps loosen phlegm and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive for adults and children 12 years old and older.
- *Ibuprofen (Ibuprofen 200 mg Liquigel Tabs)* provides temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, and menstrual cramps, and to temporarily reduce fever, for adults and children 12 years of age and older.
- *Ibuprofen/pseudoephedrine (Advil Cold & Sinus Liquigels)* provides temporary relief of symptoms associated with the common cold, sinusitis, or flu, including nasal decongestion, headache, fever, body aches and pains, in adults and children 12 years of age and older.
- *Ibuprofen/pseudoephedrine (Children's Advil Cold Suspension)* provides temporary relief of symptoms associated with the common cold, sinusitis, or flu, including nasal decongestion, headache, fever, body aches and pains, in children 2 to 11 years of age.
- *Ibuprofen/pseudoephedrine/chlorpheniramine (Advil Allergy Sinus Caplet)* provides temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold in adults and children 12 years of age and older.
- *Nicotine polacrilex (Commit Lozenge 2 mg and 4 mg)* reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking, for use in adults 18 years of age and older.
- A *nicotine transdermal system (Nicotrol TD)* is approved to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking, for use in adults 18 years old and older.

Over-the-counter drug statistics

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

First nonsedating antihistamine approved for OTC use

Loratadine provides temporary relief of symptoms of hay fever or other upper respiratory allergies, runny nose, sneezing, itchy, watery eyes and itching of the nose or throat.

We approved six formulations. The first three are for people age 6 and older, the syrup is for those as young as 2, while combinations with a decongestant are for those 12 and older.

□ Loratadine (Alavert)

□ Loratadine (Claritin)

□ Loratadine (Claritin Reditabs)

□ Loratadine (Claritin Syrup)

□ Loratadine and pseudoephedrine (Claritin-D 12)

□ Loratadine and pseudoephedrine (Claritin-D 24 Hour)

Generic Drug Review

We approved 321 generic drug products in 2002, including 80 products that represent the first time a generic drug was available for the brand-name product. The median approval time for generic drugs was 18.3 months.

The median statistic for total approval time has hovered at about 18 to 19 months for five years. We are making changes to decrease the overall time to approval of applications. We are improving the efficiency of our generic drug review process and increasing the number of chemistry reviewers by one-third.

Notable 2002 generic drug approvals

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

- *Loratadine* (Claritin) used as an antihistamine.
- *Isotretinoin* (Accutane) used to treat severe acne.
- *Potassium Iodide Tablets* for use in protecting the thyroid gland in the event of a radiation emergency.
- *Metformin* (Glucophage) used to treat diabetes.
- *Cefuroxime Axetil* (Ceftin) used to treat infections.

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 63 tentative approvals and 20 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 321 approvals in 2002 represent conversions of tentative approvals granted in 2002 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://www.fda.gov/cder/ogd/.

Electronic submissions

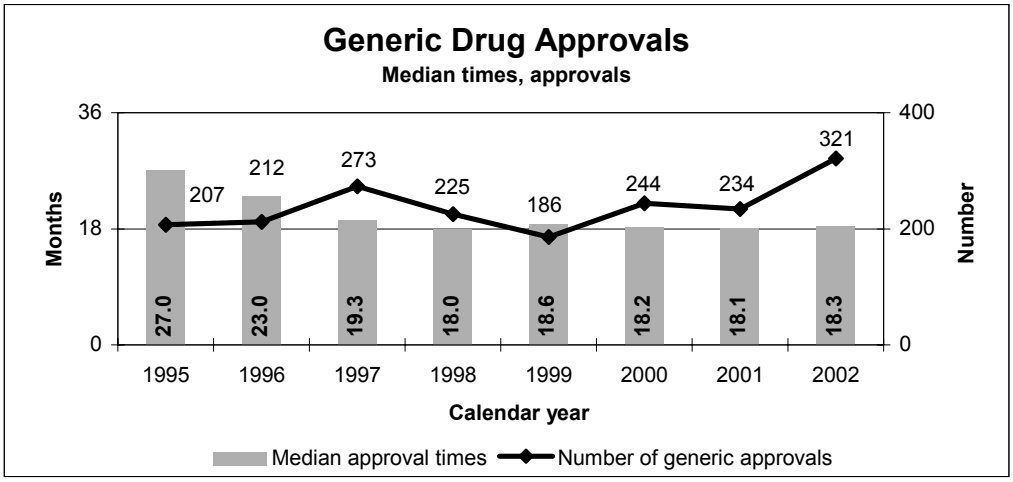
Through public presentations, we are encouraging the generic drug industry to submit their applications electronically. More information electronic submissions is on page 18.

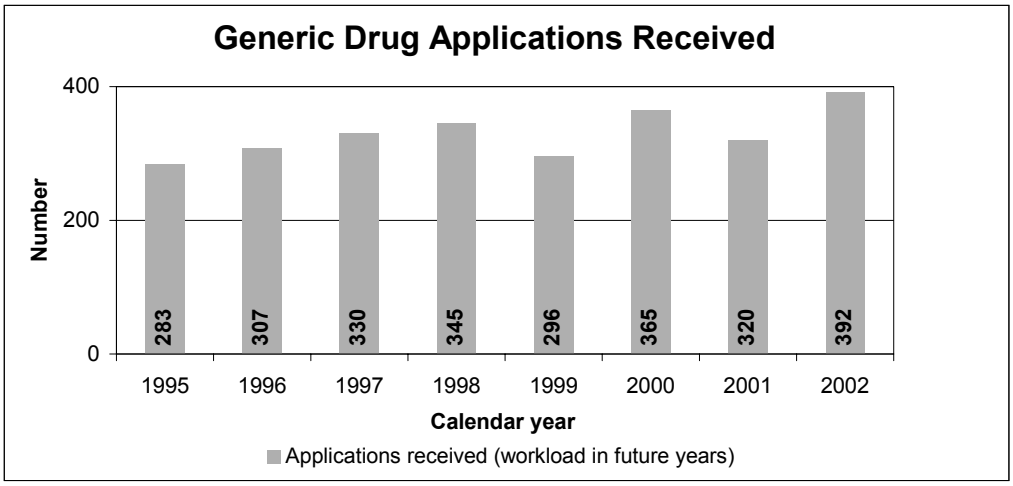
How we approve generic drugs

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

- 321 generic drug approvals
- Median approval time: 18.3 months
- 392 receipts
- 63 tentative approvals
- 20 approvables

