Center for Drug Evaluation and Research

REPORT TO THE NATION 2005

Improving Public Health Through Human Drugs

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U.S. Department of Health and Human Services

Food and Drug Administration
Center for Drug Evaluation and Research

U.S. Department of
Health and Human Services

Food and Drug Administration
Center for Drug Evaluation
and Research

Center for Drug Evaluation and Research ***2005***

Report to the Nation

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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 ensuring 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/2005/rtn2005.pdf.
- HTML: http://www.fda.gov/cder/reports/rtn/2005/rtn2005.htm.
- Slides: http://www.fda.gov/cder/reports/rtn/2005/rtn2005.ppt.

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Director's Message

I am pleased to provide our 2005 Report to the Nation from the Center for Drug Evaluation and Research.

In this report, we outline our initiatives and document our performance across our program areas during 2005. I am very proud to report that we have made substantial advances in identifying, managing and communicating safety-related issues. We have also made major advances in our efforts to improve the science of drug manufacturing.

As an organization, our Center is becoming more transparent, flexible, results-oriented and high-performing. These improvements are helping us maintain our place as the world leader in the review of the safety and efficacy of pharmaceutical products and in responding to the challenges of emerging public health threats. Through our participation in the FDA's Critical Path Initiative, we are playing a key role in helping to enhance the efficiency of drug development. Although, we play an important role in many areas, I would like to focus on just a few key efforts to give you an idea of what we are doing to ensure the success of our mission.

Addressing public concerns about drug safety

All medicines have benefits and risks. We have continued to focus on the importance of minimizing these risks and improving the way medicines are used. For example, during 2005, we issued 16 public health advisories about important drug safety issues. To sustain a multi-disciplinary, cross-Center approach to drug safety, we elevated the Office of Surveillance and Epidemiology (formerly the Office of Drug Safety) to report directly to the Center Director, and we appointed an Associate Center Director for Safety, Policy and Communication to focus on broad drug-safety policy and communication, including overseeing MedWatch and the Drug Safety Oversight Board staff. We anticipate that this reorganization will help us successfully promote the efficient assessment of and response to emerging safety issues.

In addition, the creation last year of the Drug Safety Oversight Board continues to foster a culture of openness and enhanced oversight around safety issues within the Center. In 2005, the board, under chair Douglas Throckmorton, M.D., the Center's Deputy Director, met five times and discussed critical safety issues including: long-acting beta agonists associated with more severe asthma episodes; *Clostridium sordellii* infections in patients taking mifepristone; antidepressants and suicidality; and the concerns with misuse of fentanyl transdermal patches. The board continues to work to help us improve how we identify and manage emerging drug safety issues and how we provide emerging information to health-care professionals and patients about the risks and benefits of medicines.

Improving our analytic and predictive tools to enhance drug development

One of the organizational changes announced in 2005 is a response to FDA's efforts to improve the science of medical product development, the Critical Path Initiative. To support this priority activity and to speed the movement of innovative therapies to patients, we created an Office of Translational Sciences, which includes the Office of Clinical Pharmacology and the Office of Biostatistics. The Office of Translation Sciences will support cross-cutting science programs such as the Regulatory Science and Review Enhancement Committee, the Research Involving Human Subjects Committee and the Critical Path Initiative. This office also has the important task of coordinating our collaborations with outside groups to help identify and resolve issues that are standing in the way of efficient drug development. We anticipate that, by putting these functions together into one office, we will be better able to promote these many scientific activities.

Improving our scientific tools to ensure product quality

We are continuing our work on the transformation of product manufacturing and how it is regulated, by extending the work done in the Agencywide Pharmaceutical cGMPs for the 21st Century initiative. Activities have included:

- Incorporating the fundamentals of quality systems into CDER operations.
- Restructuring the chemistry, manufacturing and controls review staff in the Office of New Drug Quality Assessment to provide for better efficiency.
- Rolling out concepts and philosophy of the changes to industry.
- Training chemistry, manufacturing and controls reviewers
- Introducing a pilot program for new drugs through which industry can submit applications using a quality-by-design framework to help expand the Agency's knowledge in this area.

All of these activities have helped strengthen the overall scientific focus for chemistry, manufacturing and controls review as well as reduce some of the regulatory burden for both the Agency and the industry.

Improving efficiency and consistency of cancer product reviews

Our efforts to improve the timely development of new drugs for the treatment of cancer have continued. To enable this, we made significant changes to our organizational structure to provide a stronger and more consistent approach to the review process for drugs and therapeutic biologics used to diagnose, treat and prevent cancer. We created a new oncology office, called the Office of Oncology Drug Products. This new office is a consolidation of three pre-existing areas within the Center: Drug Oncology Products, Biologic Oncology Products and Medical Imaging and Hematology Products. Creation of this new office will improve consistency of review and policy for oncology products and bring together a critical mass of oncologists who can help during the development of new cancer therapies. This office will also provide technical consultation to other FDA components.

Speeding the development of medical countermeasures

We recognize the need to facilitate the development of countermeasures to protect Americans from biological, chemical, nuclear and radiological agents of terrorism. Many parts of the Center contribute to this effort, focused through the Office of Counter-Terrorism and Emergency Coordination, an office we formed in 2006. One important goal we have identified is to foster the development of medical countermeasures for vulnerable populations. For example, in 2005, following an expedited review, we approved ThyroShield, a ready-to-use, liquid medicine to block the uptake of radioactive iodine in vulnerable populations. Unlike already approved tablets, which are not ideally suited for young children, this black raspberry flavored solution is dosed using an eyedropper to enable easy treatment of young children and newborns.

We are extremely proud of the work outlined in this report and look forward to another year of important strides in approving therapies to improve the health of Americans.

Steven Galson, M.D., MPH
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 U.S. 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 2,200 employees. Approximately half of us are physicians or other kinds of scientists.

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.

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 safe and effective 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 it from the market. We monitor changes in manufacturing to make sure they won't adversely affect safety or efficacy. We evaluate reports about suspected problems from manufacturers, health-care professionals and consumers. We try to make sure an adequate supply of needed drugs is always available to patients who depend on them.

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.

Over-the-counter drugs

You can buy over-the-counter drugs without a doctor's prescription.

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

These range from acne products to cold medications.

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

Generic drugs

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

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

Monitoring drug information and advertising. Accurate and complete information is vital to the safe use of drugs. We regulate information that accompanies or is displayed with an over-the-counter drug. In the past, drug companies promoted their products almost entirely to physicians. More frequently now, they are advertising directly to consumers. We oversee advertising of prescription drugs, whether to physicians or consumers. We pay particular attention to broadcast ads that can be seen by a great many consumers. The Federal Trade Commission regulates advertising of over-the-counter 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.

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. To ensure a safe and effective drug supply, we enforce federal requirements for drug approval, manufacturing and labeling. When necessary, we take legal action to stop distribution of products in violation of these requirements. 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.

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 with 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 policy and technical proposals in advance. This gives members of the public, academic experts, industry, trade associations, consumer groups and professional societies the opportunity to comment before we make a final decision. In addition, we take part in FDA-sponsored public meetings with consumer and patient groups, professional societies and pharmaceutical trade associations. These help us obtain enhanced public input into our planning and priority-setting practices.

Scientific research

We conduct and collaborate on focused laboratory research and testing. This 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.
- Regulatory standards and consistency.

HIGHLIGHTS AND INITIATIVES

We are pleased to present our 10th performance report. Our work in 2005 offered many Americans new or improved choices for protecting and maintaining their health or new ways to use existing products more safely. We worked hard at our mission of ensuring that Americans have safe and effective drugs and also developed these initiatives to bring the latest science and technology to bear on our mission:

- Reforming our drug safety oversight.
- Identifying ways to improve the science of drug development.
- Improving manufacturing practices.
- Protecting the homeland with improved medical countermeasures to be used in the event of a terrorist attack or disaster.
- Conducting targeted scientific research to improve our regulatory practices.

We accomplished our work on these initiatives while maintaining our performance on our reviews of safety and efficacy and our oversight and surveillance of the safety of products sold to Americans.

- *Reviews.* We approved 80 new medicines, including 20 truly new medicines that had not been marketed in any form before in this country. We approved 141 new or expanded uses for already approved medicines. We approved 344 generic versions of existing drugs.
- *User-fee performance.* We met almost all of our goals for review performance in fiscal year 2005.
- *Drug safety surveillance.* We processed and evaluated more than 460,000 reports of adverse drug events, including more than 25,000 submitted directly from individual health-care providers and patients.
- *Drug promotion and advertising.* We issued 60 letters on violations in drug promotion and more than 800 letters to help ensure manufacturers comply with regulations concerning drug promotion.
- *Public database of electronic labels.* We required manufacturers to begin submitting drug labeling information electronically so that it can be made publicly available rapidly.
- *Public health advisories.* We issued alerts on non-steroidal anti-inflammatory pain medicines and 15 other safety concerns.
- *Manufacturing compliance.* We acted to halt distribution of drugs that were unapproved, poorly manufactured or improperly labeled.

Drug Safety Initiative

Our highest priority is assuring that safe and effective medicines are available to the American public. Safe medicines, where the benefits outweigh the risks, were the focus of a number of high-profile initiatives in 2005. We worked to ensure that our systems for assessing and evaluating safety continue to be robust and that we communicate new information for health-care providers and patients in a timely and clear manner. Our efforts included:

- Establishing the Drug Safety Oversight Board.
- Sharing drug safety information sooner and more broadly.
- Laying the foundations of an electronic information infrastructure that will give patients, health-care professionals and consumers quick and easy access to the most up-to-date and accurate information on medicines.
- Obtaining public input on our drug risk communications strategies.

Drug Safety Oversight Board

The 15-member board provides drug safety oversight and recommendations to the Center Director on drug safety issues. The board held five meetings in 2005. In its initial meetings, members explored the methods we use in risk assessment of marketed drugs, including:

- Review and analysis of spontaneous reports of adverse events.
- Drug use data.
- Health-care administrative data.
- Epidemiologic and observational studies.
- Clinical trials.
- Active surveillance systems.

In later meetings, members discussed pre- and post-decisional risk management examples to further clarify and define their oversight and advisory responsibilities including their role in helping establish policies and managing the communication of important drug safety issues to stakeholders. Members include representatives from each of our offices with responsibility for drug safety, a representative from each of the two other FDA centers dealing with human medical products, a representative the Veterans Administration and a representative the National Institutes of Health.

More information about the board is at http://www.fda.gov/cder/drugSafety.htm. Public summaries of board meetings are at http://www.fda.gov/cder/drug/DrugSafety/DSOBmeetings/default.htm.

Comprehensive oversight of drug safety

Our professional staff spends about one-half their time addressing safety issues, including:

- Watching for problems once we approve a drug.
- Overseeing clinical trials.
- Evaluating new therapies and new or expanded uses for existing therapies to balance risks against expected benefits.
- Overseeing manufacturing, distribution and promotional activities.
- Preventing medication errors by evaluating proposed proprietary names, labeling and packaging.
- Developing proactive risk management strategies both before and after approval.

Institute of Medicine study

We contracted with the Institute of Medicine to study the effectiveness of the nation's drug safety system. The study will emphasize the post-market phase and assess what additional steps could be taken to learn more about the side effects of drugs as they are actually used.

The institute, a component of the National Academy of Sciences, is the nation's foremost body for science-based advice on matters of biomedical science, medicine and health.

More information about their study and transcripts of the public meetings are available at http://www.iom.edu/CMS/3793/26341.aspx.

Drug safety communication channels

We began sharing "emerging" drug safety information broadly through public health advisories and through specific drug safety information sheets that are tailored to the needs of health-care professionals and patients. In some cases, we are sharing safety information even before we have reached conclusions that would prompt a regulatory action. Our communications in 2005 included:

- *Public Health Advisories.* We issued 16 advisories to alert health-care providers and consumers to safety concerns about drugs (page 41).
- *Health-care professional information sheets.* We published sheets on 44 drugs with detailed information about emerging important drug safety concerns, including a description of the concern along with recommendations and considerations about the concern for the prescriber.
- *Patient information sheets.* We published 41 information sheets containing new information about emerging drug safety concerns for approved drugs and provided in a consumer-friendly format.

More about drug safety communication is at http://www.fda.gov/cder/drugSafety.htm.

Public hearing on communication of drug safety information

Making us a reliable "trusted source" of health-care provider and consumer information about medicines emerged as the key theme at a two-day public hearing in 2005 on our risk communications. We were urged to engage health-care professional organizations, simplify our risk communications, improve provider and consumer access to our Internet site, develop consistent communication approaches and address those with limited health literacy and English skills.

Prescription drug information infrastructure

Accurate, up-to-date information about a prescription drug is critical for its safe and effective use. Too frequently, information about a prescription drug reads more like a legal disclaimer than useful or actionable health information. We worked hard in 2005 to bring to fruition several interconnected regulatory actions, including:

- *Electronic submission of drug labeling.* We issued final guidance to assist manufacturers in submitting prescription drug label information to us in a new electronic format (page 32).
- *Launching the DailyMed public database of drug information.* This multi-agency effort to improve patient safety is enabling us—through the National Library of Medicine—to provide an up-to-date electronic repository of medication labeling in a standard format. This information will be useable in computer systems that support patient safety, such as electronic prescribing and decision-support systems.
- *Working to bring out our final requirement for revised prescription drug labeling.* Our final regulation, issued in January 2006, amends the content and format of information in prescription drug labeling, commonly called the package insert. The new label will provide the most important information about new and recently approved prescription drugs and new uses in a format that is better understood, more easily accessible and more memorable for physicians.

Personalized medicine

The Critical Path recognizes "pharmacogenomics" and encourages its use in drug development.

Pharmacogenomics allows health-care providers to identify differences in people's drug risk response profiles and predict the best possible treatment options for them.

In 2005, we helped lay the regulatory groundwork for pharmacogenomics in the Critical Path by issuing:

- A final guidance on voluntary submissions of pharmacogenomic data
- A draft concept paper on how to co-develop a drug or biological therapy along with a device test in a scientifically robust and efficient way.

We received 15 voluntary genomic data submissions from industry in 2005.

More information is available at www.fda.gov/cder/genomics.

Critical Path Initiative

Our role in the Agency's Critical Path Initiative is to stimulate and facilitate a national effort to modernize the scientific processes through which a potential human drug or therapeutic biologic is transformed from a discovery or "proof of concept" into a medical product.

In our view, the applied sciences for product development have failed to keep pace with the tremendous advances in the basic sciences. New science is not being used to guide the development process in the same way that it is accelerating the discovery process.

To focus the attention of the public, academic researchers, funding agencies and industry, an FDA report in 2004 described an urgent need to modernize the medical product development process—the Critical Path—to make product development more predictable and efficient. Because of our unique vantage point, we can work with companies, patient groups, academic researchers and other stakeholders to coordinate, develop and help disseminate solutions to scientific hurdles that are impairing the efficiency of medical product development.

Critical Path Opportunities List

During 2005, we helped the Agency describe and provide examples of how new scientific discoveries—in fields such as genomics, proteomics, imaging and bioinformatics—could be applied to improve the accuracy of the tests we use to predict the safety and efficacy of investigational medical products. The list was released in early 2006.

The list provides a concrete focus for public and private efforts and investments in new tools that could revolutionize product development. The goal is to encourage others to undertake such work in their areas of interest. It was developed based on feedback from stakeholders and the special insights of FDA's product reviewers.

The list's 76 scientific projects mark a starting point in identifying the essential development priorities. These are highly-targeted research projects divided into six key areas:

- Better evaluation tools—biomarkers and disease models.
- Streamlining clinical trials.
- Harnessing bioinformatics.
- Moving manufacturing into the 21st century.
- Products to address urgent public health needs.
- At-risk populations.

The comprehensive Web site on the Critical Path is at http://www.fda.gov/oc/initiatives/criticalpath/.

Pharmaco-genomics workshop

In 2005, we held the third in a series of scientific workshops on how pharmaco-genomics could enable efficient and successful drug development in such areas as:

- The efficiency and informativeness in clinical trials.
- Clinical trials for cancer therapy.
- International harmonization of pharmacogenomics guidances.
- Strategies to bridge pharmacogenomics information from drug development research to clinical practice.
- Clinical qualification of genomic biomarkers for decision making.
- Creation of diagnostic tests for clinical practice.

21st Century Drug Quality System

Our overhaul of the regulatory and quality control systems for pharmaceutical products encourages manufacturers to modernize their methods, equipment and facilities. Our goal is to help eliminate both production inefficiencies and undue risks for consumers. Our initiative implements improved policies that are making better use of our limited resources through more targeted and effective inspections.

We are improving both our external polices, known as "current good manufacturing practices" or cGMPs as well as our internal programs for the review of an application's chemistry, manufacturing and controls sections. *Pharmaceutical cGMPs for the 21st Century* is the umbrella name for this strategic initiative, and more information is available at http://www.fda.gov/cder/gmp/.

New drug quality assessment

Our chemists reorganized during 2005 to transform drug quality assessment from a checklist review to a scientifically sound, risk-based process. The mission of our new Office of New Drug Quality Assessment is to:

- Assess the critical quality attributes and manufacturing processes of new drugs.
- Establish quality standards to assure safety and efficacy
- Facilitate new drug development.

Our chemists are now focusing on critical pharmaceutical quality attributes and their relevance to safety and efficacy. These include chemistry, pharmaceutical formulation, stability, manufacturing processes, bioavailability and product performance. Our long-term goal is to:

- Emphasize quality by design in the evaluation of critical aspects of pharmaceutical quality.
- Have a strong focus on manufacturing science.
- Integrate review and inspection functions.
- Use modern statistical methodologies.

Our vision for "desired state" in manufacturing

- Product quality and performance assured by effective and efficient manufacturing processes.
- Product attributes based on mechanistic understanding of how formulation and process impact performance.
- Continuous improvement and continuous real-time assurance of quality enabled.
- Regulatory policies recognize level of product and process knowledge.

Workshop explores drug quality system

We held a three-day scientific workshop for industry to explore how we can achieve the new drug quality system. We worked with industry scientists to:

- Identify scientific training gaps that must be filled for the successful implementation of the new system.
- Obtain industry input on building a scientific, risk-based regulatory system that maintains high quality and facilitates continuous improvement.
- Help determine how to best use information from the pharmaceutical development phase in the industrialization phase.
- Identify the roles and responsibilities for industry and us in the new system.
- Propose ways to reduce the number of post-marketing supplements.

Chemistry, manufacturing, controls pilot program

We launched a formal pilot program in July 2005 under which pharmaceutical companies can voluntarily submit new drug applications that apply quality-by-design principles and demonstrate their product knowledge and process understanding.

This scientific information—more relevant than found in a traditional submission—-will enable us to:

- Perform a risk-based assessment of product quality and process performance.
- Consider an applicant's proposal for regulatory flexibility in setting product specifications and post-approval changes.

Counterterrorism, Emergency Response

We have been taking an aggressive and proactive approach to our role in helping to prepare the nation for terrorist events, emerging health threats and emergency response to natural and man-made crises, including:

- Assuring the availability of medicines during a crisis.
- Addressing issues on procurement, packaging, labeling, use and shelf-life extension of products in the Strategic National Stockpile.
- Utilizing regulatory mechanisms to provide emergency access to new therapies and to approved therapies used in novel ways.
- Assuring alternative manufacturing sites for critical medicines.
- Protecting the nation's drug supply from attack or deliberate contamination.
- Leveraging with other federal agencies to answer scientific questions about treatments for emerging health threats and terrorist events.
- Preparing ourselves to continue operations during a crisis.

Interagency collaborations

- *Post-event surveillance planning.* Along with the FDA's other medical centers and the Centers for Disease Control and Prevention, we developed a plan to identify processes for collecting adverse event and outcome data on medical products distributed in response to an emergency.
- *Project BioShield prioritization.* We participated in many interagency counterterrorism working groups that have contributed to gap analyses in medical countermeasures and authored many of the requirements documents that will be used to prioritize products for development and eventual procurement under BioShield.