Tentative approvals

- 1995: 15
- 1996: 25
- 1997: 40
- 1998: 40
- 1999: 56
- 2000: 61
- 2001: 73
- 2002: 63

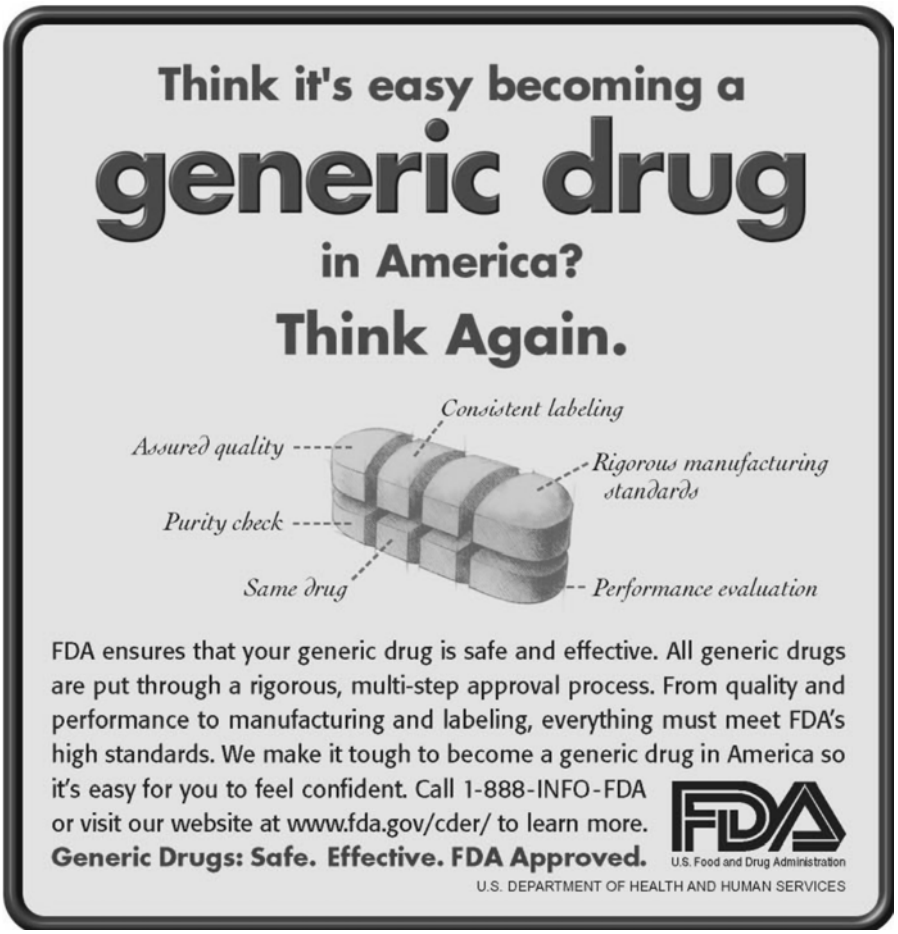
Generic drugs a top priority

"Encouraging rapid and fair access to generic medications after the expiration of appropriate patent protection" is one of the major priorities for new FDA Commissioner Mark McClellan, M.D., Ph.D. He noted that the generic drugs play an essential role in promoting the health of Americans.

He assured the generic industry that we would work to reduce the time to approval for generic products and that generics must be safe and effective.

We will work to identify steps such as improving guidance and communication to help improve the overall quality of applications thus gaining faster approvals.

A copy of his remarks is available at http://www.fda.gov/oc/speeches/2002/gpha.html.



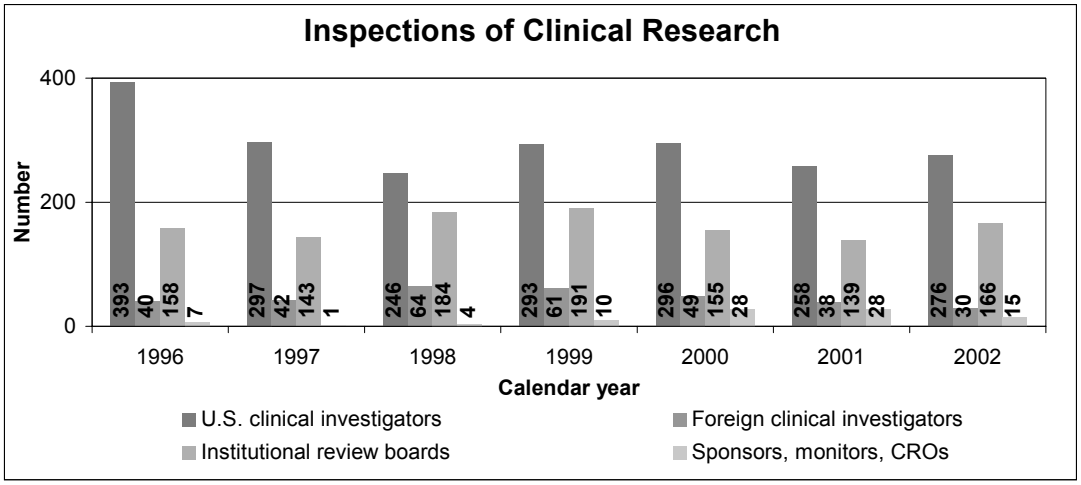
Building consumer confidence in generic drugs

Internet availability

Our generic drug public service announcements are at http://www.fda.gov/cder/consumerinfo/generic_info/default.htm.

We launched our program to promote consumer confidence in the safety and effectiveness of generic drugs. We are informing health care practitioners and consumers about the rigorous review and approval process that generic drugs undergo before we approve them for sale in this country. Partnerships and networking with other groups are helping us to bring the message to more people. The consumer education program includes:

- Newspaper articles. For example, 420 articles have appeared in local newspapers in 30 states.
- Posters, brochures and give-away items.
- Public service announcements, which have appeared in magazines such as *JAMA, Forbes, Chain Drug Review* and *Geriatric Times.*
- Advertisements on buses in Chicago, Los Angeles and New York.
- We are developing a Web-based course on generic drug safety and effectiveness for pharmacists and other health professionals.



Inspections of clinical research in 2002

We conducted a total of 487 inspections of clinical research:

- **276 U.S. clinical investigators**
- **30 foreign clinical investigators**
- **166 institutional review boards**
- **15 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 490 inspections of clinical research in 51 countries from 1980 to 2002.

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.**

User Fee Program

Americans deserve timely access to potentially lifesaving new drugs as soon as possible once they are proven safe and effective. The *Prescription Drug User Fee Act of 1992* received its third five-year extension last year, known as PDUFA III. This reauthorization will ensure that we have the expert staff and resources to review applications promptly and get safe, effective new drugs into the hands of the people who need them.

PDUFA III maintains the high review performance goals of PDUFA II, which included reduced drug review times and increased and accelerated our consultations with drug sponsors. In addition, PDUFA III remedies resource shortages that affected the program in recent years.

Under PDUFA II, we collected significantly less in user fees than estimated due to a reduced number of new drug applications and an increased proportion of submissions whose fees were waived. The reauthorization puts the user fee program on a sound financial basis.

We are also concerned about the safety of new medicines following approval. In recent years, 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.

PDUFA III allows us to spend some user fees to increase surveillance of the safety of medicines during their first two years on the market or three years for potentially dangerous medications. It is during this initial period, when new medicines enter into wide use, that we are best able to identify and counter adverse side effects that did not appear during the clinical trials.

Full information on PDUFA III, including the latest performance and procedure goals, is on the Web at http://www.fda.gov/oc/pdufa/PDUFA3.html.

User fee performance

Under legislation authorizing us to collect user fees for drug reviews, we agreed to specific performance goals for the prompt review of submissions.

- **We met or exceeded 12 of the 14 performance goals for the fiscal year 2001 receipt cohort, the latest year for which we have full statistics.**
- **In addition to surpassing all goals for original new drug applications in fiscal year 2001, we exceeded all three of the goals for new molecular entities.**
- **We are on track for meeting or exceeding all of the user fee performance goals for fiscal year 2002.**

Internet resources for user fees

Our user fee Web site has links to more documents and information including our user fee performance report to Congress.

The page is at http://www.fda.gov/cder/pdufa/default.htm.

2

DRUG SAFETY AND QUALITY

Mission

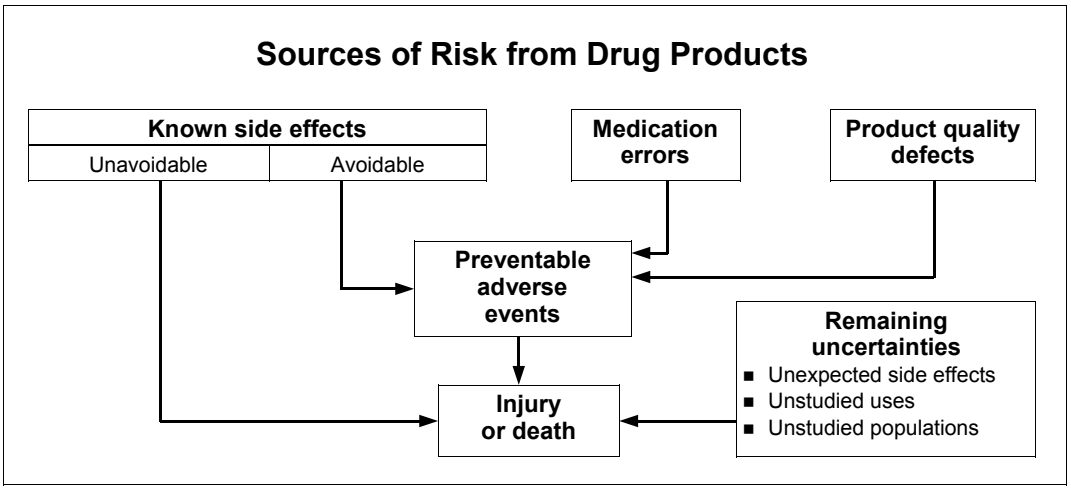
Protect the public health by ensuring that human drugs are safe and effective.

The practical size of premarketing clinical trials means that we cannot learn everything about the safety of a drug before we approve it. Therefore, a degree of uncertainty always exists about the risks of drugs. This uncertainty requires our continued vigilance, along with that of the industry, to collect and assess data during the post-marketing life of a drug.

We monitor the quality of marketed drugs and their promotional materials through product testing and surveillance. As Americans are increasingly receiving the benefits of important new drugs before they are available to citizens of other countries, we must be especially vigilant in our surveillance. In addition, we develop policies, guidance and standards for drug labeling, current good manufacturing practices, clinical and good laboratory practices and industry practices to demonstrate the safety and effectiveness of drugs.

Highlights of drug safety and quality activities in 2002 include:

- Processing and evaluating 320,860 reports of adverse drug events, including 20,455 submitted directly from individuals.
- Reviewing about 3,000 reports of medication errors, half of which are due to error-prone labeling.
- Mandating that five drug products be dispensed with specific consumer information to help make sure that they are used safely and effectively.
- Issuing 688 letters to help ensure that the promotion of drug products presents a fair balance of risks and benefits and isn't false or misleading.
- Issuing warnings for misbranded or fraudulent products and products marketed as "street drug alternatives."
- Issuing 4,733 export certificates for U.S. drug products.
- Developing technology for the rapid identification of counterfeit drug products.
- Conducting shelf-life extensions for stockpiled drugs.



Types of Risks from Medicines

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

Known side effects. Predictable adverse events are identified in the drug's labeling. 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.

Drug Safety

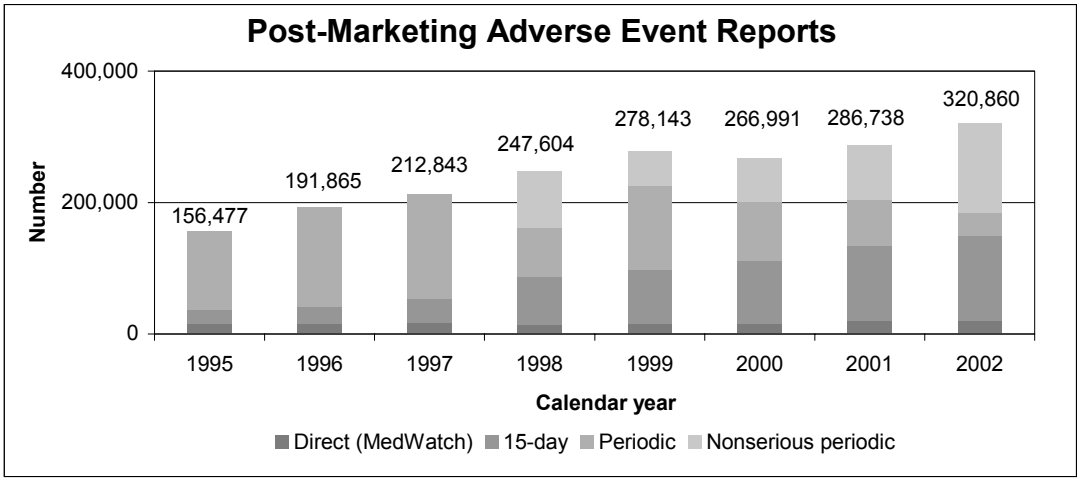
We evaluate the ongoing safety profiles of drugs available to American consumers using a variety of tools and disciplines. We maintain a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process. We monitor adverse events such as adverse reactions, drug-drug interactions and medication errors.