Counterterrorism guidances published in 2005

- *Draft Guidance for Industry: Internal Radioactive Contamination-Development of Decorporation Agents.*
- We participated in developing FDA's *Draft Guidance: Emergency Use Authorization of Medical Products.*

Pandemic flu preparedness

We are preparing for an influenza pandemic by:

- Participating in the FDA Pandemic Influenza Preparedness Task Force, as well as in the Antiviral Subgroup and the Emergency Preparedness, Response and Communications Subgroup.
- Helping to develop FDA's Pandemic Influenza Preparedness Strategic Plan and our center's portion of FDA's Pandemic Influenza Continuity of Operations Plan.
- Providing input on the *HHS Pandemic Influenza Plan* from the Department of Health and Human Services.

Hurricane response

We assisted in the response to hurricanes Katrina, Rita and Wilma by coordinating the Internet posting of information about:

- The safety of medications potentially damaged by flooding or high temperature.
- Insulin use.
- Safety of using combination sunscreen and insect repellent in children.
- Reporting prescription drug sample losses.
- Assisting investigators conducting clinical trials in hurricane-affected areas.
- Facilitating donation of drugs.
- Coordinating volunteer responses for relief efforts.

About 150 Public Health Service Commissioned Corps officers—one-half the total assigned to our center—were deployed to provide medical and pharmacy services in areas affected by the hurricane.

Emergency preparedness

We provided rapid responses to requests for information on medical countermeasures during a five-day interdepartmental exercise, known as TOPOFF 3 ("Top Officials"). The exercise simulated simultaneous terrorist attacks using multiple threat agents—both pneumonic plague in New Jersey as well as the release of mustard gas and a high-yield explosive in Connecticut.

Emergency use authorization

We worked with the Centers for Disease Control and Prevention to identify potential medical countermeasures in the Strategic National Stockpile as candidates for Emergency Use Authorization for an unapproved use under the Project BioShield Act of 2004.

We also began to outline the internal processes and procedures we need to handle emergency use requests.

Medical countermeasure approvals

- *Potassium iodide oral solution (ThyroShield).* This oral solution of a thyroid blocking agent for use in radiation emergencies is appropriate for children or adults who cannot swallow tablets. We advised the Department of Health and Human Services in a BioShield procurement of the product, which was approved as a generic drug.
- *Generic ciprofloxacin.* We approved four additional new generic ciprofloxacin drug products, all with approved labeling for the management of inhalational anthrax (post-exposure).
- *Revised labeling for ciprofloxacin (Cipro).* We approved revisions for the sections of the package insert concerning Indications and Usage, Adverse Reactions and Inhalational Anthrax—Additional Information. These changes for the tablets, intravenous solution and oral suspension were based on information obtained by the Centers for Disease Control and Prevention during the 2001 anthrax attacks. Because of these data, we released the manufacturer from its accelerated approval commitment to report data from confirmatory anthrax studies.

Facilitating medical countermeasure development

- *Plague.* The Centers for Disease Control and Prevention continued to enroll patients in the second year of an FDA-funded clinical trial to assess the efficacy of the antibiotic gentamicin for endemic plague in Madagascar, where antimicrobial options for plague are extremely limited. We contributed to protocol design and the formation of a data safety monitoring board to oversee the safe conduct of the study. We are continuing our collaboration with FDA's Center for Devices and Radiological Health to evaluate the performance of a novel, rapid, bedside plague diagnostic test kit under study conditions.
- *Pneumonic plague.* We also continued our collaboration with the National Institute of Allergy and Infectious Diseases and the U.S. Army Medical Research Institute of Infectious Diseases to evaluate the safety and efficacy of five antibiotics—gentamicin, ciprofloxacin, levofloxacin, doxycycline and ceftriaxone—in a non-human primate model of pneumonic plague.
- *Inhalational Anthrax.* We continued our collaboration with both institutes to establish a non-human primate natural history model for inhalational anthrax.
- *Radiological and nuclear threats.* We continued to collaborate with the National Institute of Allergy and Infectious Diseases to identify promising new products for use against radiological and nuclear threats. We discussed scientific and regulatory issues with manufacturers of such products and informed them about possible funding sources, both for early development and for procurement by the federal government.

Flu prevention for children

In December, we approved *oseltamivir (Tamiflu)* for prevention (prophylaxis) of influenza in children 1 to 12 years of age. This gives health-care providers an option for preventing influenza in children following close contact with an infected individual.

Our approval followed presentation of an adverse event safety update on the drug to the Pediatric Advisory Committee. The meeting provided a public forum to discuss the safety of the drug's use in children as part of a routine drug safety update required by the Best Pharmaceuticals for Children Act.

Internet resources

We provide the most current information on medical countermeasures and vaccines, plus advice on purchasing and taking medication, at http://www.fda.gov/cder/drugprepare/default.htm.

Counterterrorism biotechnology research

We have used congressionally mandated special funding to initiate research in several areas relevant to counterterrorism. Our scientists are studying:

- Microarray technologies, which could assist in identifying infectious biowarfare agents.
- Non-specific immune boosters, which could provide transient protection against such agents.
- Monoclonal antibodies as neutralizers of biological toxins.
- Various strategies to defend against anthrax.
- Development of Anthrax Toxin assays for assessment of potential therapies.

By establishing a core of scientists experienced in several areas of bioterrorism, these projects anticipate high-priority regulatory submissions likely to require rapid science-based evaluation.

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

- *Biomarkers for organ damage.* We are identifying, evaluating and establishing relevant protein biomarkers in blood in both animal models and in humans. These will help detect the very earliest damage that can be caused by certain drugs to the heart, kidney, immune system and liver.
- *Biomarkers for inflammation.* 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.
- *Medicinal plants, herbs.* We established scientific research capabilities in the analyses of medicinal plant and herbal products.
- *Imaging drug targets.* We continue to explore noninvasive imaging technology to extend 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.
- *Better use of exposure-response data.* We are developing a standardized approach for using exposure-response information to help evaluate the risks and benefits of drug therapies and recommending dose adjustments in special populations.
- *Pediatric pharmacokinetics.* We are developing a pediatric population pharmacokinetics study design template to facilitate implementation of sparse sample strategies in pediatric drug development.

Evaluation of new technologies

We conduct targeted research to understand how new technologies will affect future regulatory decision making.

For example, we are evaluating how microarrays that can identify thousands of genes or proteins rapidly and at the same time could improve the interface between drug development and regulatory practice.

Biotechnology research

Our Office of Biotechnology Products consists of about 80 scientists and other staff who are responsible for evaluating therapeutic biotechnology product submissions as well as carrying out scientific research related to biologics regulatory issues.

- *Immune responses.* We review many submissions aimed at inhibiting unwanted immune responses, such as autoimmune diseases or rejection of transplanted organs, or aimed at enhancing desired immune responses, such as those against infections or cancer. To facilitate review of such immunology-related submissions, we study the mechanisms by which immune cells are activated, suppressed or channeled from one kind of active response to another.
- *Metabolic pathways.* We study the mechanisms by which various regulated products induce their intended effects, as well as unintended adverse effects. Our investigations also examine various normal and pathogenic pathways that are targeted by regulated agents.

Our research enhances the ability of our scientist/regulators to evaluate risks and benefits of biotech products, to advise industry on difficult regulatory problems, such as potency assays, and to develop hands-on expertise in the modern technologies used by sponsors of biotech products.

Informatics and computational safety analysis

- *Cancer toxicity predictive software.* Our cooperative research and development agreements with several commercial software developers have resulted in the development and marketing of new computer software to predict the cancer-causing potential of chemicals based on their molecular structure. The software makes use of our extensive rodent carcinogenicity database without compromising proprietary information.
- *Safe starting dose models.* We have successfully developed computer models to estimate the safe starting dose for clinical trials of drugs based on their molecular structure. The current method for estimating the starting dose is highly inexact and requires the use of multiple safety factors because it is based exclusively on an extrapolation from animal toxicity studies. We have begun studies to validate the new method.

Scientific research in pregnancy and lactation

See page 26 for studies to evaluate fetal safety from drug exposure or whether the dose of a drug should be adjusted during pregnancy or lactation.

Pharmaceutical analysis

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

We collaborated with state pharmacy boards to evaluate Internet pharmaceuticals.

We evaluated the quality of a select group of the most-often-ordered pharmaceutical products from foreign Internet suppliers.

Laboratory support

Our efforts included:

- Development of methods to evaluate quality attributes of drug products and raw materials by chemical imaging. These properties include polymorphic form, hydration state, stability and purity.
- Rapid identification of counterfeit products using near-infrared spectroscopy and chemical imaging to discriminate drug products and raw materials.
- Development of a methodology for determining glove permeability to lindane shampoo and lotion, treatments for lice whose active ingredient is highly toxic.

1

DRUG REVIEW

Many Americans benefited from last year's timely reviews of new prescription medicines, over-the-counter medicines and the generic equivalents for both. When we review a medicine, we use the best science available to determine if a medicine's benefits outweigh its risks for its intended use. An internal study showed that about half of our professional staff time is spent on safety assessment. We oversee the development of new medicines in the United States, and our paramount concern is the safety of patient volunteers in clinical trials.

Highlights for 2005 include:

- *80 new medicines.* We approved 78 drugs and two biologics (22 priority and 58 standard reviews).
- *20 truly new medicines.* We approved 18 drugs and two new biologics that had never been marketed before in any form in this country (15 priority and 5 standard reviews).
- 141 *new treatment options.* We approved new or expanded uses for 126 already approved drugs and 15 already approved biologics (36 priority and 105 standard reviews).
- *5 over-the-counter drugs.* Our approvals included five new medicines to be sold over the counter without a prescription, and four of them can be used by children. We approved three new uses for existing OTCs, all of which can be used by children.
- *10 "orphan" medicines.* Our approvals included nine drugs and one biologic for patient populations of 200,000 or fewer.
- *344 generic drugs.* We gave final approval to 344 generic versions of existing drugs and tentative approval to another 108. We received 777 marketing applications for generic drugs.
- *User fee goals.* We exceeded all our performance goals for the fiscal year 2004 receipt cohort, the latest year for which we have full statistics. We are on track for exceeding most user-fee performance goals for the fiscal year 2005 cohort.
- *652 clinical trial inspections.* We conducted foreign and domestic inspections that help protect volunteers in clinical trials from research risks and validate the quality and integrity of data submitted to us.

Drugs@FDA

Drugs@FDA—the most frequently used application on the FDA Web site—has official information about FDA approved brand-name and generic drugs such as:

- Approved and tentatively approved drug products.
- The regulatory history of an approved drug.
- Labels for approved drug products.
- All drugs with a specific active ingredient.
- Generic drug products for a brand-name drug product.
- Therapeutically equivalent drug products for a brand-name or generic drug product.
- Consumer information for drugs approved after 1998.

To use Drugs@FDA, go to our home page (http://www.fda.gov/cder) and click on "Drugs@FDA."

Approval totals

- **80 drugs and biologics**
  - 78 drugs
  - 2 biologics
- **20 truly new medicines**
  - 18 drug NMEs
  - 2 new biologic NMEs
- **14 orphan approvals**
  - 9 NDAs (includes 6 NMEs)
  - 1 new biologic
  - 4 approvals for 3 new or expanded uses

New Drug and Biologic Review

Definitions

- *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.
- *Priority approvals.* These products represent significant improvements compared with marketed products. We have a goal of reviewing 90 percent of these applications within six months.
- *Standard approvals.* These products have therapeutic qualities similar to those of already marketed products. We have a goal of reviewing 90 percent of these applications within 10 months.
- *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.
- *Orphan drugs.* We administer a program that provides incentives to develop drugs for use in patient populations of 200,000 or fewer. Sponsors of orphan drugs receive inducements that include seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance from FDA and grants of up to $200,000 a year.
- *Accelerated approval.* This program helps make products for serious or life-threatening diseases available earlier in the development process. We base our approval on a promising effect of the drug that can be observed significantly sooner than a long-term clinical benefit. Sponsors perform additional studies to demonstrate long-term clinical benefit.
- *Fast track development.* This program facilitates the development and expedites our review of new drugs and biologics that demonstrate the potential to address unmet medical needs for serious or life-threatening conditions. Fast track emphasizes our close, early communication with sponsors.
- *Median times.* Our charts show review and approval 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.

New molecular entities

NMEs contain an active substance that has never before been approved for marketing in any form in the United States. Because of high interest in truly new medicines, we report approvals of NMEs and "new BLAs." The charts for all NDAs and all BLAs include NMEs and new BLAs.

Additional statistics

More review statistics are available at http://www.fda.gov/cder/rdmt/default.htm.

Data updates

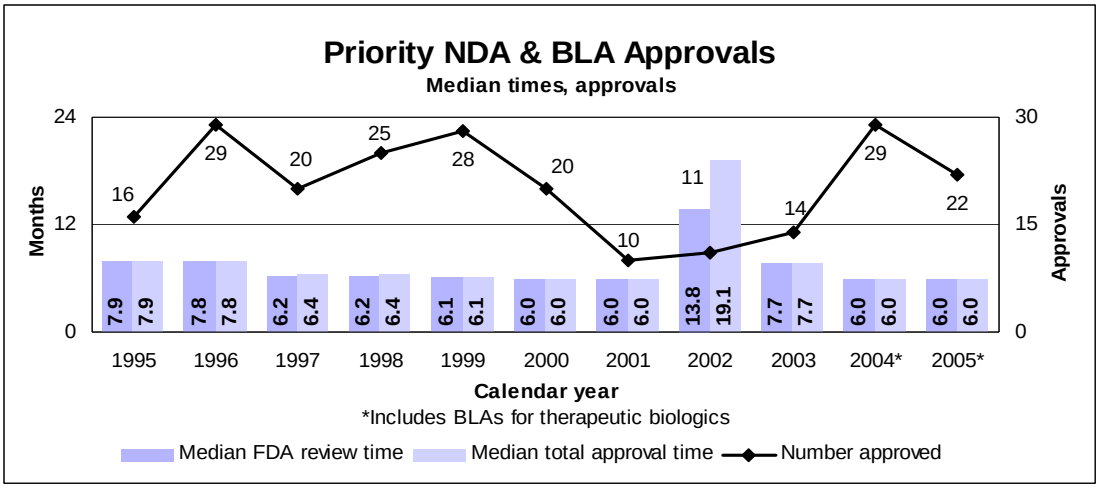
You should be aware that these data may differ from those in previous issues of this report. We have revised data from previous years.

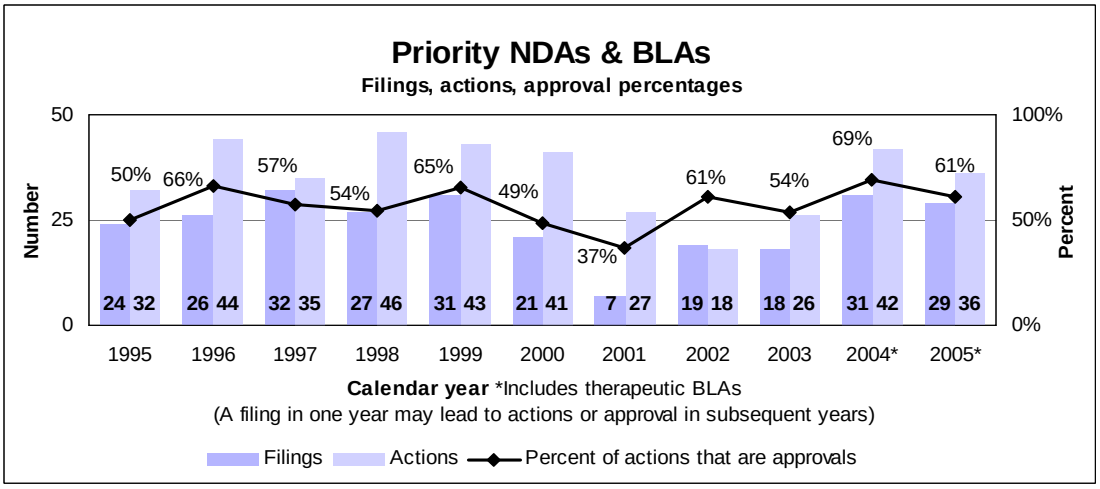
New drug applications

NDAs are the formal submissions of data that sponsors send us when they are seeking approval to market a "new drug" in the United States. Some NDAs are NMEs; however, "new drugs" can also include an active substance previously sold in a different form.

Biologic license applications

BLAs are the formal submissions of data that sponsors send us when they are seeking approval to market a biologic in the United States. A "new BLA" is an application for a biologic that has never been approved for marketing in the United States.





Priority new drugs and biologics

- **22 approvals**
  - 20 drugs
  - 2 biologics
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 29 filings
- 36 actions

- **9 orphan approvals**
  - 8 drugs (6 NMEs)
  - 1 new biologic

Notable 2005 New Approvals

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

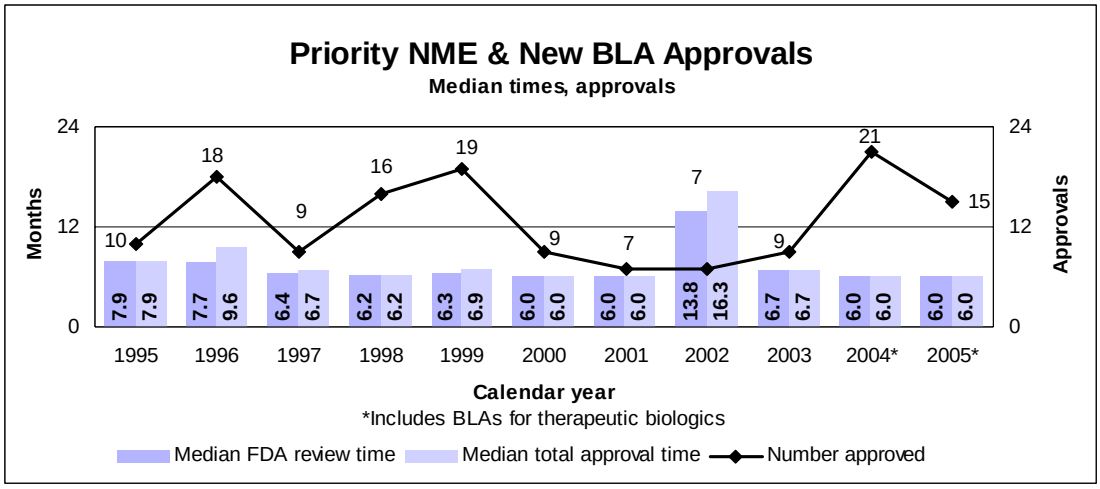
Children

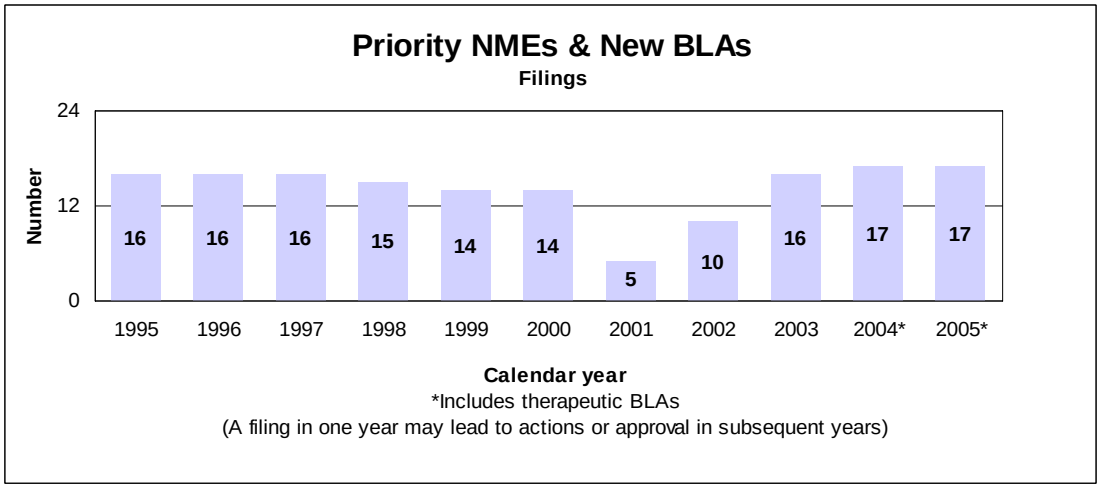
Emtricitabine (Emtriva) is an oral solution of an antiretroviral medicine that can be used in combination with other antiretroviral agents for the treatment of HIV infection in children 3 months old and older. The drug, first approved as a capsule for adults in 2003, is an HIV nucleoside reverse transcriptase inhibitor that helps to block an enzyme needed for HIV to multiply. Related to Best Pharmaceuticals for Children Act. *(priority)*