Medication error prevention

We work hard to ensure the safe use of drugs we approve by weeding out brand names that look or sound like the names of existing products. We identify and avoid brand names, labels and packaging that might contribute to problems or confusion in prescribing, dispensing or administering.

We review about 250 reports of medication errors each month. About half are due to error-prone labeling such as look-alike labels, poor package design and confusing names.

Our comprehensive Web site on medication errors is at http://www.fda.gov/cder/drug/MedErrors/default.htm.



Adverse event reporting

In 2002, we received 320,860 reports of suspected drug-related adverse events:

- **20,455 MedWatch reports directly from individuals**
- **128,869 manufacturer 15-day (expedited) reports**
- **171,546 manufacturer periodic reports (35,095 serious and 136,451 nonserious)**

We have access to commercial databases that contain non-patient-identifiable information on the actual use of marketed prescription drugs in adults and children. This dramatically augments our ability to determine the public health significance of adverse event reports we receive.

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 may include new labeling, drug names, packaging, "Dear Health Care Practitioner" letters, education or special risk communications, restricted distribution programs or product marketing termination.

Adverse Event Reporting System

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.

AERS on Internet

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

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. Electronic submissions into AERS represent 15 percent of the total expedited reports we received. We estimate the cost of receiving a report is cut from $31 per report to $3 to $19 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.

MedWatch Outreach and Reporting

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.

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 increased to about 30,000.

We issued 36 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.

Medication Guides

We may require specific written patient information for selected prescription drugs that pose a serious and significant public health concern. This information is called a Medication Guide. Medication Guides must be distributed to patients with each prescription dispensed. We require Medication Guides when the information is necessary for patients to use the product safely and effectively or to decide whether to use or to continue to use the product. Last year, we approved Medication Guides for four innovator products and one generic product:

- Alosetron (Lotronex).
- Isotretinoin (Amnesteem), generic product; Medication Guide previously approved for Accutane.
- Ribavirin (Copegus).
- Sodium oxybate (Xyrem).
- Teriparatide, rDNA origin (Forteo).

Patient information for prescription drugs

We continued our research and evaluation activities in support of the private sector providing patients with useful information about their prescription drugs. The target goal for 2006 is for 95 percent of patients to receive useful information with new prescriptions. This past year we worked on evaluating the written patient medication information materials they received.

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

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 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.

Drugs with special safety restrictions

Controls on 10 prescription drugs include limiting distribution to specific facilities; limiting prescription to physicians with special training or expertise; or requiring certain medical tests with their use.

Consumers should not buy these drugs over the Internet.

As of April 30, 2003, these drugs are:

□ Alosetron

□ Bosentan

□ Clozapine

□ Dofetilide

□ Fentanyl citrate

□ Isotretinoin

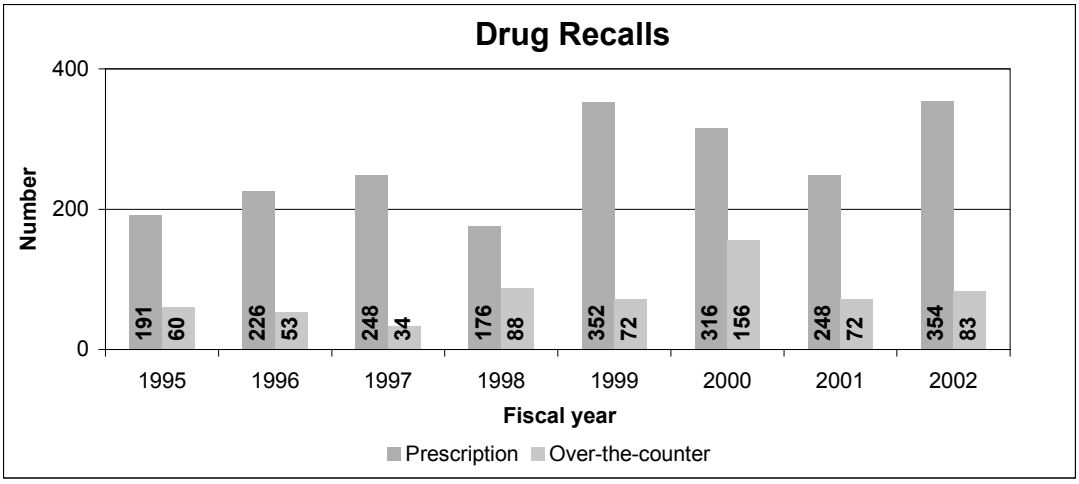
□ Mifepristone

□ Sodium oxybate

□ Thalidomide

□ Trovafloxacin mesylate or alatrofloxacin mesylate injection

More information is at http://www.fda.gov/oc/buyonline/consumeralert120902.html.



Drug recalls in fiscal year 2002

- **354 prescription drugs**
- **83 over-the-counter 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.

No safety-based withdrawals in 2002

In some cases, there is an intrinsic property of a drug that makes it necessary to withdraw the drug from the market for safety reasons. There were no drugs withdrawn from the U.S. market last year for safety reasons.

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.

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.

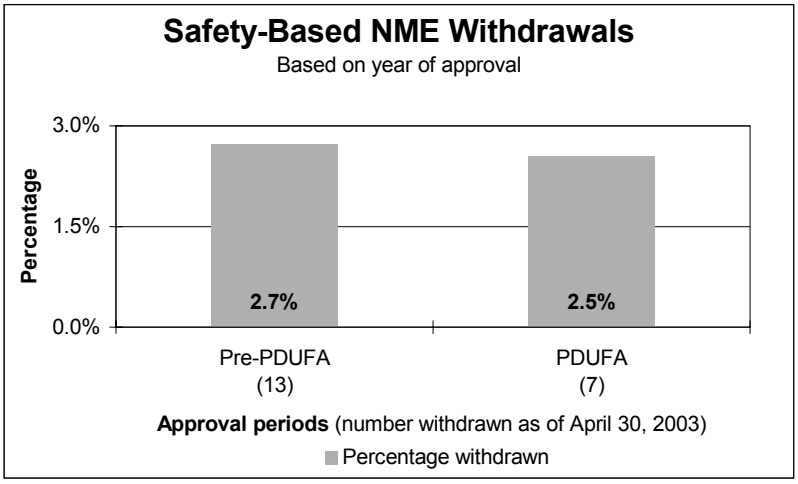
Top 10 reasons for drug recalls in fiscal year 2002:

- **Penicillin cross contamination**
- **Lack of assurance of sterility**
- **Labeling: wrong or incorrect expiration date**
- **Subpotency**
- **Dissolution failure**
- **Stability data do not support expiration date**
- **Labeling: incorrect product or mispacking/ miscarton**
- **Particulate matter**
- **cGMP deviations: failure to perform or document performance of requirement**
- **Foreign substance**

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)**



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, 2002, we approved 275 NMEs, and 7 (2.5 percent) have been withdrawn. Nearly all drugs we approved in this period were reviewed under PDUFA goals.

Risk management plan for alosetron

Immediately after the announcement of the safety-related withdrawal of alosetron in 2000, distraught patients, stunned that this therapy had been taken away from them, began to contact us demanding access to a drug they characterized as "giving them their lives back."

Alosetron, a treatment for diarrhea-predominant irritable bowel syndrome in women, had been withdrawn because outcomes from ischemic colitis, a known side effect, were more serious than predicted by the results of clinical trials and because of serious complications of constipation.

We worked with the manufacturer to compile a formal risk management program for alosetron, which we approved last year. This program includes:

- A prescribing program encompassing physician qualifications, physician agreements and a prescription sticker procedure.
- An education program for physicians, pharmacists and patients.
- Commitments by the manufacturer to report adverse events.
- An evaluation of program effectiveness.

The indicated patient population was narrowed, and a lower starting dose was specified in the label.

We have approved a number of programs designed to limit the risks of specific drugs. In the case of certain drugs such as thalidomide and clozapine, these programs are of proven benefit.

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)**

*Returned to market in 2002 with restricted distribution.

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 2002, we issued 186 advisory letters to companies regarding their promotional materials for launch campaigns.

We issued 304 other advisory letters to the industry regarding proposed promotional pieces, both professional and consumer directed. In addition, we issued 161 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

Regulatory actions

We issued 37 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, oral representations, Internet sites, plus traditional materials such as journal advertisements and sales brochures. We are also making sure that our warning and untitled letters will stand up in court, to provide more effective deterrence to recurrent patterns of misleading advertising.

Direct-to-consumer promotion

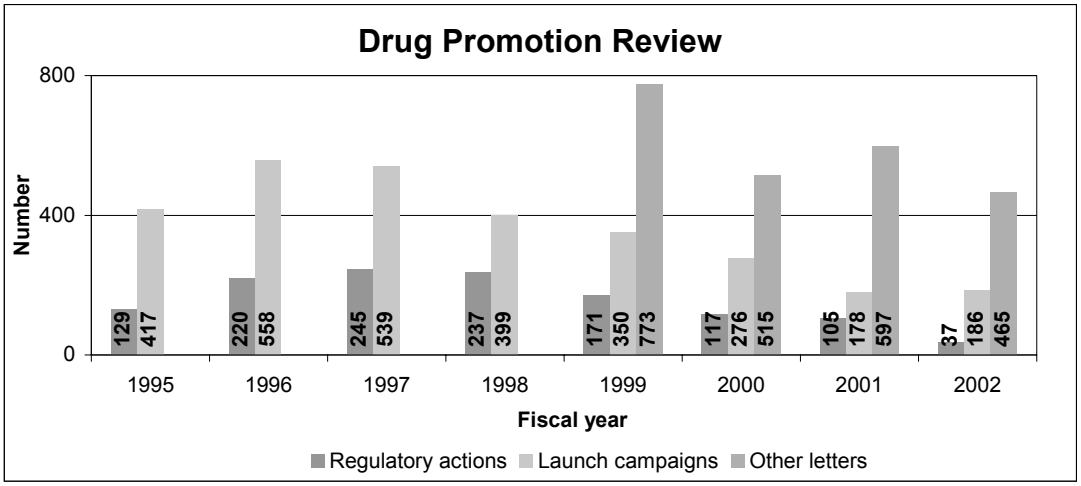
Included in our letters were 188 regarding direct-to-consumer promotion. This compares with 190 letters in 2001. Of last year's letters, 36 were for launch campaigns, 142 for non-launch advisories, and 10 were regulatory letters.

We are working on improving our oversight of DTC advertising. Evidence from our studies as well as those conducted by consumer groups and other entities consistently shows that DTC ads lead to more patients seeking care for undertreated conditions. This often results in a different treatment that is more appropriate for the patient than the advertised drug. But physicians and others are concerned that consumers may not always get a balanced

Proposed rule to revise prescription drug labeling

We continued to work on a final rule, based on comments from the public to our proposal in 2001.

The main purpose of labeling is to communicate essential information about prescription drugs to health care providers.



Drug promotion review statistics

We issued a total of 688 drug promotion letters last year.

- **37 regulatory action letters**
- **186 launch campaigns**
- **465 advisory acknowledgement or closure letters**

view of the benefits and risks of a product. Consequently, we are working on the issue of how manufacturers could provide clearer and more concise information for consumers derived from the drug's approved labeling.

DTC advertising surveys

We completed two national telephone surveys and conducted preliminary analyses. One survey of 943 consumers is a follow-up to the 1999 survey of patients' attitudes and behaviors associated with direct-to-consumer advertisements. The other is a new survey of 500 physicians' attitudes and behaviors associated with direct-to-consumer advertisements.

Preliminary findings of the two surveys include:

- About 40 percent of patients and about 45 percent of physicians feel DTC advertising encourages information seeking about potentially serious medical conditions.
- About 80 percent of patients and 70 percent of physicians feel DTC advertising creates awareness of new treatments.
- About 40 percent of patients and 75 percent of physicians feel DTC advertising make it seem that the drug will work for everyone or make the patients think the drug works better than it does.
- About 40 percent of physicians believe that patients understand the possible risk and negative effects of drugs, compared to 80 percent who believe patients understand the benefits and positive effects.
- Over half of physicians report feeling at least a little pressure to prescribe when asked for a prescription.