Mecasermin [rDNA origin] (Increlex) and *Mecasermin rinfabate [rDNA origin] (Iplex)* are for the long-term treatment of children who are very short for their age because their bodies do not make enough insulin-like growth factor-1. Both drugs contain human insulin-like growth factor-1 from genetically engineered bacteria, but mecasermin rinfabate also contains insulin-like growth factor binding protein-3 from genetically engineered bacteria. *(2 NMEs, priorities, orphans)*

Priority new molecular entities and new biologics

- **15 approvals**
- 13 NMEs
- 2 new BLAs
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 17 filings



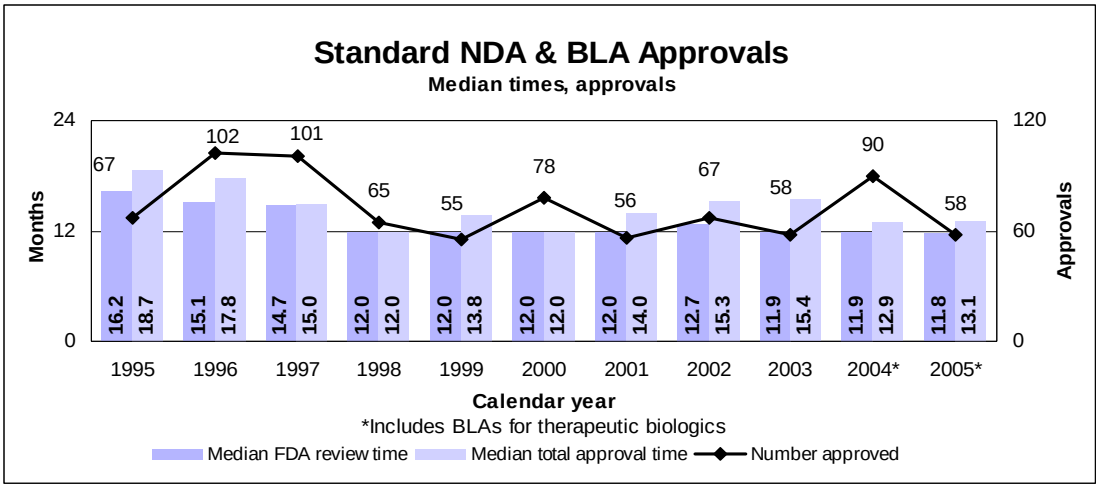


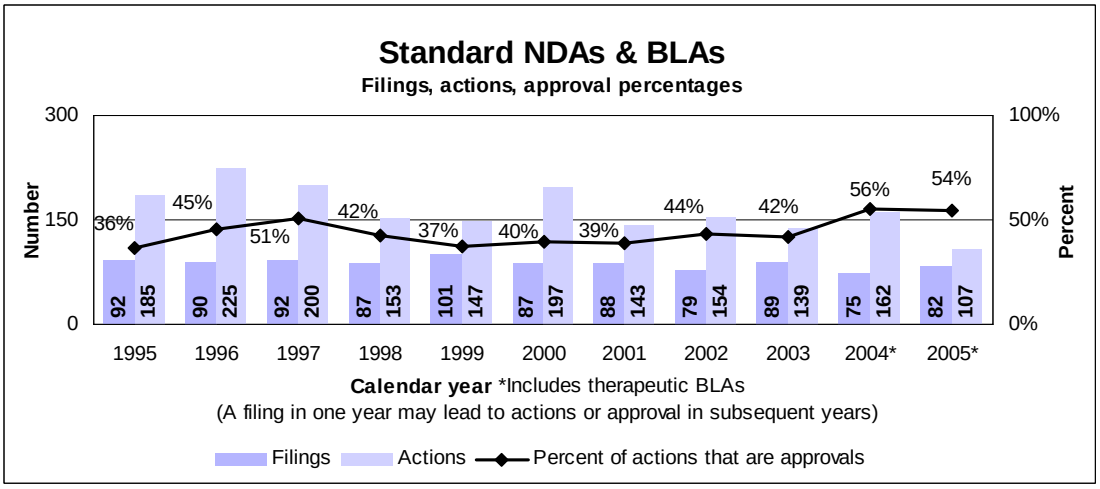
People with HIV infection

Lopinavir/ritonavir (Kaletra) is a new formulation in a tablet form that may be prescribed for once-daily use in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past. *(priority)*

Tipranavir (Aptivus) is a protease inhibitor taken with 200 mg of ritonavir and two other anti-HIV medicines to treat adults with HIV infection. The drug blocks HIV protease, an enzyme needed for HIV to make more virus. Tipranavir helps reduce the amount of HIV in the blood and keep the immune system healthy so it can help fight infection. *(NME, priority)*

Lamivudine/zidovudine/nevirapine is the first three-drug HIV regimen in one package approved for purchase under the President's Emergency Plan for AIDS Relief (page 51). We gave it "tentative approval" in less than two weeks because patent or exclusivity provisions prevent its sale in the United States. It can also serve as a reference product for generic versions. *(priority)*





Standard drugs and biologics

- **58 approvals**
- 58 drugs
- Median review time: 11.8 months
- Median approval time: 13.1 months
- 82 filings
- 107 actions
- 1 orphan approval

Notable 2005 new drug approvals (continued)

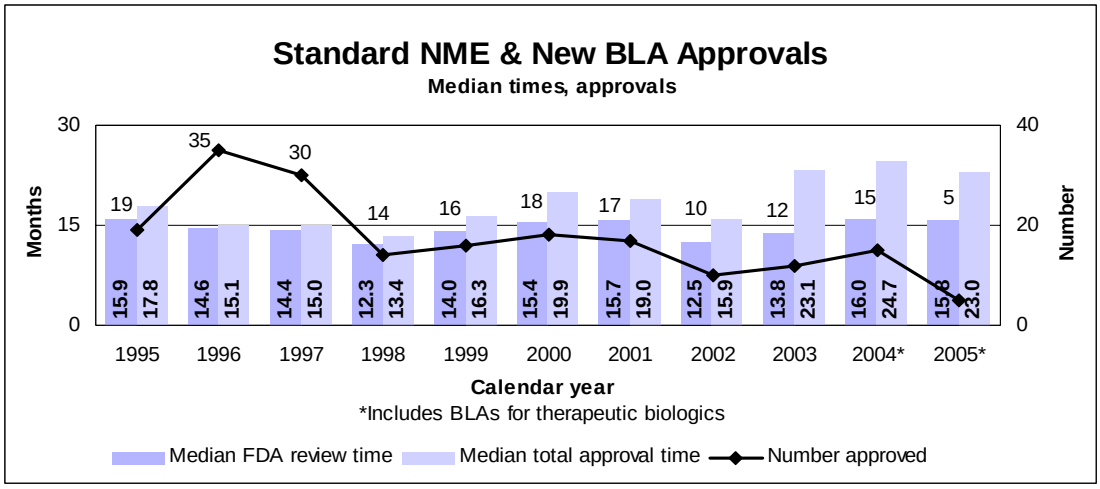
People with cancer

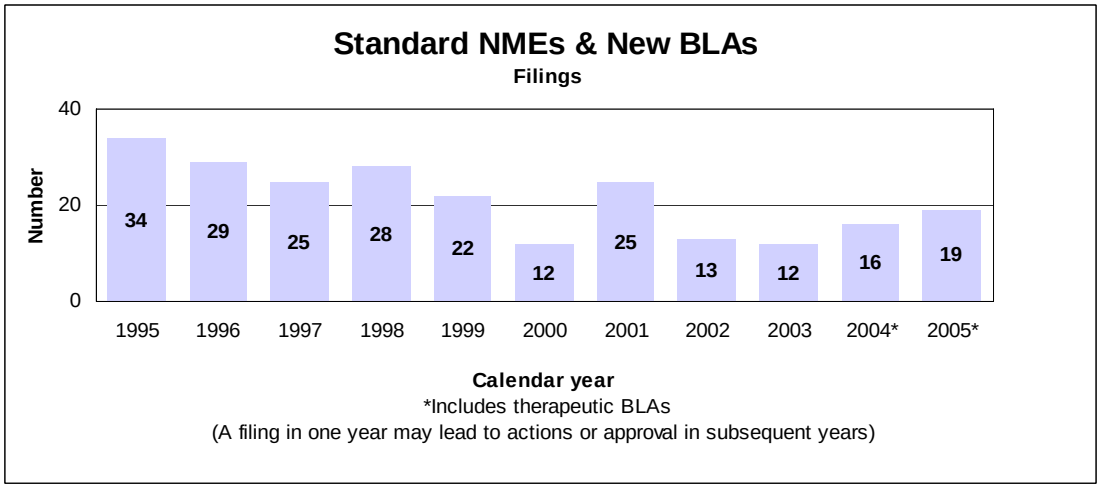
Nelarabine (Arranon) is a chemotherapy drug for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. *(NME, priority, orphan)*

Sorafenib tosylate (Nexavar) is a chemotherapy agent indicated for the treatment of patients with advanced cancer of the kidney cells. *(NME, priority, orphan)*

People with infections

Entecavir (Baraclude), in tablets and oral solution, treats chronic infection with hepatitis B virus in adults who also have active liver damage. Entecavir, a nucleoside analogue, competes with a natural substance needed for viral replication. The tablet form was counted as an NME. We also provided priority approval to a separate application for the oral solution. *(1 NME, both priorities)*





Standard new molecular entities and new biologics

- **5 approvals**
- 5 NMEs
- Median review time: 15.8 months
- Median approval time: 23.0 months
- 19 filings

Therapeutic BLAs included starting with 2004 data

Beginning with 2004, our charts incorporate data on the review of therapeutic biologics transferred to us in late 2003. These include:

- Monoclonal antibodies.
- Cytokines.
- Growth factors.
- Enzymes.
- Other therapeutic immunotherapies.

Micafungin sodium (Mycamine) is used to prevent fungal infections caused by *Candida* in patients who are undergoing a stem-cell transplantation. Micafungin inhibits synthesis of a component of the fungal cell wall. *(NME, priority)*

Tigecycline (Tygacil) treats adults who have complicated skin or intra-abdominal infections caused by certain strains of bacteria. It belongs to the glycylcycline class of antibiotics. *(NME, priority)*

People with eye disease

Fluocinolone acetonide intravitreal implant (Retisert) treats chronic non-infectious inflammation of the tissue in the rear of the eye. The drug product is surgically implanted into the affected eye and slowly releases an inflammation-controlling steroid over approximately the next 30 months. *(orphan)*

Nepafenac (Nevanac) treats the pain and inflammation associated with cataract surgery. Nepafenac is a nonsteroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by eye tissue to amfenac, a nonsteroidal anti-inflammatory drug. *(NME, priority)*

NMEs
(P=priority, S=standard, O=orphan)

- Conivaptan hydrochloride (S)
- Deferasirox (P, O)
- Entecavir (P)
- Exenatide (S)
- Hyaluronidase (P)
- Hyaluronidase human (P)
- Insulin detemir (S)
- Lenalidomide (P, O)
- Mecasermin [rDNA origin] (P, O)
- Mecasermin rinfabate [rDNA origin] (P, O)
- Micafungin sodium (P)
- Nelarabine (P, O)
- Nepafenac (P)
- Pramlintide acetate (S)
- Ramelteon (S)
- Sorafenib tosylate (P, O)
- Tigecycline (P)
- Tipranavir (P)

New BLAs

- Abatacept (P)
- Galsulfase (P, O)

Notable 2005 new drug approvals (continued)

People with arthritis

Abatacept (Orencia) treats adults with moderate to severe rheumatoid arthritis who have not been helped by other medicines. Abatacept may be used alone or with other arthritis medicines except those known as TNF antagonists. Abatacept modulates parts of the immune system implicated in causing rheumatoid arthritis. *(biologic, priority)*

People with other rare disorders

Deferasirox (Exjade) is an iron chelating agent for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. *(NME, priority, orphan)*

Galsulfase (Naglazyme) is an enzyme replacement therapy for patients with mucopolysaccharidosis VI. Also known as MPS VI or Maroteaux-Lamy syndrome, the inherited condition results when the body fails to make sufficient enzymes to break down certain complex carbohydrates that then accumulate and cause widespread cellular, tissue and organ dysfunction. The biotechnology product provides an injectable enzyme that helps the body break down the appropriate proteins. *(biologic, priority, orphan)*

Lenalidomide (Revlimid) treats people with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes that are associated with a specific genetic abnormality. The syndromes result when the bone marrow does not make enough normal blood cells. Patients may need blood and platelet transfusions and antibiotic therapy for infections. In clinical trials, most patients treated with the drug became independent of transfusions by three months, and the transfusion-free period lasted for an average of 44 weeks. Because the drug is structurally similar to thalidomide, which is known to cause severe birth defects, it is sold under a risk management plan designed to prevent fetal exposure. *(NME, priority, orphan)*

Hospitalized people with dangerously low sodium

Conivaptan hydrochloride (Vaprisol) is an injectable medicine and the first indicated to treat hospitalized patients with a potentially life-threatening condition that occurs when the body's blood sodium level falls significantly below normal. Known as euvolemic hyponatremia, the condition is the most common electrolyte disorder in clinical medicine and one of the most difficult to treat. It often results from elevated levels of antidiuretic hormone, a hormone that regulates water and salt balance in the body. The drug blocks the activity of this hormone, resulting in increased urine output without loss of valuable electrolytes such as sodium and potassium. *(NME)*

Other NDA priority approvals
(T=tentative)

- Emtricitabine (new formulation)
- Entecavir (new formulation)
- Fluocinolone acetonide (new formulation, O)
- Lamivudine; zidovudine; nevirapine (new combination, T)
- Lopinavir; ritonavir (new formulation)
- Sildenafil citrate (new formulation)
- Sodium benzoate; sodium phenylacetate (new formulation, O)

Notable 2005 new drug approvals (continued)

People with pulmonary hypertension

Sildenafil citrate (Revatio) treats pulmonary arterial hypertension to improve exercise ability. This serious condition, which can lead to fatal heart failure, is caused by continuous high blood pressure in the artery carrying blood from the heart to the lung. *(priority)*

People with diabetes

Pramlintide acetate (Symlin) is an injectable medicine for adult patients with either type 1 or type 2 diabetes. It slows down the movement of food through the stomach. This affects how fast sugar enters the blood after eating. It is always used with insulin to help lower blood sugar during the three hours after meals. The synthetic drug is similar to a naturally occurring human hormone that contributes to blood sugar control after eating a meal. *(NME)*

Exenatide (Byetta) is used to help improve blood sugar control in patients with type 2 diabetes who have not achieved adequate control on metformin, a sulfonylurea or a combination of metformin and a sulfonylurea. The drug, chemically different from other diabetes treatments, enhances insulin secretion, suppresses inappropriately elevated secretion of a hormone that raises blood sugar and slows emptying of the stomach. *(NME)*

Insulin detemir [recombinant DNA origin] (Levemir) can be injected once or twice a day under the skin by patients with type 1 or type 2 diabetes who require a long-acting insulin for the control of high levels of blood sugar. Because the medicine, made by recombinant DNA technology, differs slightly from human insulin, it is released more slowly to target tissues. *(NME)*

People with insomnia

Ramelteon (Rozerem) treats insomnia in adults where the problem is trouble falling asleep. The drug is active at the body's melatonin receptors, which are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. *(NME)*

Other priority approval

Sodium benzoate/sodium phenylacetate (Ammonul) was approved to be manufactured by a different company. The drug, first approved in 1987 and discontinued by its original manufacturer, helps treat acutely elevated levels of ammonia and associated brain swelling in patients with deficiencies in enzymes of the urea cycle. *(priority, orphan)*

Treatment and diagnostic aids

Hyaluronidase (Hydase) and *Hyaluronidase human (Hylenex recombinant)* help increase the absorption and dispersion of other injected drugs and improve resorption of X-ray contrast agents. The first drug is a purified enzyme derived from cow tissue, and the second is a purified preparation of the human enzyme hyaluronidase produced by genetically engineered hamster cells. *(2 NMEs, priorities)*

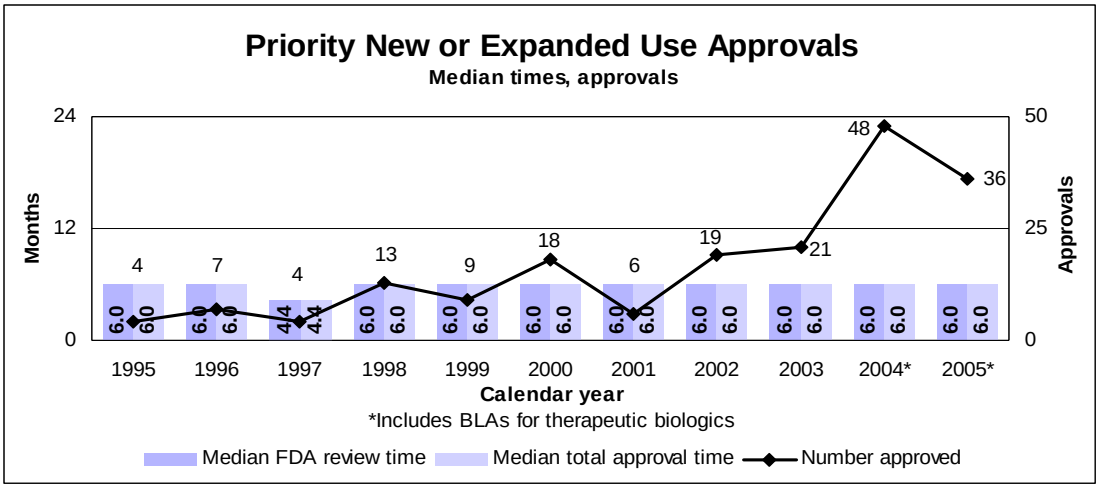
New drug review consolidated at White Oak campus

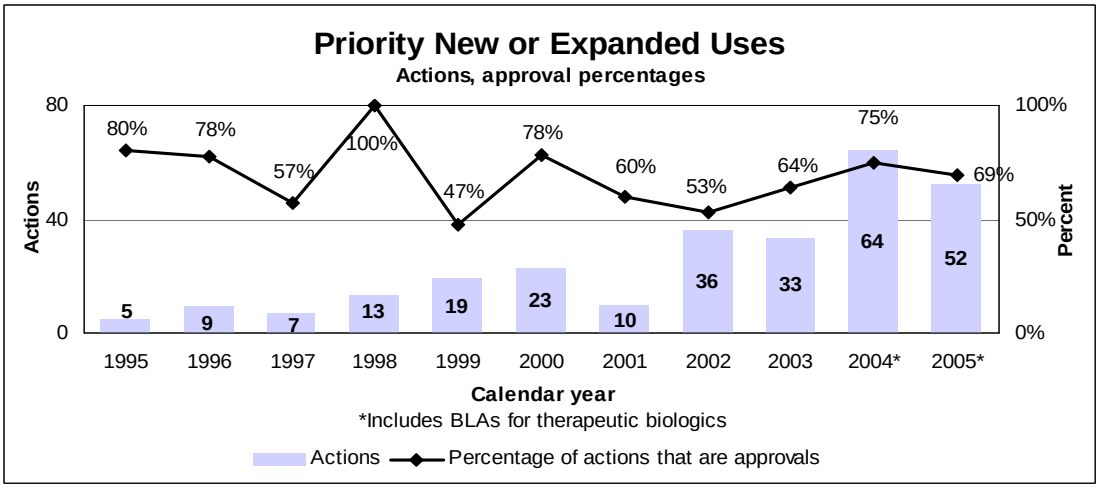
Most of our review operations were successfully consolidated in a new facility in White Oak, Md. We took advantage of the move to reorganize the Office of New Drugs in a way that created logical groupings in the same divisions, created divisions with better balanced workloads and resource allocation and completed the integration of biologics reviewers and indications within our review divisions.

Within OND, we renamed two offices—the Office of Oncology Drug Products and the Office of Antimicrobial Products. We created a new Office of Nonprescription Products with two divisions (page 27).

Review of psychiatric and neurological products was separated into two divisions.

More information is at http://www.fda.gov/cder/cderorg/ond_reorg.htm.