More is available at http://www.fda.gov/cder/ddmac/globalsummit2003/index.htm.

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.

Reporting systems for drug quality problems

Two important post-marketing 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 drug quality defects associated with marketed drugs. We evaluate and prioritize the reports to determine potential health hazards and industry trends. These reports significantly assist us in developing special programs and surveys. We identify significant health hazards associated with drug manufacturing, packaging and labeling and initiate field inspection 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 possible 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.

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 according to safety considerations, effects on public health or subversion of the new drug approval process.

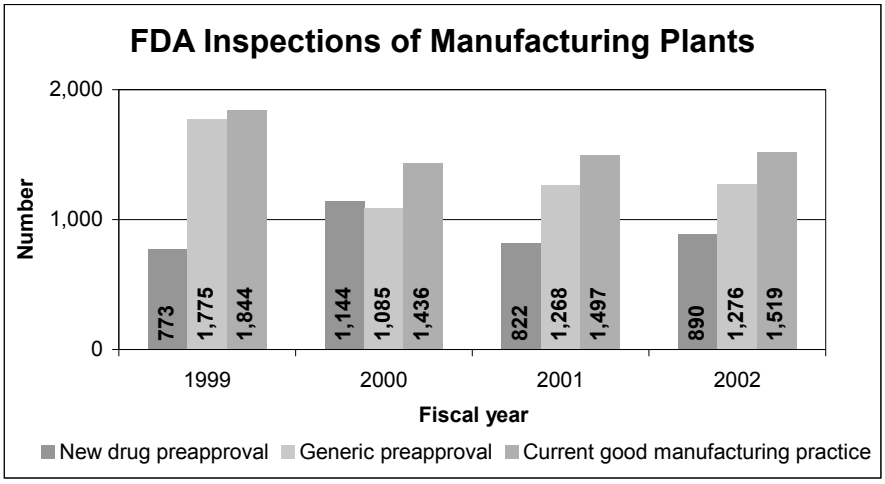
Risk-based surveillance sampling of drugs

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

- ☐ **Microbial/endotoxin concerns**
- ☐ **Stability concerns**
- ☐ **Sterility issues**
- ☐ **Dissolution issues**
- ☐ **Impurities/ contaminants**
- ☐ **Product quality history**
- ☐ **Counterfeit drugs**
- ☐ **History of violations**



Protecting consumers from misbranded or fraudulent drugs

We protect consumers from mislabeled, fraudulent or hazardous products by identifying and taking steps to remove products that pose public health risk from the market. We issue enforcement letters and pursue enforcement actions such as seizures of violative products and injunctions against firms or individuals.

Last year, more than 30 such letters were issued based on misbrandings or fraudulent claims found in labeling and on Internet sites. These addressed various illegally marketed products, many masquerading as dietary supplements, including several containing androstendione, ephedra-related compounds or human growth hormone.

We also sent letters concerning "street drug alternatives," products intended for recreational use as alternatives to illicit controlled substances.

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.

Misbranded drugs, unsubstantiated claims

Mislabeled, fraudulent, hazardous products. We often encounter mislabeled and fraudulent products that make unsubstantiated claims. Consumers may use these products inappropriately or incorrectly. They may use a fraudulent product for treating a serious disease condition in place of an effective treatment or delay the use of effective treatment. For these reasons, products that are mislabeled, fraudulent or make unproven claims may pose a significant health risk.

Occasionally, fraudulent products may also contain toxic compounds that are likely to cause serious illness or injury. In addition, the marketing of products that are either mislabeled or fraudulent threatens to undermine the U.S. drug development and approval process as well as the ongoing over-the-counter drug review process.

Preapproval inspections

During fiscal year 2002, FDA evaluated:

- **890 plants in support of new drug applications**
- **1,276 domestic firms in support of generic drug applications**

Good manufacturing practice inspections

There were 1,519 good manufacturing practice inspections (1,109 non-gas) in fiscal year 2002.

- **We reviewed 28 field recommendations for regulatory action and approved 12. These included six injunctions, two seizures and four warning letters.**
- **We reviewed 210 foreign establishment inspection reports, resulting in one warning letter.**

Drug Product Quality Science

Laboratory support

Last year our efforts included:

- Rapid identification of counterfeit products using near-infrared spectroscopy and chemical imaging to discriminate drug products and raw materials.
- 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

Our goal for this initiative is to facilitate the introduction of new and emerging technologies that will improve the capability and efficiency of the pharmaceutical manufacturing 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. These systems involve in-line, on-line or at-line monitoring, measuring and controlling in manufacture of drug substance and drug products.

We are using a collaborative process to develop this initiative. 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.

We are encouraging the adoption of this technology in drug manufacturing because it can enhance process understanding, improve overall product quality and lead to increased efficiencies. This also addresses many of the objectives of the Pharmaceutical cGMPs for the 21st Century Initiative (page 4).

A steering committee comprised of senior FDA managers is involved in the development of a general guidance on the use of these new technologies. We have formed a special review team to evaluate process analytical technologies when used by the industry. On the team, our own chemistry reviewers and compliance officers will join FDA's field investigators on inspections.

By organizing public meetings and workshops, we have gathered information related to development and use of process analytical technologies and shared our own research data.

Microbiology

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

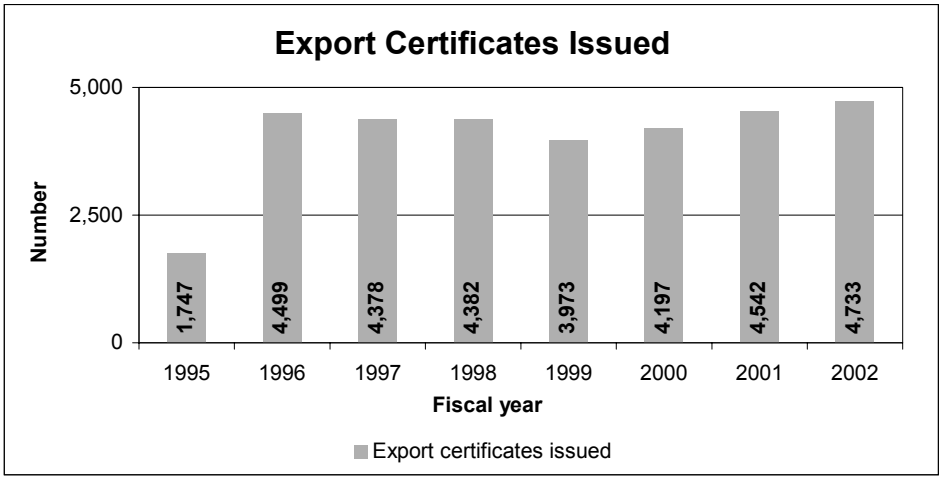
Our microbiology review assures the safety of sterile and non-sterile products through scientific evaluation and communication with the industry and assures consistency through guidance documents.

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 heave a new program to advance rapid microbiology test methods.

Export certificates issued in fiscal year 2002:

- **4,733**



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

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.

Highlights from 2002 include:

- Completing the electronic Common Technical Document.
- Publishing seven ICH documents.

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.

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.

Common Technical Document

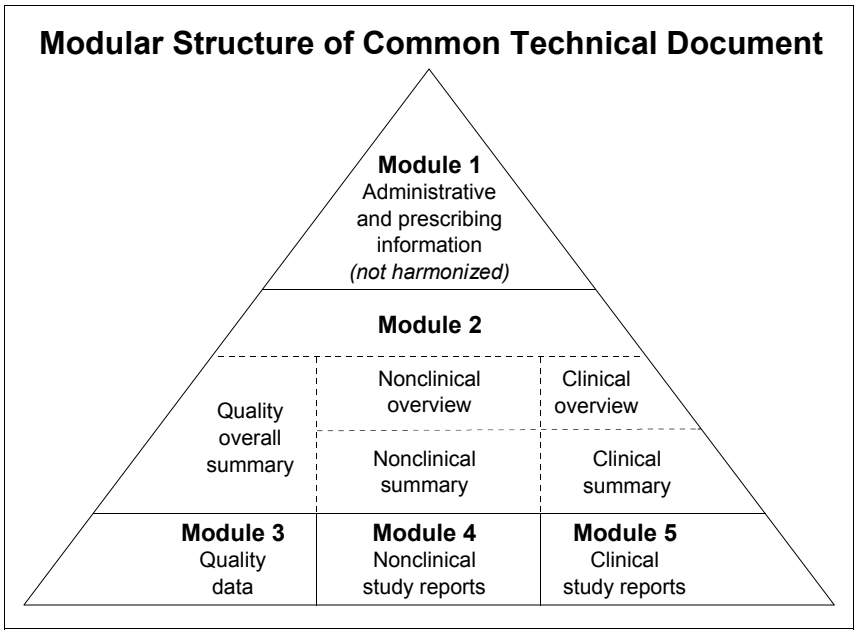
The ICH Common Technical Document allows data in the same format to be submitted to drug review authorities in all three ICH regions.

Last year, we completed work on making the document suitable for electronic submission.

ICH guidance documents

Last year we published seven ICH guidance documents.

As of April 30, 2003, we had published 45 final documents and eight drafts.



U.S.-European Union Mutual Recognition Agreement

This agreement would provide 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 would 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 would allow us to use an inspection report from one of our European counterparts as though it were our own, the actual regulatory decision would 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.

A planned three-year transition to full implementation has ended, and two important issues remain to be resolved:

- The European Union says it will not proceed until we provide a complete schedule for assessment of all of the member state authorities.
- We want assurance of being able to exchange information with regulators as they are found equivalent, rather than waiting for all of them to be done as the European Union has wanted.

MRA update

□ This past year we proposed a joint procedure providing for the exchange of inspection reports and provided an assessment of the progress made in exchanging certain product quality information. These issues were provided for review to the European Union.

□ Our audit team prepared to visit the second member state after substantially completing the first, but the assessment was put on hold by the European Union.

□ The European Union has not resumed their assessment of our system.

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.

4

COMMUNICATIONS

Highlights from 2002 include:

- Meeting almost weekly with outside experts on difficult scientific and public health issues.
- Responding to more than 73,000 individual requests for information.
- Receiving nearly 9 million visits and more than 163 million hits on our Internet information site, which has 50,000 pages and documents, five databases and 250,000 hyperlinks.

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 44,000 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.

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 analyze public comments on proposed new rules, and we seek and receive comments on our guidances to industry.

Risk management public hearing. We received valuable input about our ongoing efforts to improve our risk communication and to develop new and effective risk management tools. The purposes of the hearing were to:

- Obtain public input into improving risk management for prescription drugs.
- Identify stakeholders for future collaboration on risk management.
- Improve our understanding of existing risk management tools.
- Guide improvements in and creation of new tools
- Explore assessment strategies.

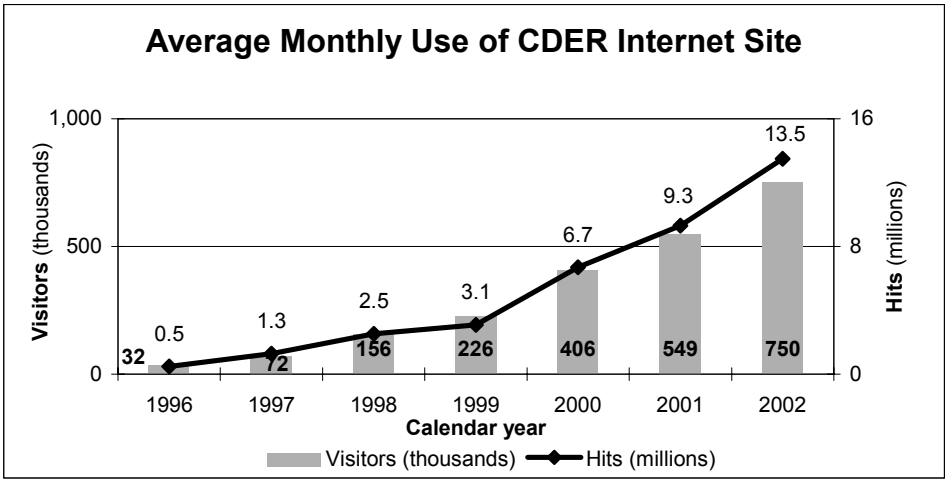
Workshops

- *New approach to plant inspections: Systems inspections.* To provide the widest possible industry access, this workshop was held in three locations.
- *Pediatric oncology drug development.* We obtained public input on various aspects of developing drugs to treat cancer in children, including prioritization of new and emerging agents, clinical trial design and access to new therapies.
- *Scientific workshops.* We held technical workshops to help identify scientific and regulatory issues in such fields as antimicrobial resistance, pharmacogenomics and pharmacogenetics, and drug substance and product specification.