Priority new or expanded uses (efficacy supplements)

- **36 approvals**
- 34 drugs
- 2 biologics
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 52 actions
- 4 orphan approvals for 3 new or expanded uses

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.

People infected with both hepatitis and HIV

Peginterferon alfa-2a (Pegasys), when used alone or in combination with Ribavirin, had its indication expanded to include treatment of adult chronic hepatitis C patients co-infected with HIV, who have clinically stable HIV disease. *(priority, biologic)*

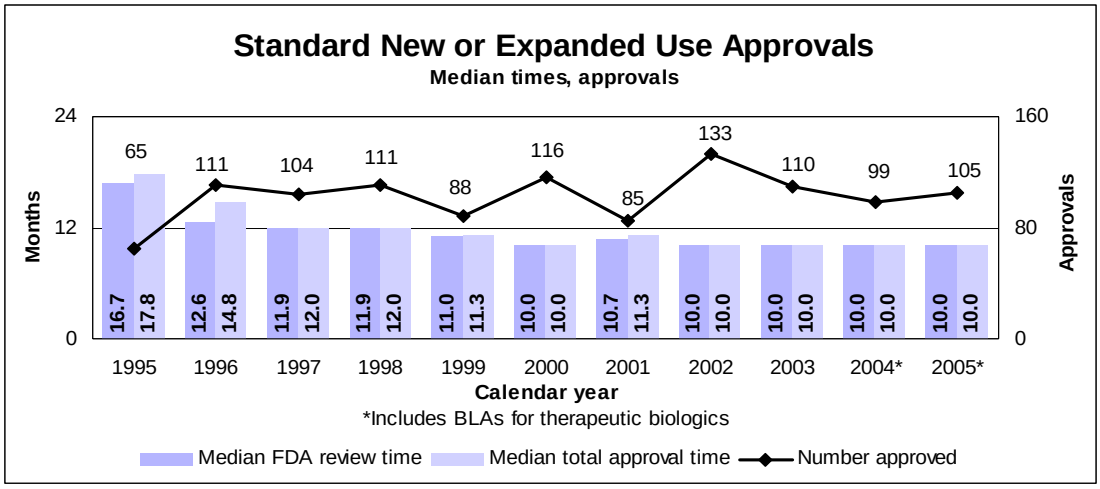
Ribavirin (Copegus), when used in combination with peginterferon alfa-2a, can now be used to treat chronic hepatitis C in adult patients co-infected with HIV. *(priority)*

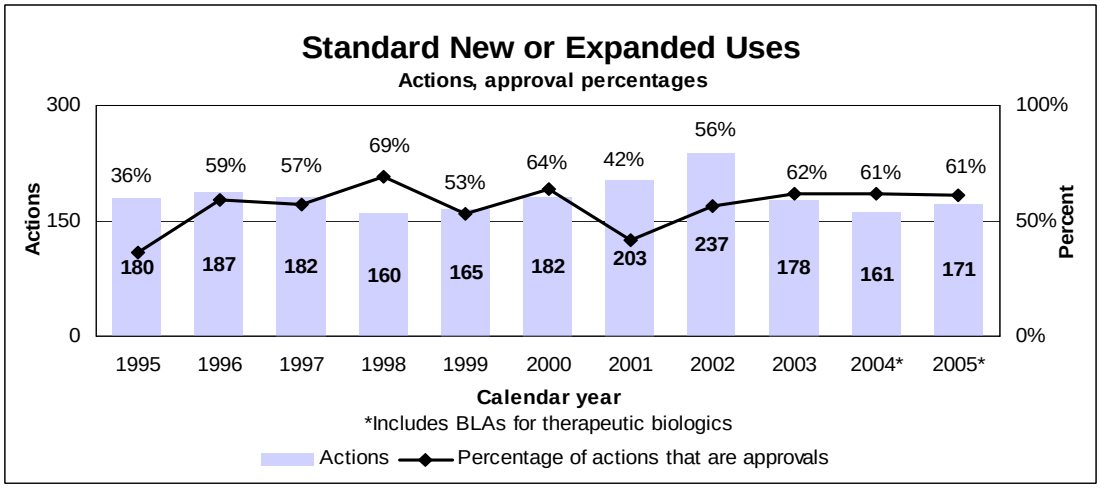
Pediatric new or expanded uses

See page 24 for the drugs with new or expanded uses in children approved under priority review required by the Best Pharmaceuticals for Children Act.

Standard new or expanded uses (efficacy supplements)

- ■ **105 approvals**
- □ 92 drugs
- □ 13 biologics
- ■ Median review time: 10.0 months
- ■ Median approval time: 10.0 months
- ■ 171 actions





Approval totals

- ■ **141 drugs and biologics**
- □ 126 drugs
- □ 15 biologics

Notable 2005 new or expanded uses

People with cancer

Bortezomib (Velcade) can be used to treat multiple myeloma patients who have received as least one prior therapy instead of the two prior therapies indicated in the 2003 approval. *(priority)*

Erlotinib hydrochloride (Tarceva), a non-small-cell lung cancer treatment, can be used in combination with gemcitabine for the first-line treatment of patients with locally advanced pancreatic cancer that cannot be removed surgically or that has spread. *(priority)*

Temozolomide (Temodar) can be used along with radiotherapy to treat patients with newly diagnosed high grade brain tumors and then as maintenance treatment. *(priority)*

Notable 2005 new or expanded uses (continued)

Letrozole (Femara) can be used to help treat postmenopausal women with hormone-receptor-positive early breast cancer. The drug, an inhibitor of estrogen synthesis, was originally approved for treating the late stage of the disease. *(priority)*

People with heart disease

Candesartan cilexetil (Atacand), a high-blood pressure treatment first approved in 1998, received two new indications. It can be used to treat heart failure in patients with left ventricular systolic dysfunction to reduce cardiovascular death and to reduce hospitalizations for heart failure and to treat heart failure to reduce the risk of death from cardiovascular causes and to reduce hospitalizations for heart failure. *(priority)*

Perindopril erbumine (Aceon), a high-blood pressure treatment, can be used in patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction. *(priority)*

People with other conditions

Fluocinolone acetonide (Derma-Smoothe/FS) ear drops can be used to treat chronic eczematous external inflammation of the ear. *(priority)*

Infliximab (Remicade), a treatment for the inflammation of the gastrointestinal tract known as Crohn's disease, has a new indication for the treatment of patients who have moderately to severely active ulcerative inflammation of the colon and who have had an inadequate response to conventional therapy. *(priority, biologic)*

Ropinirole hydrochloride (Requip), a Parkinson's disease therapy, can be used for restless legs syndrome, which is characterized by an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant leg sensations. *(priority)*

Antimicrobial Resistance

Drug-resistant bacteria continue to be a major threat to the public health. We continued our antimicrobial resistance education campaign partnership with the Centers for Disease Control and Prevention and jointly released two new print public service announcements—one English and one Spanish. In addition to the print public service announcements, a Spanish-language brochure also was produced.

Pediatric Drug Development

The Best Pharmaceuticals for Children Act of 2002 (BPCA) 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. In calendar year 2005, we approved 25 pediatric labeling changes as a result of studies conducted under the exclusivity provision.

Pediatric exclusivity. As of April 30, 2006, we had received 467 proposed pediatric study requests from manufacturers, issued 320 written requests, made 130 exclusivity determinations, granted exclusivity to 118 drugs and added new pediatric information to 109 labels.

Improved safety, dosing information. About one-fourth of the new pediatric labels have safety or dosing information. We are discovering important differences between adults and children in the clearance and metabolism of drugs. Underdosing leads to ineffective treatment, and overdosing poses a greater risk of adverse reactions. Pediatric safety signals identified in these studies include effects on growth, school behavior, suppression of the adrenal gland and suicidal ideation. The failure to produce drugs in dosage forms that can be taken by young children—such as liquids or chewable tablets—can deny them access to important medications. As a result of pediatric testing we now have 12 drugs with new pediatric formulations and six drugs with recipes in their labels to provide directions for the pharmacist to compound an age-appropriate formulation.

Off-patent drugs. The law also established a publicly funded contracting process to study drugs that lack patent protection or market exclusivity, referred to as "off-patent." In consultation with FDA and other pediatric experts, the National Institutes of Health have published five lists of off-patent drugs for which additional pediatric studies are needed. To date, we have issued 17 written requests—five in 2005—for these off-patent drugs. We also have forwarded eight written requests – two in 2005-for on-patent drugs, for which sponsors declined pediatric studies.

Public disclosure. We publish a summary of the medical and clinical pharmacology reviews of the pediatric studies conducted under the law. As of April 30, 2006, we have posted 60 summaries, regardless of the regulatory action, at http://www.fda.gov/cder/pediatric/Summaryreview.htm.

Adverse events reported. The act mandates review of all adult and pediatric adverse event reports for a one-year period after pediatric exclusivity is granted. The reviews of the reports are then presented to the Pediatric Advisory Committee. As of April 2006, reports for 54 drugs have been presented. Significant pediatric safety signals have been found, including neonatal withdrawal with antidepressant use during pregnancy and serious adverse events, including deaths, due to fentanyl transdermal use in children.

Pediatric Research Equity Act of 2003

In September 2005, we published a draft guidance on how to comply with the law.

The law gave us the authority to require pediatric studies of certain new drugs and biological products when such studies are needed to ensure the safe and effective use of the products in children. However, the law does not require the same public disclosure of pediatric studies required under the Best Pharmaceuticals for Children Act.

2005 new approvals with pediatric indications

- *New molecular entities*. Two orphan treatments for children who are very short for their age (page 14) and an iron chelating agent indicated for patients 2 and older. (page 18).
- *Biologics.* An enzyme replacement therapy for a rare inherited condition that can affect children (page 18).
- *New drugs.* An oral solution of an antiretroviral medicine (page 14) and four *over-the-counter* drugs (page 27).

Notable 2005 pediatric new or expanded uses

The Best Pharmaceuticals for Children Act requires us to give priority status to pediatric supplements for drug studies submitted in response to a written request. An efficacy supplement may change labeling to reflect new information about pediatric use, even if there are no new or expanded uses. The review of these pediatric supplements resulted in labeling that describes new and expanded uses of these medications in children:

Ertapenem sodium (Invanz), an injectable antibiotic, had its labeling expanded to include the treatment of susceptible moderate to severe infections in children 3 months of age and older. Clinical pharmacokinetic studies proved that ertapenem is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration.

Ethinyl estradiol and norgestimate (Ortho Tri-Cyclen), an oral hormone combination, had its labeling revised to indicate that there was no significant difference between treatment and placebo in bone mineral density in 123 adolescent females with *anorexia nervosa* in a one-year clinical trial.

Insulin aspart (NovoLog), a rapid-acting injectable human insulin analog, labeling was expanded to include treatment of patients 6 to 18 years old with type 1 diabetes.

Levetiracetam (Keppra), available as tablets and oral solution, labeling was expanded to include use as adjunctive therapy in the treatment of partial onset seizures in pediatric patients 4 years and older with epilepsy.

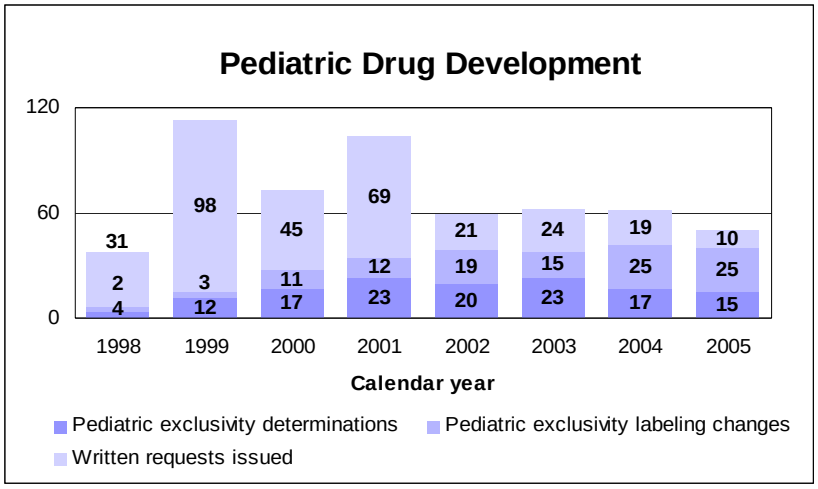
Meloxicam (Mobic), a nonsteroidal anti-inflammatory drug available as tablets and oral suspension, labeling was expanded to include treatment of certain types of juvenile rheumatoid arthritis in patients 2 years of age and older.

Safety issues for children's uses

We issued Public Health Advisories (page 41) about pediatric safety issues including:

- A boxed warning about using the eczema therapies *pimecrolimus* and *tacrolimus* only as directed and not at all in children younger than 2 years of age.
- Suicidal thinking in children and adolescents treated with *atomoxetine* for attention deficit hyperactivity disorder.

We added a black box warning about suicidality in children and adolescents to the labeling for antidepressants. Full information and a list of the drugs is at http://www.fda.gov/cder/drug/antidepressants/default.htm.



Notable 2005 pediatric new or expanded uses (cont.)

Mixed salts of a single entity amphetamine (Adderall XR), a once or twice daily extended-release central nervous system stimulant, labeling expanded to include treatment of attention deficit hyperactivity disorder in patients 13 to 17 years of age. Previously approved for use in children 6 to 12 years old.

Ondansetron (Zofran), an antiemetic available as tablets and an injectable, labeling expanded to include dosing in children down to 6 months of age for the prevention of chemotherapy-induced nausea and vomiting, as well as dosing in children down to 1 month of age for the prevention of postoperative-induced nausea and vomiting. Labeling previously provided dosing down to 4 years of age for the prevention of chemotherapy-induced nausea and vomiting and dosing down to 2 years of age for the prevention of postoperative-induced nausea and vomiting.

Oxcarbazepine (Trileptal), an anticonvulsant available as tablets and oral suspension, labeling expanded to include treatment as adjunctive therapy in children aged 2 years and above with epilepsy. Previously approved for children 4 years and older. In clinical studies, it was observed that children 2 to <4 years of age may require up to twice the dose per body weight compared to adults.

Sibutramine (Meridia), a weight loss aid, labeling modified to reflect that data from a clinical study in obese adolescents are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients. In addition, important safety information was added.

Notable non-BPCA pediatric new or expanded use

Nitazoxanide (Alinia) can be used to treat diarrhea caused by *Cryptosporidium parvum* in non-HIV infected patients 12 years of age and older.

Priority pediatric labeling changes

[number of approvals]

Our priority review of these pediatric supplements was consistent with the BPCA unless noted:

- Alendronate sodium
- Amphetamines, Mixed salts
- Ertapenem
- Gemcitabine hydrochloride
- Glimepiride
- Insulin aspart recombinant
- Levetiracetam [2]
- Linezolid [3]
- Meloxicam [3]
- Nefazodone
- Nitazoxanide [2] (unrelated to BPCA)
- Ethinyl estradiol and norgestimate
- Ondansetron
- Oxcarbazepine [2]
- Ritonavir [2]
- Rosiglitazone
- Sibutramine
- Sirolimus [2]

2005 pediatric drug statistics

- 10 written requests issued
- 25 pediatric exclusivity labeling changes granted
- 15 exclusivity determinations made

Internet resources

Our Web site for up-to-date pediatric labeling changes for drugs studied under the pediatric exclusivity process is at http://www.fda.gov/cder/pediatric/index.htm.

Pregnancy and Lactation Labeling

To improve our knowledge of the use of drugs during pregnancy and lactation, we sponsor research and provide scientific guidance to industry and our reviewers.

Women who are pregnant often need to use prescription medicines. In many cases, a disease or condition left untreated may be more harmful to a woman and her fetus or nursing baby than a drug treatment. In other cases, a different drug treatment than she is already on may be safer.

We have reviewed the current system of labeling drugs for use by pregnant and lactating women and are developing an improved, more comprehensive and clinically meaningful approach. We are consulting with government agencies, medical experts, consumer groups and the pharmaceutical industry to develop this new labeling format. We work with our reviewers and pharmaceutical companies to update product labels with available human data regarding exposure to drugs during pregnancy and lactation.

Scientific guidance

- *Risks of drug exposure in human pregnancies.* In 2005, we issued our final guidance for our reviewers on how to evaluate human data on the effects of *in utero* drug exposure on the developing fetus.
- *Lactation studies in women.* In 2005, we published a draft guidance for industry that provides the basic framework for designing, conducting and analyzing clinical lactation studies.
- *Determining the appropriate dose of a drug for pregnant women.* In 2004, we published a draft guidance for industry that provides the basic framework for designing, conducting and analyzing pharmacokinetic and pharmacodynamic studies in pregnant women.
- *Pregnancy exposure registries.* In 2002, we published a final guidance for industry that provides advice on how to establish registries that prospectively monitor the outcomes of pregnancies in women exposed to a specific drug. These registries can provide clinically relevant human data for treating or counseling patients who are pregnant or anticipating pregnancy.

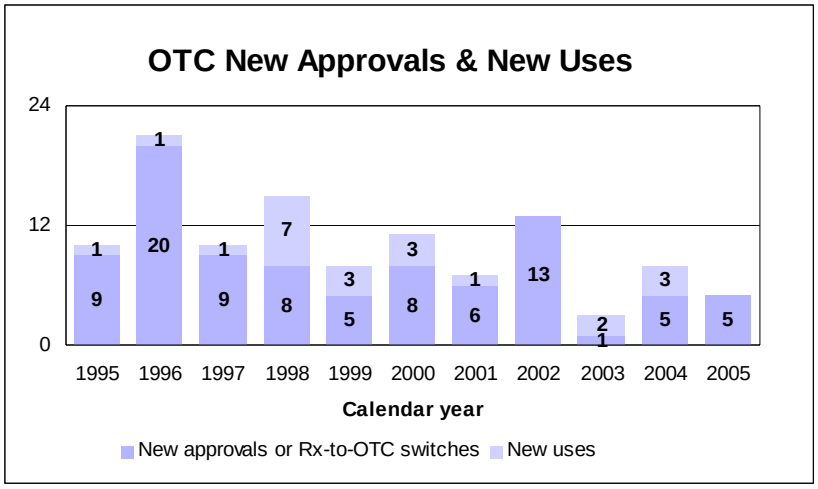
Research on drugs for high blood pressure, depression

FDA's Office of Women's Health funded studies to look at specific drugs used to treat high blood pressure and depression and determine if the doses of these drugs should be adjusted during pregnancy.

Scientific research on drug use in pregnancy and lactation

We funded several studies to evaluate either fetal safety from drug exposure or whether the dose of a drug should be adjusted during pregnancy or lactation:

- *Counter-terrorism.* These studies look at specific anti-infective drug products that would be used for treatment following exposure to specific bioterrorism agents. They focus on use in special patient populations, such as women who are pregnant or lactating and the elderly. They evaluate either the need for dose adjustments in these special patient populations or fetal safety following *in utero* drug exposure.
- *Liver enzymes.* These studies look at the effects of pregnancy on specific drug-metabolizing enzymes in the liver.



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 and is now complete for all products, with a few exceptions, as of May 2005.

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

More information about the OTC drug review process is at http://www.fda.gov/cder/about/smallbiz/OTC.htm.

Over-the-Counter Drug Review

We approved five new drug applications for first-time over-the-counter sale. There were no prescription-to-OTC switches or new uses approved in 2005. Our OTC approvals were:

- *Ibuprofen* and *diphenhydramine hydrochloride (Advil PM Liquigels* and *Caplets)* for relief of occasional sleeplessness associated with pain in adults.
- *Loratadine (Loratadine Oral Suspension)* for the temporary relief of these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the throat or nose in adults and children 2 years of age and older.
- *Chlorhexidine gluconate (2% Chlorhexidine Gluconate Cloth)* for use as a patient preoperative skin preparation in adults and children 2 months of age and older.
- *Loperamide (Loperamide HCl soft gelatin capsules)* to control symptoms of diarrhea, including traveler's diarrhea in adults and children 6 years of age and older.
- *Chlorhexidine gluconate* and *isopropyl alcohol (Chlorascrub Swab, Chlorascrub Swabstick* and *Chlorascrub Maxi Swabstick)* for use as a patient pre-injection preparation and as a patient preoperative skin preparation *(Chlorascrub Swabstick* and *Chlorascrub Maxi Swabstick)* in adults and children 2 months of age and older.