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 final regulations, and we sought public comment on another three proposed regulations.
- *Guidances.* We published 11 guidances for industry that explain our position on best practices in scientific and technical areas. We published another 19 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 23 documents last year.
- *Trade press.* We responded to about 2,400 telephone and e-mail requests from the specialized press covering the pharmaceutical industry.
- *Exhibits*. We exhibited at 19 conferences, reaching an estimated audience of more than 111,000 consumers, educators and health care professionals.
- *Videoconferencing.* We held about 100 domestic and foreign videoconferences for academia, industry and associations.
- *CDER Live!* We produced two satellite television broadcasts and Web transmissions for a largely pharmaceutical audience estimated at over 5,000 viewers. The first program dealt with managing the risks of medicines, and the second highlighted new provisions in PDUFA III. Both programs featured our own and industry experts.
- *Drug reviews on Internet.* Our Internet site now contains our reviews of more than 200 approved new drugs or new uses for approved drugs.
- *Freedom of Information requests.* We responded to nearly 5,000 requests under the Freedom of Information Act.
- *General information requests.* We answered more than 32,000 telephone inquiries, 23,000 e-mails and 5,000 letters from consumers, health professionals and industry. We responded to 5,800 requests for documents and guidance publications.

Ombudsman's activity

In its seventh year, our ombudsman provided informal dispute resolution for both regulated industry and our own employees.

He provided information and guidance to industry, health professionals and consumers.

He helped management identify better ways of conducting business.

Lastly, he represented us in product jurisdiction issues submitted to FDA's Ombudsman's Office. This has been a particularly active area with the development of novel medical products.

Public education programs

- ☐ **Benefits vs. risks of medication use**
- ☐ **Buying drugs from outside the United States**
- ☐ **Buying prescription drugs online**
- ☐ **Drug interactions**
- ☐ **Generic drug quality**
- ☐ **Medical gas safety**

- ☐ **Misuse of prescription pain relievers**
- ☐ **Over-the-counter medicine labels**
- ☐ **Pregnancy and drug use**
- ☐ **Proper drug dosing for children**

Many of these are available on the Internet at http://www.fda.gov/cder/consumerinfo/DPAdefaultht.htm.

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
- *From Test Tube to Patient: New Drug Development in the United States:* http://www.fda.gov/fdac/special/newdrug/ndd_toc.html
- 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.

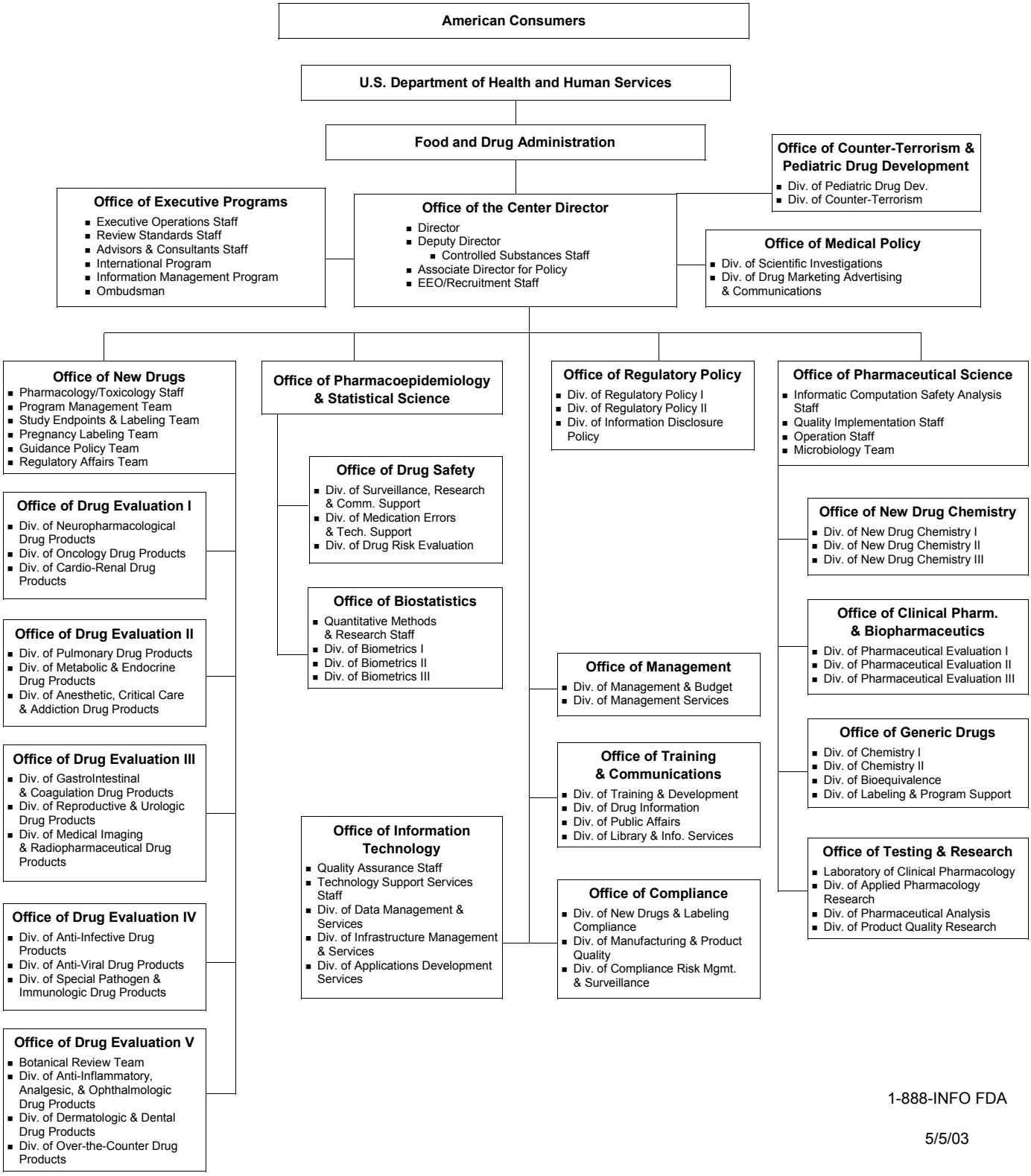
E-mail

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



1-888-INFO FDA

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