Office of Nonprescription Products created

We created an Office of Nonprescription Products in our reorganization of the Office of New Drugs. Within the office, the Division of Nonprescription Clinical Evaluation focuses mainly on the review of investigational new drugs and new drug applications. The Division of Nonprescription Regulation Development focuses mainly on the development of OTC drug monographs.

Over-the-counter drug statistics

- 5 approvals for first-time OTC sale

Education campaign on safe use of OTCs

We developed a national education campaign to provide advice on the safe use of over-the-counter pain and fever reducers (http://www.fda.gov/cder/drug/analgesics/).

Because many OTC medicines for different uses have the same active ingredients, an unintentional overdose is possible. We are focusing on OTC drug products that contain acetaminophen and non-steroidal anti-inflammatory agents, which include products such as aspirin, ibuprofen, naproxen sodium and ketoprofen.

Generic Drug Review

We approved 344 generic drug products in 2005, including a substantial number of products that represent the first time a generic drug was available for the brand-name product. The median approval time was 16.4 months.

The median statistic for total approval time had hovered at about 18 to 19 months for six years. We have made several changes to improve the efficiency of our generic drug review process in order to try to keep up with the dramatic increase in applications. These efforts will continue.

Notable 2005 generic drug approvals

Examples of first-time generic drug approvals are:

- *Azithromycin.* An antibiotic used for the treatment of mild to moderate infections of various types.
- *Fentanyl transdermal system.* Used for managing chronic pain.
- *Fexofenadine.* Used to relieve seasonal allergic rhinitis symptoms.
- *Levofloxacin.* A broad spectrum antibiotic used for various conditions such as pneumonia, bronchitis and sinusitis.
- *Ramipril.* Used to treat high blood pressure, heart failure after a heart attack and risk reduction for certain cardiac events.
- *Zidovudine.* Used in combination with other antiretroviral agents for the treatment of HIV infection.

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

Consumer communication

Our efforts to build consumer confidence in generic drug products are continuing through our Generic Drug Quality Awareness program.

We have partnered with a number of professional and consumer organizations to launch programs about the quality and benefits of generic drugs. We have helped design messages that appear in waiting rooms and on prescription bags in chain drug stores.

Radio public service announcements with the generic drug quality message will be appearing in several geographic areas.

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

How we approve generic drugs

Generics are not required to repeat the extensive clinical trials used in the development of the original, brand-name drug.

For many products such as tablets and capsules, the generics must show *bioequivalence* to the brand-name reference listed drug. This means that the generic version must deliver the same amount of active ingredient into a patient's bloodstream over the same time period as the brand-name reference listed drug.

The rate and extent of absorption is called *bioavailability*. The bioavailability of the generic drug is then compared to that of the brand-name. This comparison is bioequivalence.

Brand-name drugs are subject to the same bioequivalency tests as generics when their manufacturers reformulate them.

Scientific basis for generic drug review

We continue to articulate the scientific underpinnings of our review process and to work on defining mechanisms to evaluate equivalence of certain unique products.

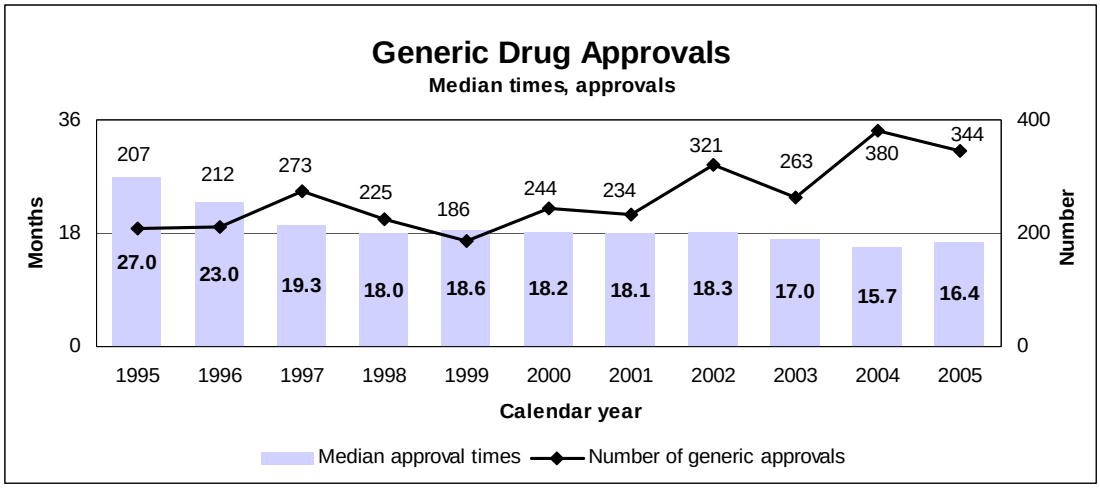
Online education

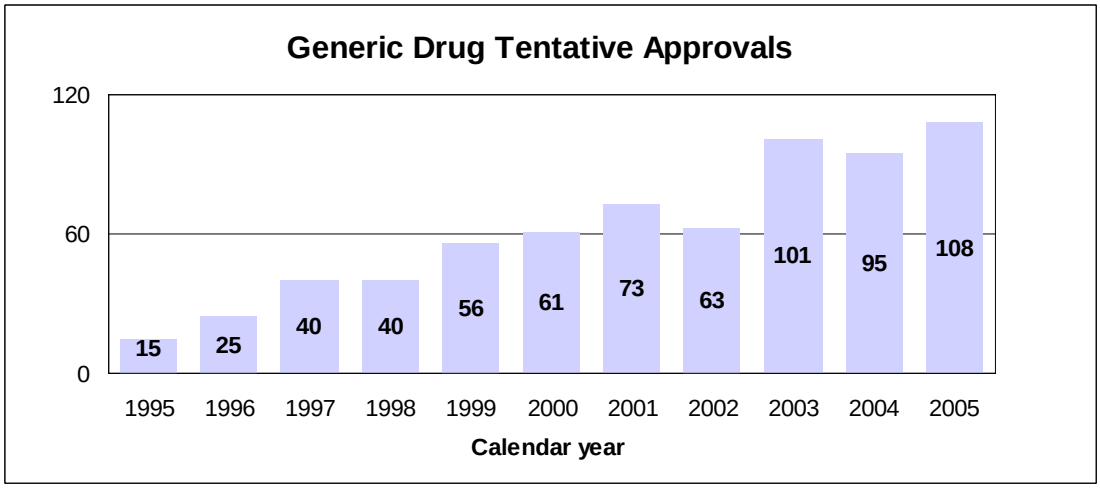
We are offering a free online educational tutorial on the generic drug approval process that offers one hour of continuing education credit for certain health professionals.

The course, available at http://www.connect-live.com/events/genericdrugs/, educates health-care professionals on how our approval assures that generic drugs are safe, effective and high quality products.

Generic drugs

- 344 generic drug approvals
- Median approval time: 16.4 months
- 108 tentative approvals
- 777 receipts





Reducing hurdles to generic drug availability

We are working on regulations to decrease time-consuming legal delays in the approval and marketing of generic products. These rules, implementing provisions of the 2003 Medicare Prescription Drug, Improvement and Modernization Act, will:

- Limit an innovator firm to one 30-month delay for courts to resolve patents challenged by a generic manufacturer.
- Prevent a generic manufacturer with 180-day exclusivity from delaying marketing in order to deny other generic firms entry into the market.

Tentative vs. full approval

The only difference between a full approval and a tentative approval is that the final approval of these applications is delayed due to an 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.

The review of an application that is tentatively approved requires the same amount of work as a review that results in a full approval.

While tentative approvals represent a full workload for us, they are only displayed in our approvals chart once they are converted to full approvals. For example, some of the approvals in 2005 represent conversions of tentative approvals granted in 2004 or previous years.

Tentative approvals key to affordable, worldwide AIDS relief

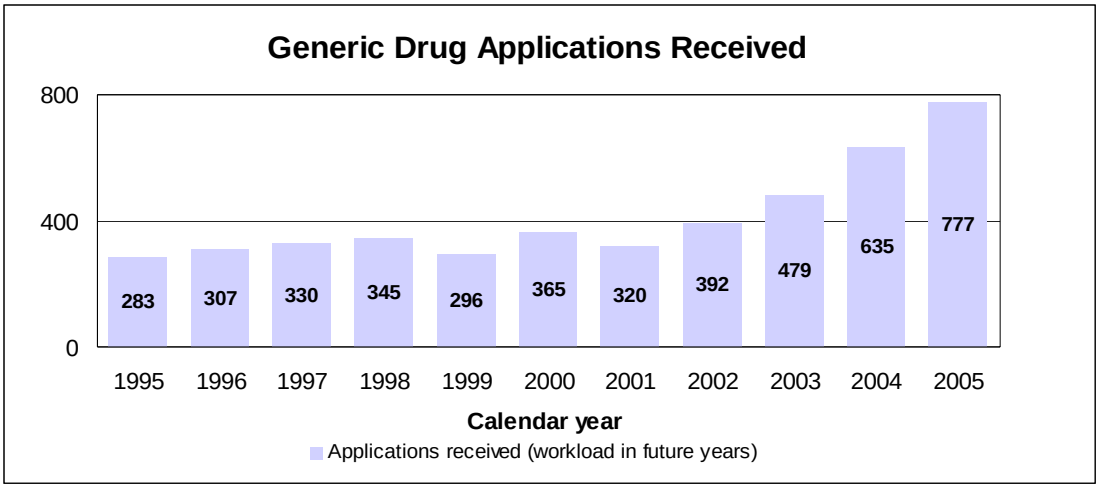
Tentative approval is a key regulatory mechanism to support the availability of drugs for the President's Emergency Plan for AIDS Relief (page 51).

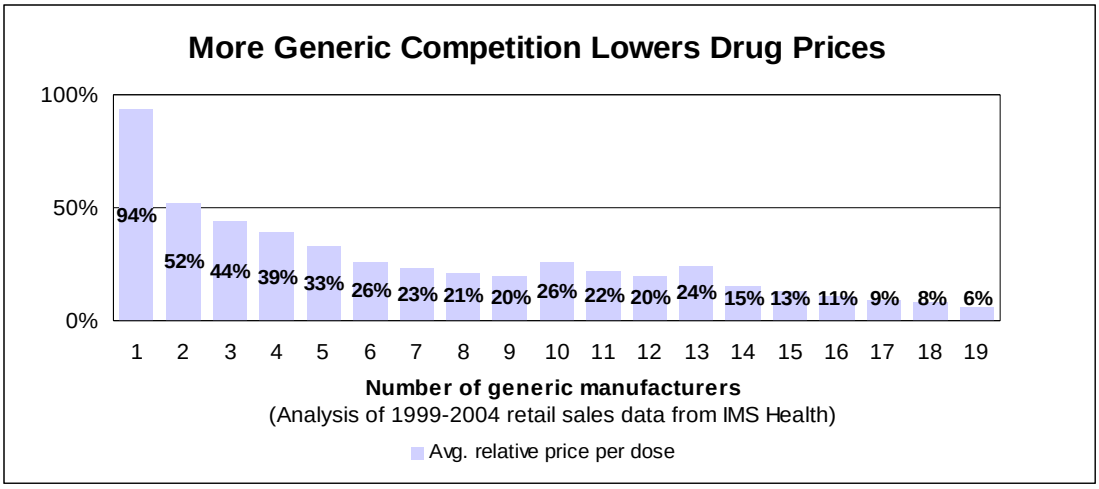
Improving manufacturing practices

The strategic initiative to develop a 21st century drug quality system (page 7) also applies to generic drugs.

Generic drug Web site

You can find more information about our generic drug program at http://www.fda.gov/cder/ogd/.





More generic competition results in lower drug prices

The entry of a second generic competitor brings about the largest price reduction. We concluded this from our analysis of IMS retail sales data for single-ingredient brand-name and generic drug products sold from 1999 through 2004. Our study is at http://www.fda.gov/cder/ogd/generic_competition.htm.

Restructuring to meet increased demands

We have constituted a third chemistry review division for generic drugs.

We also are augmenting our clinical, microbiology and bioequivalence review staffs to meet the needs for review of a growing number of generic drug applications.

Generic drug review efficiencies

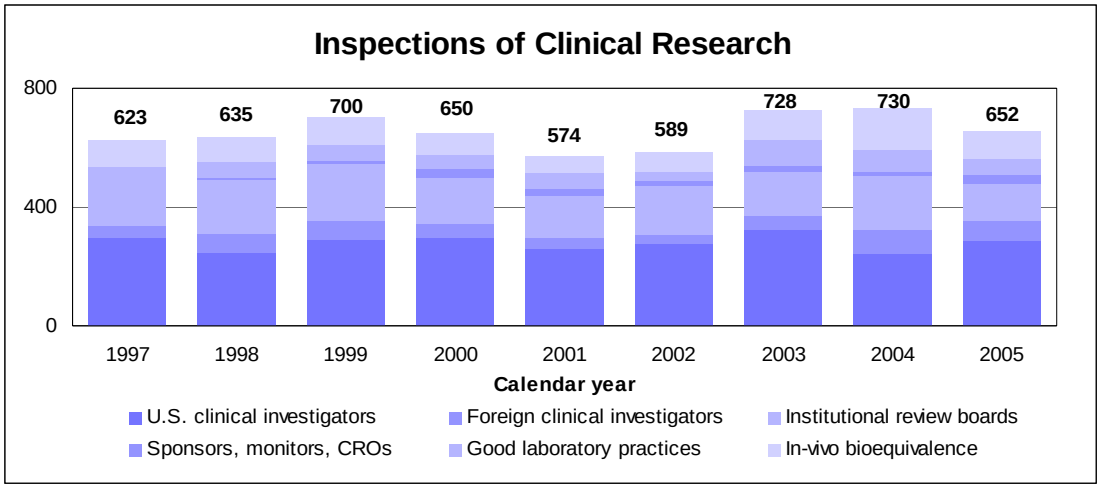
The dramatic increase in receipts of generic drug applications makes it imperative that we process generic drug applications more efficiently. With the overall goal of getting generic drug products to the consumer as efficiently as possible, we continue to look for ways to improve our processes and also to provide communication and guidance to industry.

Our steps to improve the content and completeness of generic drug applications and assure the applications contain the needed information to be evaluated successfully in one cycle include:

- Enhanced communication with applicants during the review process.
- Working with the generic drug industry association to help their members submit applications that can be reviewed more efficiently.
- Exploring further enhancements to the review process.
- Holding joint meetings and workshops with industry to enhance knowledge of topics of interest.
- Efforts to encourage electronic-submission applications (page 32).

Public presentations encourage electronic submissions

Through public presentations, we are encouraging the generic drug industry to submit their applications electronically for greater efficiency.



Inspections for data quality, research risks in 2005

We conducted a total of 652 inspections in 2005:

- 284 U.S. clinical investigators
- 70 foreign clinical investigators
- 122 institutional review boards
- 31 sponsors, monitors or contract research organizations
- 56 good laboratory practices
- 89 *in-vivo* bioequivalence

Top 5 deficiencies found during inspections of clinical investigators in 2005

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

Assessing Data Quality, Research Risks

When obtaining data about the safety and effectiveness of drugs, sponsors rely on high-quality laboratory studies and 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.

We perform on-site inspections to protect the rights and welfare of volunteers and verify the quality and integrity of data submitted for our review. We inspect domestic and foreign clinical trial study sites; institutional review boards; sponsors, monitors and organizations conducting research; laboratories that obtain data; and sites performing bioequivalence studies in humans (page 28) and preclinical studies in animals.

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.

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 at-risk populations, such as children and the mentally impaired.

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

International inspections of clinical research

We conducted 70 inspections of clinical research in 25 countries in 2005.

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. This includes our work with the International Conference on Harmonization (page 54) and the Declaration of Helsinki.

Internet resources

More information on data integrity and patient safety is at http://www.fda.gov/cder/offices/dsi/index.htm.

Electronic Submissions

We cooperated with outside organizations working to publish standards for submitting study data. These groups include the Clinical Data Interchange Standards Consortium and Health Level 7, also known as CDISC and HL-7 respectively. Some of these projects are:

- *Clinical trial data.* We adopted the consortium's Study Data Tabulation Model version 1.0 for submission of information from clinical trials.
- *Preclinical data.* The consortium is working to extend the model to handle animal toxicity and microbiology data.
- *Database development*. We completed a database model for storing and accessing both clinical and animal toxicity data submitted using the Study Data Tabulation Model. We are collaborating with the National Cancer Institute and software vendors to implement the database and develop "smart" tools for accessing the data.
- *Electrocardiogram data.* We adopted the Health Level 7 standard for annotated electrocardiogram waveform data. We are working with a vendor to develop software for analyzing the data and a warehouse for storing it.

We continue to receive electronic submissions using the specifications of the electronic Common Technical Document (page 54).

Electronic submission of labeling required

In 2005, we issued final guidance to assist manufacturers in submitting prescription drug label information to us in a new electronic format. These electronic product labels are the key element and primary source of medication information for "DailyMed"—a new interagency online health information clearinghouse that will provide the most up-to-date medication information free to consumers, health-care providers and health-care information providers (page 5).

Using embedded computer tags, the prescribing and product information can be electronically managed, allowing a user to search for specific information. These tags can instruct computers to read specific sections of a drug label including product names, indications, dosage and administration, warnings, description of drug product, active and inactive ingredients, and how the drug is supplied.

With this information, physicians will be able to quickly search and access specific information they need before prescribing a treatment, resulting in fewer prescribing errors and better informed decision making. In addition, the electronic labels will improve our drug labeling review process, so that we can provide immediate access to the most recent information about medications to prescribers and patients.

Internet resources

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

Structured product labeling.

We are accepting Health Level 7 Structured Product Labeling for content of labeling submissions. We are developing a repository for storing the data and software to improve the processing and reviewing of labeling changes. This is part of our effort to improve patient safety through access to the most recent information about medicines (page 5).

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 second five-year extension in 2002, known as PDUFA III. This reauthorization is helping us 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. The current user fee law maintains our high review performance goals, includes increased consultations with drug sponsors and provides for earlier feedback on their submissions.

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 exceeded all our performance goals for the fiscal year 2004 receipt cohort.
- We are on track for exceeding most user-fee performance goals for the fiscal year 2005 cohort.

Continuous marketing application pilot programs

Under PDUFA III, we are assessing the value of both early review of parts of marketing applications and of more extensive feedback to sponsors during their development programs. Two pilots for "continuous marketing applications" apply to drugs and biologics in our fast track program:

- *Pilot 1* allows applicants to submit predefined portions of their marketing applications called "reviewable units" before submitting the completed application. Each reviewable unit has a six-month goal for issuing a discipline review letter. In fiscal year 2005, we met our performance goal for reviewable unit submissions.
- *Pilot 2* allows us to enter into agreements with sponsors for frequent scientific feedback and interactions during the clinical trial phase of product development. As of Aug. 1, 2005, there were nine development projects entered in the Pilot 2 program.

The pilots have limitations and specific criteria for entry. More information is available at http://www.fda.gov/cder/pdufa/CMA.htm.

Internet resources for user fees

Our user fee Web site at http://www.fda.gov/cder/pdufa/default.htm has links to PDUFA:

- Legislation
- *Federal Register* documents
- Guidances
- Letters
- Performance reports

User fees support risk assessment and minimization

The reauthorization allows user fees to support some safety activities, both during development and for newly approved medicines (page 40).

Drug Review Team

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

- *Biologists, biochemists* and *immunologists* evaluate the manufacturing processes for biological products to ensure the continued purity, potency and safety of these products. They also provide insights to the review team regarding the mechanism of action and potential and observed adverse events associated with specific products.
- *Chemists* focus on how a 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.
- *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.
- *Microbiologists* evaluate the effects of anti-infective drugs on germs. These medicines—antibiotics, antivirals and antifungals—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.
- *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.
- *Safety reviewers* propose and evaluate risk management plans as well as review proposed brand names, packaging and labeling to minimize errors when a drug is prescribed, dispensed or administered.
- *Statisticians* evaluate the designs and results for each important clinical study.

Scientific training for reviewers

Our systematic, internal training program is based on core competencies, learning pathways and individual development plans. In 2005:

- We presented 30 scientific seminars and scientific rounds.
- We offered a strong and innovative curriculum of 45 scientific courses. Subjects included therapeutic biologics, nanotechnology, toxicology for the non-toxicologist and orally disintegrating tablets.
- We brought in 49 visiting professors to talk directly to individual review divisions about critical, new drug-related research and techniques.
- We offered additional courses in job skills, research tools, leadership and management.

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.

Academics to CDER

Each spring, we collaborate with five local universities to present an up-to-date course on a compelling scientific topic. Recent topics were:

- 2005: Critical path science
- 2004: Exposure-response concepts
- 2003: Drug safety
- 2002: Pharmaco-genetics
- 2001: QT prolongation

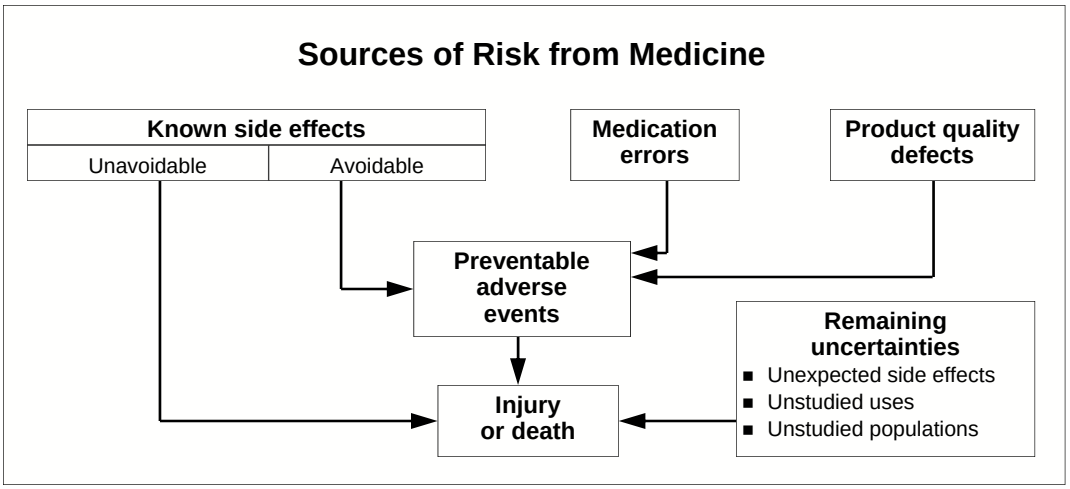
2

DRUG SAFETY AND QUALITY

The practical size of premarketing clinical trials means that we cannot learn everything about the safety of a medicine before we approve it. Therefore, a degree of uncertainty always exists about the risks of a medicine, not only when we approve it but also after we approve it. This uncertainty requires our continued vigilance, along with that of the industry, to collect and assess safety data for medicines on the market. 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.

We also monitor the quality of marketed drugs and their promotional materials through product testing and surveillance. In addition, we develop policies, guidance and standards for drug labeling, current good manufacturing practices, clinical and good laboratory practices and industry practices to demonstrate the safety and effectiveness of drugs. Highlights of medication safety and quality activities in 2005 include:

- Improving the electronic infrastructure to support real-time availability of the most up-to-date drug information for health-care providers and consumers (pages 4-5).
- Establishing and operating the Drug Safety Oversight Board (page 5).
- Processing and evaluating more than 460,000 reports of adverse drug events, including more than 25,000 submitted directly from individuals.
- Issuing 60 letters on violations in drug promotion and more than 600 letters to help ensure manufacturers comply with regulations concerning drug promotion. Included in the total were more than 200 letters concerning direct-to-consumer advertising.
- Issuing warning and other regulatory letters to firms selling drugs that were unapproved, poorly poor manufactured or labeled incorrectly. We also supported successful federal lawsuits against a firm importing unapproved drugs and a firm distributing unapproved and poorly manufactured prescription and over-the-counter drugs.
- Evaluating more than 3,100 reports concerning problems that occur in the manufacturing, processing, packing, labeling, storing or distributing drugs.
- Issuing 16 Public Health Advisories regarding drug safety issues.
- Approving Medication Guides for prescription non-steroidal anti-inflammatory drugs with any of 18 active ingredients and for five additional prescription drugs.



Safety System for Medicines

Our current system for evaluating drug safety provides:

- Extensive premarket testing with rigorous review, including evaluation of remaining uncertainties. Premarket testing cannot, however, detect very rare, serious adverse events (see below).
- Risk management strategies before and after approval.
- Mandatory and voluntary adverse event reporting systems, before and after approval, with additional population-based information.
- User-friendly communication through an improved drug label compatible with e-prescribing and electronic decision support.

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.* Drug therapy requires an individualized treatment plan and careful monitoring. Other avoidable side effects are caused by 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 cancer chemotherapy.

Medication errors. For example, the drug is administered incorrectly or the wrong drug or dose is administered.

Remaining uncertainties. In addition to rare events occurring in about 1 in 10,000 persons,these include long-term effects and unstudied uses and populations.

Capacities of current postmarketing safety system

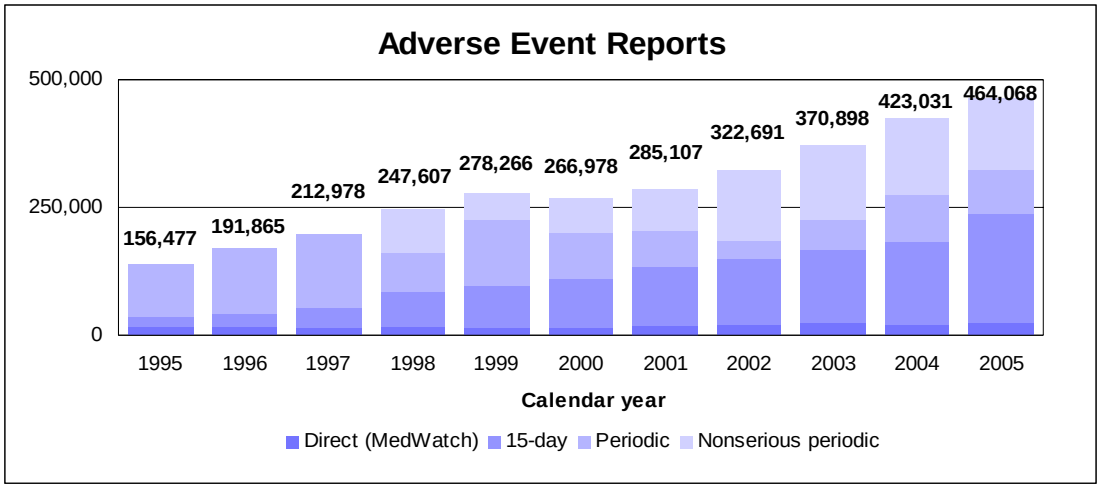
- Profile of common adverse events in populations studied during development.
- Understanding of medication metabolism and common metabolism-based drug-drug interactions.
- Management and evaluation of certain anticipated postmarketing risks.
- Identification of adverse events that occur after marketing with a focus on serious adverse events.

Knowledge gaps in postmarketing safety system

- Differences in the frequency of events between those taking and not taking a drug.
- Detection of events after long-term exposure.
- Adverse events in populations not normally studied in trials, such as those who are very sick or on multiple drugs.
- Adverse events occurring more frequently with off-label use.
- Detection of many types of medical errors or abuse.
- Unreported events.

Approaches to resolving knowledge gaps

- Surveillance with emerging automated health-care data systems.
- Randomized trials or registries in practice settings.
- Surveillance systems in specialized settings such as emergency rooms or nursing homes.
- Large real-world studies of drug use.



Adverse event reporting

In 2005, we received 464,068 reports of suspected drug-related adverse events:

- 25,325 MedWatch reports directly from individuals.
- 213,537 manufacturer 15-day (expedited) reports.
- 84,770 serious manufacturer periodic reports.
- 140,436 nonserious manufacturer periodic reports.

Drug Safety Surveillance

We evaluate the safety 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.

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 (page 40).

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, known as AERS. This computerized system combines the voluntary adverse drug reaction reports from MedWatch (page 39) 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 features both 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.

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 serious and unexpected adverse events to us as soon as possible but 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 electronic submissions

Electronic submission of adverse event reports permits more timely receipt and evaluation at considerable cost savings for us and industry.

Our initiative to encourage electronic reports continues to make progress and remains a high priority.

We provide useful information on electronic adverse event reports at http://www.fda.gov/cder/aerssub/default.htm.

Adverse event reporting compliance

We monitor the pharmaceutical industry's processing of adverse event reports. A firm's procedures for collection, evaluation and submission may affect the transfer and quality of safety data that we have for analysis. Our surveillance of industry is based upon the risks associated with specific drug products and specific data processing procedures.

Risk-based inspections

We inspect drug firms' adverse event reporting based upon risk criteria associated with specific drug products and corporate performance. These include:

- Newly marketed drugs.
- Emerging safety signals.
- Previous violations.
- Corporate transitions.

Inspection outcome

In fiscal year 2005, our field investigators inspected 106 domestic and six foreign firms to assess compliance with our regulations for adverse event reporting. We sent three firms official notification that they had significant uncorrected deficiencies. We were able to work with about 40 firms to obtain voluntary correction of deficiencies identified by our monitoring.

User fees support risk assessment, minimization

In recent years, about half of all new medicines marketed worldwide have been launched in the United States, and American patients have had access to about three-quarters of the world's new medicines within the first year of their introduction.

The law authorizing us to collect user fees (page 33) allows us to spend some of those funds to increase our assessment and minimization of risks of medicines both before they are approved and after approval:

- *Preapproval.* Sponsors are invited to submit proposed risk management plans before they submit an application for a new drug or biologic. Our drug safety experts carefully review the proposals and begin discussions with sponsors at this early stage that continue through application review and after approval.
- *Postapproval.* User fees also fund 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 most likely to identify and counter adverse side effects that did not appear during the clinical trials.

Outreach and education

In addition to our inspectional program for adverse event compliance, we improve safety reporting through educational presentations to industry.

These provide industry with a direct opportunity to expand their understanding of reporting requirements and best practices in drug safety and to alert them to pending regulatory changes.

These meetings also serve to expand our own knowledge of industry's worldwide pharmacovigilance activities.

Our educational activities include formal presentations at global industry meetings and training for FDA field investigators.

MedWatch Outreach and Reporting

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

- Rapidly disseminating new safety information on the Internet and by providing e-mail notification to health professionals, institutions, the public and our MedWatch partners consisting of professional societies, health agencies and patient and consumer groups.
- Providing a mechanism for health professionals and the public to voluntarily report serious adverse events, product quality problems and product use errors for 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.

Individual health-care professionals and consumers can subscribe to our e-mail notification service, which now has 56,000 members. We also have 160 MedWatch Partner organizations. In 2005, these individuals and groups received:

- 109 safety alerts for drugs and therapeutic biologics.
- 25 to 70 safety-related labeling changes for drugs each month.

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. We require Medication Guides when the information is necessary for patients to use the product safely and effectively.

In 2005, we approved Medication Guides for prescription pain relievers with any of 18 nonsteroidal anti-inflammatory ingredients (right) and these five other drugs:

- Atomoxetine hydrochloride (Strattera).
- Lenalidomide (Revlimid).
- Pramlintide acetate (Symlin).
- Tamoxifen citrate (Soltamox).

These Medication Guides must be provided to patients with each prescription dispensed.

Data mining

We concluded work under our two-year data mining cooperative research and development agreement with a commercial firm to develop advanced software tools for quantitative analysis of drug safety data. The resulting software, WebVDME, is now in full production use by safety evaluators and epidemiologists.

Data mining for simple drug-event signal generation is one potential contribution data mining and related quantitative methods can make to increase our awareness and understanding of trends and patterns in adverse drug reactions.

MedWatch Internet resources

- You can find the latest medical product safety information 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/elist.htm.

NSAID MedGuide active ingredients

- Celecoxib
- Diclofenac
- Diflunisal
- Etodolac
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Ketoprofen
- Ketorolac
- Mefanamic acid
- Meloxicam
- Nabumetone
- Naproxen
- Oxaprozin
- Piroxicam
- Sulindac
- Tolmetin

Population-based drug safety evaluation

New contracts will help us evaluate the safety of newly marketed drugs faster and more effectively. We awarded four contracts that give us access to databases that include more than 20 million patients in different geographic areas and include special populations. The contracts, which give us more flexibility and access to a wider range of data resources than we previously had, can be used to:

- Conduct safety analyses.
- Respond in a timely manner to urgent public safety concerns.
- Provide a mechanism for collaborative research designed to test hypotheses, particularly those arising from suspected adverse reactions reported to us.
- Enable our rapid access to U.S. population-based data sources to ensure public safety when necessary.

Medication Error Prevention

Avoiding name, label, labeling and packaging confusion

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, labeling and packaging that might contribute to problems or confusion in prescribing, dispensing or administering drug products.

We review about 300 post-marketing reports of medication errors each month. About half are due to error-prone labeling such as similar looking labels and labeling, poor package design, confusing instructions for use and confusing names. We investigate the causes and contributing factors of these errors and recommend revisions to the label, labeling and/or packaging of these products to avert further error.

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

Bar codes required on medicines

Our regulation that calls for medicines to have a bar code became final in February 2004. It covers most prescription medicines and certain over-the-counter medicines commonly used in hospitals. The bar code rule aims to protect patients from preventable medication errors by helping ensure that health professionals give the right patient the right drug, at the appropriate dosages, at the right time. The rule will support and encourage widespread adoption of advanced information systems that, in some hospitals, have reduced medication error rates by as much as 85 percent.

We estimate that the rule will help prevent nearly 500,000 adverse events and transfusion errors while saving $93 billion in health costs over 20 years.

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.

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.

Public Health Advisories in 2005

We issued 16 advisories to alert health-care providers and consumers to:

- Increased liver toxicity associated with the anti-HIV drug *nevirapine.*
- Concerns about the risk of sudden death in patients treated with *Adderall XR,* a drug product containing amphetamines, and a Canadian regulatory action on the product.
- Our warning to avoid using the epilepsy drug *tiagabine* in patients without epilepsy because of seizures.
- The suspended marketing of *natalizumab,* a treatment for multiple sclerosis, which was remarketed in 2006 with a risk management plan.
- Our advice that the eczema therapies *pimecrolimus* and *tacrolimus* only be used as directed—that is for short term use and not at all in children younger than 2 years of age—and only after other treatments have failed to work because of a potential cancer risk.
- An increased risk for serious muscle toxicity associated with the cholesterol lowering drug *rosuvastatin,* especially at the highest approved dose.
- The increased risk of heart attack and stroke associated with the long-term use of *non-steroidal anti-inflammatory drugs.*
- Increased deaths when *atypical antipsychotic drugs* are used to treat behavioral disorders in elderly patients.
- Suicidality in adults being treated with *antidepressants.*
- The suspended marketing of *Palladone,* an extended-release formulation of an opioid pain medication.
- Our highlighting the importance of the safety information in the labeling when using *fentanyl transdermal skin patches* for pain control because of reports of death and other serious side effects.
- Four cases of fatal infection in women following medical abortion with *mifepristone.*
- Suicidal thinking in children and adolescents associated with *atomoxetine,* a drug approved to treat attention deficit hyperactivity disorder.
- Possible increased risk of worsening wheezing and death in some people treated with several long-lasting *bronchodilator* medicines.
- Increased risk for congenital malformations when the antidepressant *paroxetine* is used in the first trimester of pregnancy.
- The marketing suspension of a diagnostic imaging agent.

Internet resources

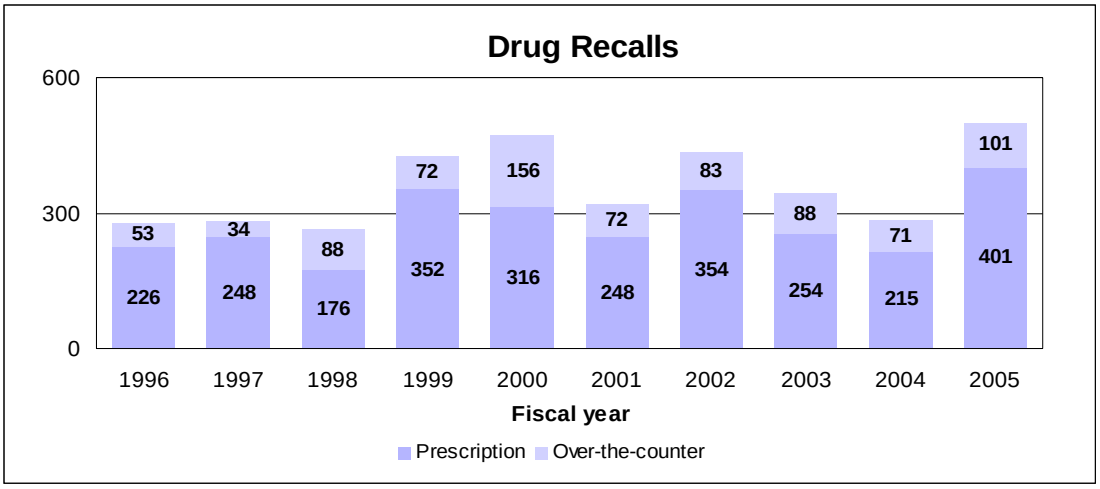
Links to our Public Health Advisories and associated information are at http://www.fda.gov/cder/news/pubpress.htm.

Risk management guidances published

We published three risk management guidances in 2005:

- *Premarketing Risk Assessment* focuses on measures companies might consider throughout all stages of a medicine's clinical development.
- *Development and Use of Risk Minimization Action Plans* describes how to address specific risk-related goals and objectives and also suggests various tools to minimize the risks of drug and biological products.
- *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* identifies recommended reporting and analytical practices to monitor the safety concerns and risks of medicines in general use.

The three guidances fulfill our commitment to the risk management goals in the 2002 reauthorization of the Prescription Drug User Fee Act.



Drug recalls in fiscal year 2005

- 401 prescription drugs
- 101 over-the-counter drugs

Top 10 reasons for drug recalls in fiscal year 2005

- Miscellaneous cGMP deviations (other than below)
- Failed USP dissolution test requirements
- Microbial contamination of non-sterile products
- Lack of efficacy
- Impurities/ degradation products
- Lack of assurance of sterility
- Lack of product stability
- Labeling: Label error on declared strength
- Misbranded: Promotional literature with unapproved therapeutic claims
- Labeling: Correctly labeled product in incorrect carton or package

Drug Recalls

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 left. In other cases, a drug is determined to be unsafe for continued marketing and must be withdrawn completely.

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.

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.

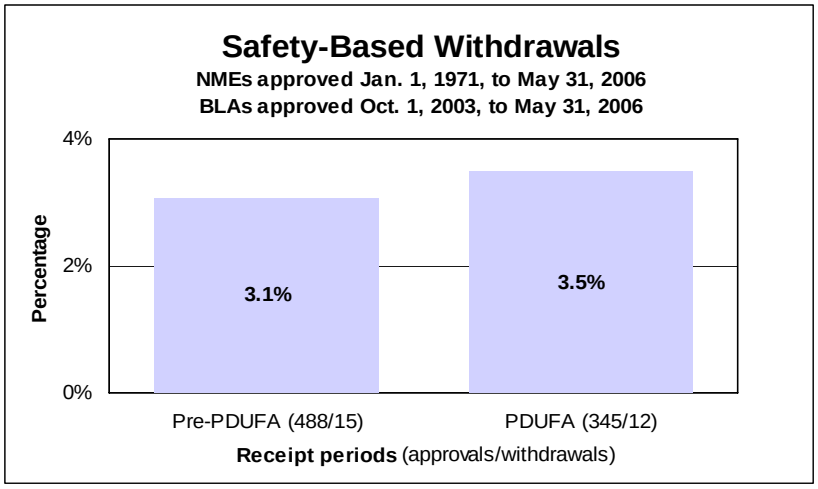
Spike in 2005 recalls

One firm had more than 100 recalls in 2005, which caused a spike in the recall figures.

NME safety withdrawals

Drug name
(FY received
[**bold=PDUFA**]/
CY approved/
CY withdrawn)
approved use/
reason withdrawn

- **Azaribine**
(1970/1975/1976)
psoriasis treatment/
serious blot clots
- **Ticrynafen**
(1978/1979/1980)
blood pressure reduction/
liver toxicity
- **Benoxaprofen**
(1980/1982/1982)
pain relief/liver toxicity
- **Zomepirac**
(1979/1980/1983)
pain relief/
fatal allergic reaction
- **Nomifensine**
(1979/1984/1986)
antidepressant/
hemolytic anemia
- **Suprofen**
(1979/1985/1987)
pain relief/
acute kidney failure
- **Encainide**
(1984/1986/1991)
irregular heartbeat/
fatal arrhythmia
- **Temafloxacin**
(1990/1992/1992)
antibiotic/kidney failure



Safety-Based Drug Withdrawals

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. The rates of safety-based withdrawals of new molecular entities are similar for an earlier period before we collected user fees and for the period, beginning Oct. 1, 1992, when we collected user fees. Our time periods are based on when we received an application rather than when we approved it. Beginning Oct. 1, 2003, approvals include new therapeutic biologics. Applications exempt from user fees are also counted.

Four safety withdrawals of NMEs or new BLAs in 2005

- *Valdecoxib,* a COX-2 selective non-steroidal anti-inflammatory pain reliever, was withdrawn because it carried an increased risk of serious skin reactions in addition to the risk of heart disease associated with NSAIDs.
- *Pemoline,* a central nervous system stimulant treatment for attention deficit hyperactivity disorder, was withdrawn because it caused fatal and life-threatening liver failure.
- *Natalizumab,* a treatment for multiple sclerosis, was withdrawn because three patients developed a serious viral infection of the brain. It was reintroduced in 2006 with a special restricted distribution program.
- *Technetium (99m Tc) fanolesomab,* a radiological imaging agent for unclear signs and symptoms of appendicitis, was withdrawn for fatal and life-threatening cardiopulmonary arrest occurring shortly after administration.

One non-NME safety withdrawal in 2005

- *Palladone,* a brand of hydromorphone hydrochloride extended-release capsules, was withdrawn because serious and potentially fatal adverse reactions could occur if the drug was taken with alcohol, which harmed the extended-release mechanism and could lead to dose-dumping.

NME safety withdrawals (cont.)

- **Flosequinan** (1991/1992/1993) congestive heart failure/ increased deaths
- **Fenfluramine** (1967/1973/1997) appetite suppression/ heart valve disease
- **Terfenadine** (1983/1985/1998) antihistamine/ fatal arrhythmia
- **Bromfenac** (**1995**/1997/1998) pain relief/ liver toxicity
- **Mibefradil** (**1996**/1997/1998) blood pressure reduction/ serious drug-drug interactions leading to muscle damage and fatal arrhythmia
- **Grepafloxacin** (**1997**/1997/1999) antibiotic/fatal arrhythmia
- **Astemizole** (1985/1988/1999) antihistamine/ fatal arrhythmia
- **Cisapride** (1991/1993/2000) heartburn/fatal arrhythmia
- **Troglitazone** (**1996**/1997/2000) diabetes/liver toxicity
- **Alosetron** [Remarketed in 2002 with restricted distribution] (**1999**/2000/2000) irritable bowel syndrome/ ischemic colitis, severe constipation

NME safety withdrawals (cont.)

- **Cerivastatin** (**1996**/1997/2001) cholesterol reduction/ muscle damage leading to kidney failure
- **Rapacuronium** (**1998**/1999/2001) anesthetic/severe breathing difficulty
- **Etretinate** (1985/1986/2002) psoriasis/birth defects
- **Levomethadyl** (**1993**/1993/2003) opiate dependence/ fatal arrhythmia
- **Rofecoxib** (**1999**/1999/2004) pain relief/ heart attack, stroke
- **Valdecoxib** (**2001**/2001/2005) pain relief/skin disease
- **Natalizumab** [Remarketed in 2006 with restricted distribution] (**2004/**2004/2005) multiple sclerosis/ brain infection
- **Technetium (99m Tc) fanolesomab** (**2000**/2004/2005) diagnostic aid/ cardiopulmonary arrest
- **Pemoline** (1969/1975/2005) ADHD/liver failure

Drug Promotion Review

The information about a drug available to physicians and consumers is criticaly important to its safe use. 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.

Direct-to-consumer promotion

We are reviewing and developing methods to increase our effectiveness in the oversight of direct-to-consumer advertising. Evidence from our own studies as well as those conducted by consumer groups and other entities consistently shows that direct-to-consumer ads encourage some patients to seek care for undertreated conditions. This often results in prescription of a treatment that is not the one advertised but a treatment that is more appropriate for the patient. But physicians and others are concerned that consumers may not always get a balanced view of the benefits and risks of a product and may sometimes be given drugs they do not need or are not the best choice.

Public meeting addresses DTC promotion issues

In November 2005, we took part in a two-day FDA public hearing on direct-to-consumer promotion of regulated medical products, including prescription drugs for humans. We heard more than 30 presentations representing the viewpoints of consumers, patients, caretakers, health professionals, managed care organizations, insurers and the regulated industry. Topics included:

- Various ways of presenting risk and benefit information to consumers, including what and how it should be presented in consumer friendly language.
- The impact of DTC promotion on the diagnosis and treatment of disease.
- How DTC promotion might impact under-treated and under-diagnosed medical conditions.
- Data from research conducted related to DTC promotion.
- The use of celebrities in DTC promotion.
- The use of disease awareness campaigns.
- The impact of images and graphics on promotions and reminder advertisements.

We are reviewing the comments from the meeting and an additional 1,200 written comments submitted to us.

DTC promotion research

We are conducting three studies to help find the best way or ways to present information in the "brief summary"—the page of risk information in a print ad:

- *Purpose.* The first study will concern the purpose of the brief summary—how do people use it and what topics do they find most useful. We hope to have data collected for this study by the end of summer 2006.
- *Content.* The second study will address content issues in the brief summary, including the amount of common side effect information and the inclusion of numerical context.
- *Format.* The third study will examine format issues, such as graphics, layout and font.

DTC promotion letters

In 2005, 203 or 30 percent of the letters we issued concerned direct-to-consumer promotion.

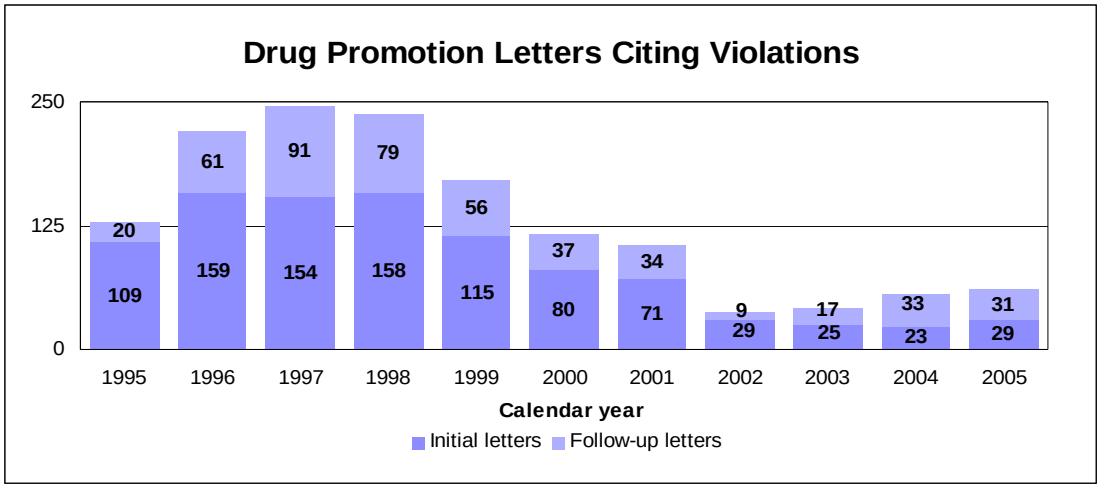
We issued guidance on direct-to-consumer broadcast advertisements in 1997. Since then, the number of letters addressing direct-to-consumer promotion and their percentage of the total letters addressing promotion have been:

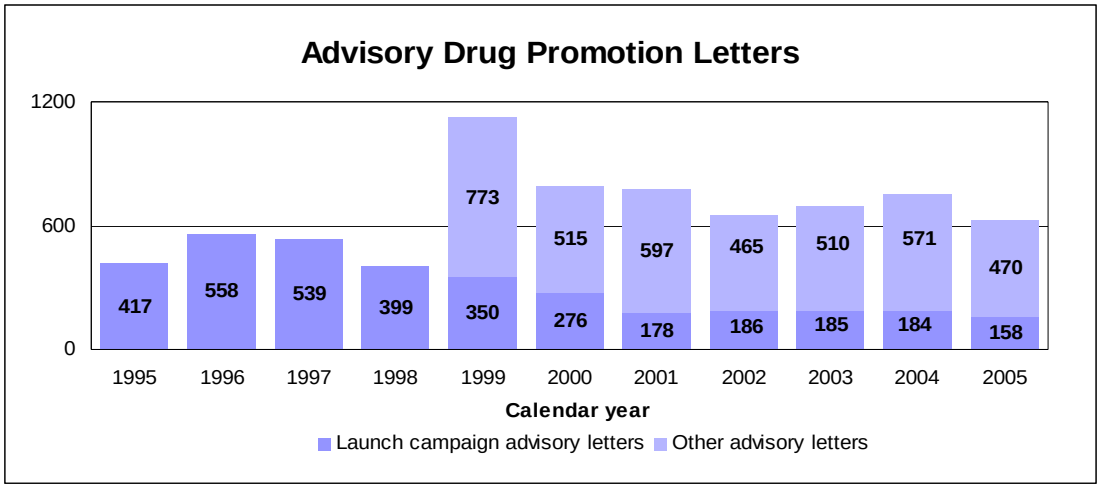
- 2005: 203 (30%)
- 2004: 217 (27%)
- 2003: 254 (34%)
- 2002: 188 (27%)
- 2001: 190 (22%)
- 2000: 215 (24%)
- 1999: 247 (19%)
- 1998: 282 (44%)
- 1997: 240 (31%)

Drug promotion letters in 2005

In 2005, we issued 688 letters concerning drug promotion. These were:

- **60 letters citing violations**
  - 29 initial
  - 31 follow-up
- **628 advisory letters**
  - 158 launch campaigns
  - 470 others





Surveillance of drug promotion activities

Drug advertising and promotion must be truthful, fair, balanced and not misleading. We issue letters to ensure compliance with our regulations when asked or as a result of our own surveillance.

Regulatory letters citing violations

We issued 60 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 violative promotions include exhibit hall displays, oral representations, Internet sites, plus traditional materials such as journal advertisements, sales brochures and TV ads.

Other advisory letters

We issued 348 other advisory letters to the industry regarding proposed promotional pieces, both professional- and consumer-directed. We also issued 122 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

Launch campaign advisory letters

When requested, we review advertisements and other promotional materials before drug companies launch marketing campaigns that introduce either new drugs or new indications or dosages for approved drugs. In 2005, we issued 158 advisory letters to companies regarding their promotional materials for launch campaigns.

Compliance Oversight

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 three basic strategies to meet this goal:

- Evaluate the findings of inspections that examine the conditions and practices in plants where drugs are manufactured, packed, tested and stored.
- Monitor the quality of finished drug products in distribution, through sampling and analysis.
- Monitor drug products to ensure that they comply with applicable approval and labeling requirements.

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

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.

Criteria for risk-based sampling

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

Compounded drugs

We generally defer to state authorities regarding the regulation of traditional pharmacy compounding—on-site compounding of reasonable quantities of drugs by a pharmacist in response to a practitioner's prescription for an individual patient to accommodate the specialized medical needs of that particular patient.

Manufacturing disguised as compounding

Some pharmacies manufacture and distribute compounded drugs in a way that goes beyond traditional pharmacy practice. Many of these pharmacies make large quantities of unapproved drugs in advance of receiving valid prescriptions. They also copy commercially available drugs when there is no medical need to do so. We hold pharmacies that manufacture drug products under the guise of pharmacy compounding to the same federal legal requirements as drug manufacturers.

Furthermore, some pharmacies have compounded drugs that are contaminated, dangerously subpotent (weak) or superpotent (strong). In these situations, we take steps to protect the public from these products. These steps include issuing enforcement letters, referring complaints to state authorities, providing support when states ask, and pursuing enforcement actions, such as seizure of violative products.

Biologics license inspections

Our experts conduct the preapproval inspections in support of biologics license applications and supplements to them. In fiscal year 2005, there were:

- 9 domestic inspections
- 3 foreign inspections

In other work to ensure the quality of biologics, we reviewed:

- 4 supplements for which we waived the inspection
- 35 supplements that did not require an inspection
- 63 annual reports

We held 38 meetings with industry and answered 38 inquiries about good manufacturing practices.

Correction

In previous editions of this report, the data labeled "preapproval inspections" were for "establishment evaluation requests." All requests are evaluated, but only some trigger an in-plant inspection.

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 periodic inspections to make sure a firm can consistently manufacture the product with the required quality. We develop compliance programs to guide the investigators in conducting these inspections, and we identify facilities that are high priority for inspection based on their identified risk potential.

Prioritizing sites for inspection

Our 2004 white paper, *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model*, creates a formal risk ranking of manufacturing plants by using an analytical process to:

- Pose a risk question.
- Identify potential hazards and risks.
- Characterize factors that can be used as variables for quantifying risk.
- Mathematically combine the variables to yield an overall risk score.

This program continues to be refined and improved by better evaluation of the risk factors available to us. For example, we added adverse experience reports data to the model in addition to the many data sources already being used. This allows us to maximize our limited resources by focusing our field force on those sites that most affect product quality and safety.

Good manufacturing practice enforcement

We have acted under our regulatory enforcement program to address products not manufactured under current good manufacturing practice regulations. We provide expert technical support that employs science and risk-based principles in applying these regulations. As a result, many corrections are achieved voluntarily or through administrative means. Some corrections, though, require the involvement of the judiciary system. One case of note resulted in a court-ordered injunction against a firm violating cGMPs and selling unapproved drugs. The judge in this case stated that he was "simply unwilling as a court of equity to place the health, safety and welfare of the general public at risk in order to accommodate the economic well-being of defendants."

Domestic drug plant inspections

In fiscal year 2005, FDA field office inspections included:

- **188 preapproval inspections in support of:**
  - 105 new drug applications
  - 98 generic drug applications
- **1,437 current good manufacturing practice inspections**

For these, we approved 22 field recommendations for regulatory action, including:

- 15 warning letters
- 6 injunctions
- 1 seizure

- **152 medical gas inspections**

We reviewed 152 medical gas inspections and approved two warning letters.

Foreign drug inspections

There were 213 foreign current good manufacturing practice inspections and 234 foreign preapproval inspections in 2005. (page 53).

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. They may use a fraudulent product for treating a serious disease in place of an approved, effective treatment, or they may delay the use of a proper treatment in favor of a fraudulent remedy. Fraudulent products may also contain toxic compounds or other hazardous substances that have the potential to cause serious illness, injury or even death. For these reasons, products that are mislabeled, fraudulent or make unproven claims may pose a significant health risk.

Protecting consumers from misbranded or fraudulent drugs

We protect consumers from mislabeled, fraudulent or hazardous products. We locate and identify these products on the Internet and other outlets, and we take steps to prevent their sale and to remove them from the market. These steps include issuing enforcement letters and pursuing enforcement actions, such as seizures of violative products and injunctions against firms and individuals. We also work with other federal agencies to coordinate enforcement action against firms and individuals who violate federal law.

We may also take steps to warn the public about misbranded and fraudulent products. These steps include issuing press releases and MedWatch alerts to warn consumers about the potential health risks associated with these products.

Drugs sold without required applications

We identify drugs that are marketed without an approved new or generic drug application. The marketing of products that lack required FDA approval may present safety risks and threatens to undermine the U.S. drug development and approval process, as well as the over-the-counter drug review process.

We estimate that there are several thousand illegally marketed drug products in the United States, comprised of several hundred unique molecules. We issued a draft guidance in 2003 that describes how we intend to:

- Encourage companies to sponsor unapproved drugs through the approval process.
- Avoid unnecessarily restricting patient access to useful medicines.
- Use risk-based criteria for enforcement action.

Regulation of over-the-counter drugs

The formulation of OTC drugs and the information that accompanies them or is displayed with them is critical to their safe use.

Approved drug applications and OTC drug monographs (page 27) define acceptable formulations and the consumer labeling and promotional statements for drugs sold over-the-counter.

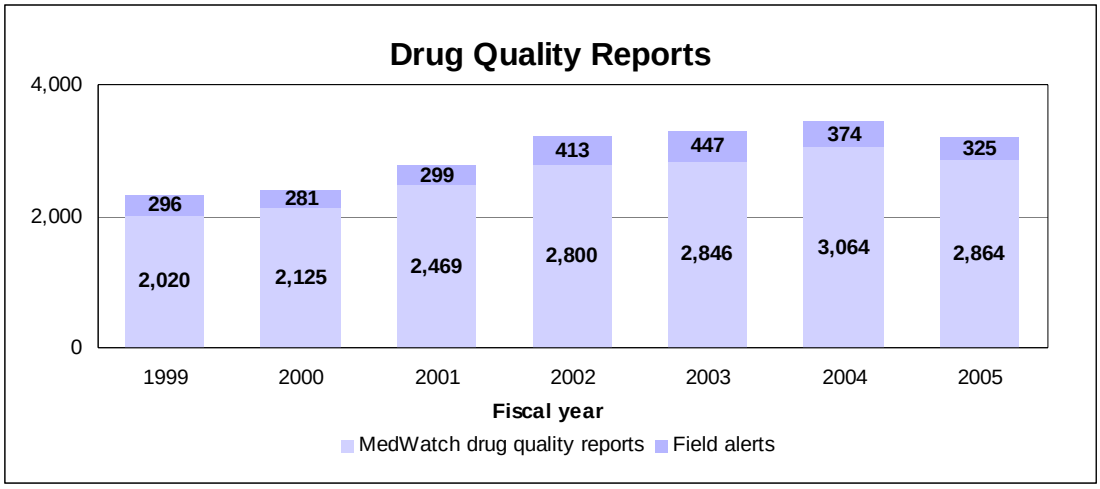
We monitor the statements that accompany these products along with their formulations to make sure they comply with the appropriate application or final monograph.

We also monitor the formulations, labeling and promotional materials associated with over-the-counter drugs marketed without an approved application or final monograph, including fraudulent drugs, and take enforcement actions against these products where necessary.

Council for Pharmaceutical Quality

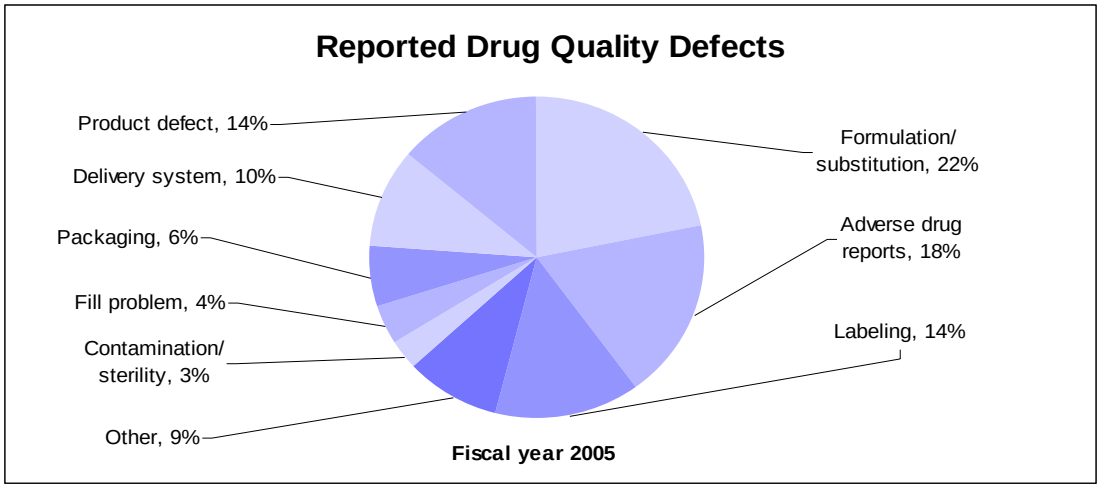
FDA formed a Council for Pharmaceutical Quality in 2005 to oversee policy development and implementation, including the ongoing implementation of internal quality management systems relating to drug quality regulations.

Through our active participation in this program, we have provided the Pharmaceutical Inspectorate advanced training on risk-based approaches to inspections, modern quality systems and the legal and scientific application of good manufacturing practice regulations to manufacturing operations. We certified the first class of these highly trained investigators and are preparing for the next class.



Drug quality reports

- 325 field alerts
- 2,864 MedWatch reports



Types of reports

- *Drug Quality Reporting System.* Through MedWatch (page 39), we receive reports from consumers and health-care professionals of observed and suspected product quality defects. Our central reporting system assists us in evaluating and prioritizing these data to identify potential manufacturing quality problems and industry trends.
- *Field Alert Reports.* Firms are required to promptly notify FDA district offices about possible quality and labeling problems that may represent a safety hazard. Experts in FDA district offices evaluate the reports and conduct further investigations when needed.

Drug Quality Surveillance Systems

Our reporting tools help us rapidly identify significant health hazards and quality problems associated with the manufacturing and packaging of medicines. Problems that may affect a medicine's safety, purity or potency may occur during manufacturing, processing, packing, labeling, storage or distribution.

We evaluate reports and FDA field inspections to identify specific firms with manufacturing quality problems with the most potential impact on public health. We target these candidates for inspection and further product sampling and laboratory analysis. We recommend appropriate corrective actions based upon our analysis of the findings. We may take enforcement action in some cases.

Types of reports (cont.)

- *Biological Product Deviation Reports.* Manufacturers are required to report any event associated with the manufacturing of a therapeutic biological that may affect its safety, purity or potency.

Product Quality Science

The Pharmaceutical cGMPs for the 21st Century Initiative (page 7) stresses the need to apply more scientific and engineering knowledge to regulatory decision making and to the evaluation of manufacturing processes. The goal is to improve upon the overall efficiency and effectiveness of manufacturing processes and to enhance product quality. We have looked closely at manufacturing science to develop recommendations for improvements.

One of the areas that we focused on was the Process Analytical Technologies Initiative. The capability to use process analytical technologies encourages manufacturers to be innovative and to apply state-of-the-art quality assurance methodologies to their manufacturing processes. Process analytical technologies incorporate assessment of a product's characteristics in real-time and feed that information back into process control systems that maintain the desired state of product quality throughout manufacturing.

2005 progress highlights

We moved into the implementation phase after the release of our final PAT guidance in 2004. We note the following highlights:

- *PAT review and inspections.* PAT applications and implementations have been approved or passed inspection for brand-name products, generics, over-the-counter drugs and active pharmaceutical ingredients.
- *Training.* There have been a number of training sessions for PAT, including training of the Pharmaceutical Inspectorate. We have developed plans for extensive internal training on PAT concepts to prepare our reviewers to routinely incorporate PAT evaluation into standard reviews.
- *Industry interactions.* We continue to facilitate the adoption of PAT. Dialogue continues with all segments of the industry.
- *Academics.* We note the development of several academic programs dedicated to PAT both domestically and in Europe and Asia.

We continue to evaluate those scientific and engineering tools that support a better understanding of product and process and that will help:

- Reduce production time and delays in product release.
- Prevent rejections, scrap and reprocessing.
- Improve operator safety and reduce human error.
- Use small-scale equipment to eliminate certain scale-up issues and dedicated manufacturing facilities.
- Improve energy and material use and increase capacity.

Laboratory support

We assessed several analytical technologies for characterizing active pharmaceutical ingredients and guarding against counterfeit product marketing. We applied near infrared, Raman, Isotope ratio mass spectrometry to the problem of distinguishing between production sources of active pharmaceutical ingredients and finished dosage forms.

We developed methodology to better characterize nasal spray products. We evaluated a new aerodynamic particle size analyzer.

We evaluated instrumentation for the determination of particle size and particle size distribution for cyclosporin drug products.

We are developing physicochemical methods to assess quality changes in liposomal drug products.

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 54).

We have a new program to advance rapid microbiology test methods.

PAT Web site

More information on process analytical technologies can be found at http://www.fda.gov/cder/OPS/PAT.htm

3

INTERNATIONAL ACTIVITIES

To meet our responsibilities to our own citizens we must increasingly look, think and act globally. We participate in harmonization committees. We are involved in bilateral and multilateral efforts to leverage scientific and financial resources with other nations to avoid duplication of effort and to cooperate in focusing on high-risk areas.

President's plan focus countries

- Botswana
- Cote d'Ivoire
- Ethiopia
- Guyana
- Haiti
- Kenya
- Mozambique
- Namibia
- Nigeria
- Rwanda
- South Africa
- Tanzania
- Uganda
- Vietnam
- Zambia

Internet resources

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

President's Emergency Plan for AIDS Relief

The president's $15 billion plan for AIDS relief around the world has a special focus on 15 countries hardest hit by the HIV epidemic. It targets three specific areas related to HIV/AIDS:

- Prevention of HIV transmission.
- Treatment of AIDS and associated conditions.
- Care, including palliative care, for HIV infected-individuals and care for orphans and vulnerable children.

We are encouraging manufacturers to submit applications for fixed-dose combination and co-packaged versions of previously approved antiretroviral therapies.

Tentative approval—whether for a new drug application or a generic drug application—will be the regulatory mechanism by which low-cost versions of innovator drugs sold in the developed world will become eligible for purchase under the emergency plan. Our tentative approval (page 29) means that a drug meets our standards for safety, efficacy and quality but that existing patents or exclusivity prevent them from being sold in the United States.

We have an expedited review process to ensure that the United States could provide safe, effective and affordable quality drugs to developing countries. We encouraged U.S. and foreign firms who were developing generic drugs to treat HIV disease to apply under the president's plan. To meet the plan's approval timelines, our generic drug reviewers (page 28) implemented many process changes, including a rolling review approach. Our average review time for these applications has been six months.

We lack information about most clinical laboratories and manufacturing sites associated with the products seeking approval under the emergency plan. Therefore, we also are engaged in outreach activities, manufacturer assistance, inspections and postmarketing monitoring.

3-drug regimen gets tentative NDA approval for purchase under president's plan

In January 2005, within two weeks of receiving a complete application, we tentatively approved a complete three-drug product. It consisted of co-packaged lamivudine/zidovudine fixed-dose combination tablets and nevirapine tablets. We also approved a generic version of this regimen.

Generic drugs eligible for purchase under president's plan

As of May 11, 2006 we had fully approved two generic drugs and tentatively approved another 14. A list and more information is at http://www.fda.gov/oia/pepfar.htm.

International agreements

- **Countries**
- Australia
- Canada
- France
- Germany
- Ireland
- Israel
- Japan
- Mexico
- Singapore
- Sweden
- Switzerland
- South Africa
- United Kingdom
- **Organizations**
- EMEA
- WHO

CGMP workshop in China

To foster compliance with current good manufacturing practices, we co-sponsored an educational public workshop in collaboration with Peking University and the International Society for Pharmaceutical Engineering.

Information-Sharing Agreements

Because of enhanced cooperation among regulators around the world, FDA has entered into international agreements in which we play a critical implementation role. We have a growing list (left) of regulatory partners worldwide with whom we can pursue more open dialogue on emerging issues as well as exchange routine information on scientific review, policy development and enforcement. Examples or our agreements include:

Japan and Australia

We routinely exchange recall information about products of interest to Japan and Australia and communicate emerging enforcement activities of mutual interest. We continue to collaborate with our counterparts regarding site inspection information. With limited inspection resources of our own, we increasingly depend on foreign regulatory inspections and incorporate their inspection findings into a risk-based program for future inspection.

European Medicines Agency (EMEA)

This agreement establishes a basis for exchanging confidential information with the European agency primarily responsible for approving drugs. It permits our review and compliance staff to share important information about pending approvals, post-marketing surveillance and enforcement actions concerning products and facilities under the European agency's oversight. Implementation, to be phased in, includes activities to build understanding and mutual confidence in one another's systems.

Mexico and Canada

FDA is working jointly with our North American neighbors to develop information exchange arrangements about drug manufacturing facilities in each of our countries and to share information about product recalls that may impact our consumers. Our recent contributions to this long-standing effort have been vital in moving this relationship in a mutually beneficial direction. Exchanges of product recalls, emerging compliance issues and site-specific information have already begun. An agreement with Canada provides for the exchange of information about pending approvals, post-marketing surveillance and enforcement actions.

Switzerland

The working arrangement with Switzerland began several years ago and has continued to progress steadily in 2005. The present agreement addresses the need for protection of confidential information and provides for the exchange of information about marketing approval decisions, post-market surveillance, policy developments and compliance or enforcement activities of mutual interest. Progress in implementing this arrangement includes the exchange of technical staff and training opportunities as well as inspection information. Successful joint inspections have helped foster mutual confidence and improve communications.

International regulators forum

In 2005, we held the first of a series of twice yearly week-long forums with international regulators. There were 27 representatives from all but one of the 15 PEPFAR focus countries, 19 from seven other African and Asian countries and three from the World Health Organization.

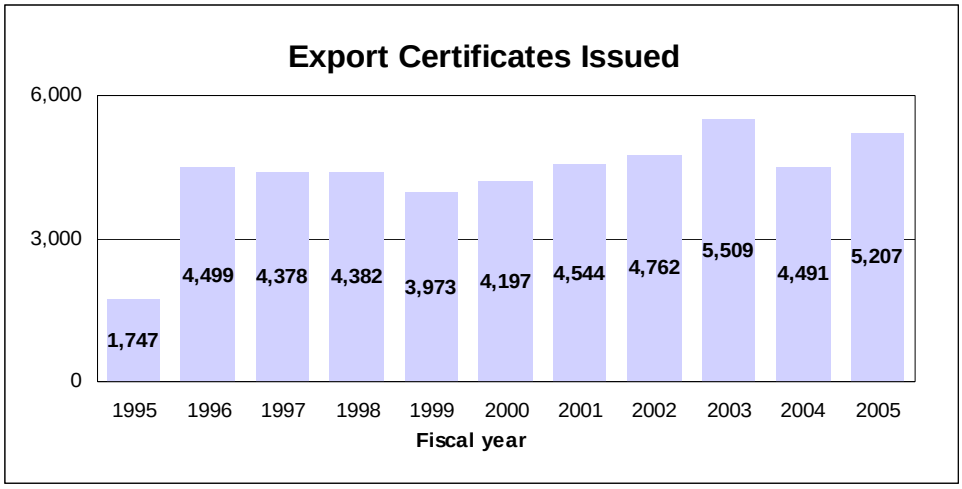
We provided information about U.S. drug regulatory processes and shared perspectives on approaches to common regulatory and scientific challenges.

Pharmaceutical Inspection Cooperation Scheme

As part or of our initiative to improve manufacturing practices, FDA applied for membership in this international organization dedicated to drug regulatory harmonization and collaboration in the area of good manufacturing practices.

Export certificates

- 5,207



Foreign inspections

- **234 preapproval inspections in support of:**
  - 143 new drug applications
  - 120 generic drug applications
- **213 current good manufacturing practice inspections**

For most foreign inspections, both a CGMP and a preapproval inspection take place and are counted twice, once under each inspection program.

Our review of 263 inspection requests for foreign establishments, resulted in three warning letters, two import alerts and several regulatory meetings.

Assuring International Trade Quality

While the globalization of pharmaceutical commerce brings the benefits of modern drugs to citizens worldwide, it poses many challenges to us and regulators in foreign countries. We share with them a common interest in ensuring our citizens have access to safe, effective and high quality products and are protected from counterfeit drugs and terrorist threats.

Drug exports

Export certificates attest that U.S. drug products are subject to inspection by FDA and are manufactured in compliance with current good manufacturing practices. These certificates enable American manufacturers to export their products to foreign customers and foreign governments. The demand for certificates remains high due to expanding world trade, ongoing international harmonization initiatives and international development agreements.

Drug imports

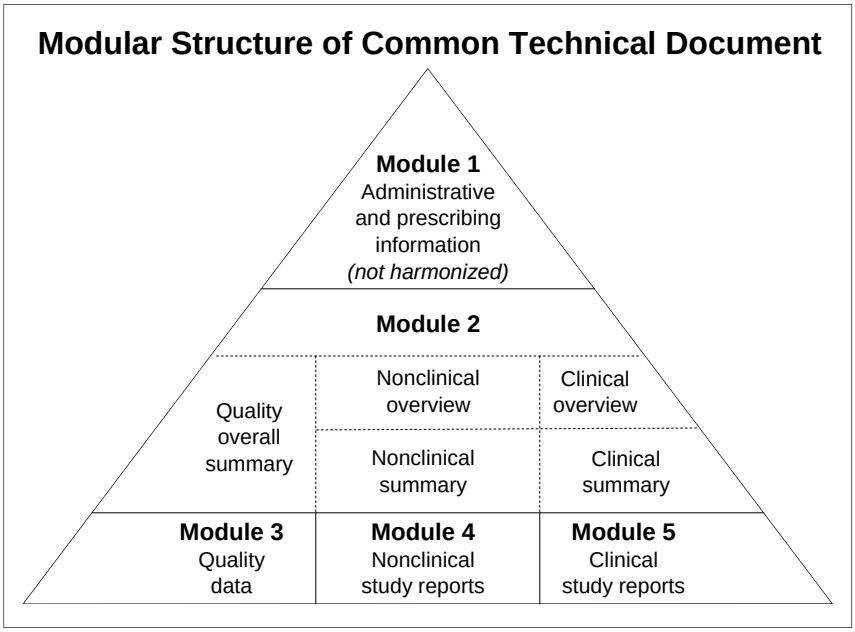
Agency resources are particularly focused on counterfeit drugs and counterterrorist activities. We work to:

- *Enforce the law.* With FDA's field force, we enforce legal requirements determining which drug products may be imported by manufacturers, distributors and consumers.
- *Identify and interdict illegal drugs.* We take steps to ensure that imported drugs are not counterfeit, unapproved, adulterated or misbranded and that they meet applicable legal requirements relating to safety and effectiveness.
- *Improve technology.* Along with the pharmaceutical and advanced technology industries, the states and other federal agencies, we are monitoring the development and implementation of "track and trace" technology that will enhance anti-counterfeiting measures by providing real-time monitoring of a drug product through the U.S. drug distribution system.

Export certificates

We issue export certificates that verify the drug products being exported:

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



Harmonization guidances

We publish International Conference on Harmonization documents as guidances to industry on our Web site at http://www.fda.gov/cder/guidance/index.htm.

As of June 12, 2006, we had:

- **55 final guidances**
  - 16 efficacy
  - 3 joint safety/efficacy
  - 21 quality
  - 15 safety
- **5 draft guidances**
  - 3 efficacy
  - 2 joint safety/efficacy

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 is making 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 in the three regions.

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.

Specifications for electronic submission of the CTD, known as the eCTD, were completed in 2002.

Internet resource

More information is on the ICH Web site at http://www.ich.org.

Electronic Common Technical Document

Electronic submissions using the eCTD can be used to submit all applications and related submissions (page 32) such as promotional materials and adverse events.

Among other things, the eCTD allows reviewers to:

- Create an up-to-date, cumulative table of contents for the entire application at any time.
- Access any electronic submission from a single screen.
- Download files so submissions can be used even when the reviewer is off the network.

4

COMMUNICATIONS

In 2005, we met 27 times with outside expert advisors in public discussions of difficult scientific and public health issues. We received more than 17 million visits and nearly 417 million hits on our Internet information site, which has nearly 115,000 files and about 700,000 hyperlinks. Our Web site accounts for 28 percent of total FDA Web site use. Drugs@FDA (page 14) is the most used content site on the FDA Web site.

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.

We held public meetings and participated in scientific workshops to both present information and gather a wide variety of viewpoints on major scientific and regulatory issues, including:

- Our risk management communications strategies (page 5).
- The use of pharmacogenomics in drug development (page 6).
- Developing a scientifically sound, risk-based system to assess drug quality (page 7).
- Direct-to-consumer promotion (page 44).

Consumer, industry outreach

- *Trade press.* We responded to more than 3,200 telephone and e-mail requests from the specialized press for the pharmaceutical industry.
- *Exhibits*. We exhibited at 25 conferences, reaching an estimated audience of more than 100,000 consumers, educators and health-care professionals.
- *Videoconferencing.* We held more than 260 domestic and foreign videoconferences for academia, industry and associations.
- *General information requests.* We answered nearly 34,000 telephone inquiries, more than 46,000 e-mails and about 1,000 letters from consumers, health professionals and industry. We respond to phone calls and e-mails within 48 hours and letters within 30 days.

Stakeholders in drug review, drug quality and safety

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

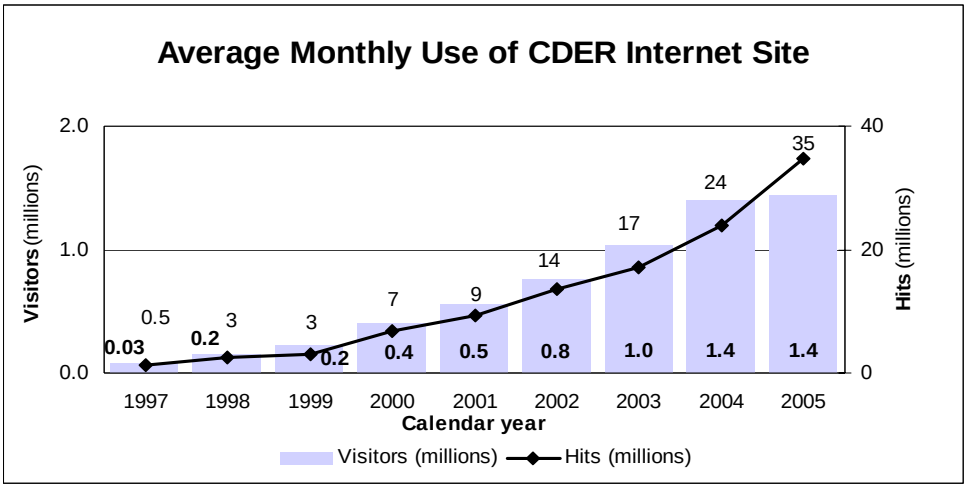
- Consumers, patients and their organizations
- Scientific and professional societies
- Industry and trade associations
- Universities, hospitals and health-care professionals
- Federal, state and local government agencies
- Foreign governments

Small business assistance workshop

Along with FDA's field operations, we co-sponsored a workshop in Kansas City, Mo., for 125 representatives from the small pharmaceutical business community.

The meeting gave small businesses the opportunity to consult with our subject matter experts and those from FDA's Office of Regulatory Affairs.

The workshop provided an introduction to the regulatory requirements for approval and marketing of drug products.



Internet updates

We have more than 25,000 subscribers to our service that provides daily e-mail updates of new content on our Web site and more than 24,000 subscribers to our weekly e-mail updates.

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

- *CDER Live!* We produced one satellite television broadcast and Web transmission for a largely pharmaceutical audience estimated at about 5,000 viewers. The program discussed our initiatives to address drug safety issues and to improve the timeliness and availability of drug safety information.
- *Leveraging.* We work with foundations and health-care organizations to help disseminate consumer information on using medicines safely and effectively. Public service announcements appeared 180 times in magazines, 188 times in newspapers and 63,000 times on 233 radio stations.

Transparency of policies, decisions

- *Regulations.* We issued a final rule that will remove albuterol metered-dose inhalers containing chloroflourocarbons or other ozone-depleting substances from the market by Dec. 31, 2008. This is consistent with certain treaty obligations and Clean Air Act requirements. We published a proposed rule on current good manufacturing practice regulations for positron emission tomography drugs. We want to ensure that these drugs meet the requirements for safety, identity, strength, quality and purity. In addition, we continued work on a number of other regulatory initiatives, including reviewing and considering comments on more than 10 previously published proposed rules.
- *Guidances.* We published 14 guidances for industry that explain our position on best practices in scientific and technical areas. We published another 29 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 17 documents last year.
- *Freedom of Information requests.* We responded to 4,876 requests under the Freedom of Information Act.

Public education programs

Our programs educate and empower consumers to make wise choices about their medications. Our messages, which reached 200 million Americans last year, include information on:

- Antibiotic resistance
- Benefits vs. risks of medication use
- Buying drugs from outside the United States
- Buying prescription drugs online
- Using medicines safely in children
- Counterfeit drugs
- Generic drug quality
- Medicines and the elderly
- Misuse of prescription pain relievers
- Over-the-counter medicine labels
- Sedating medicines and driving

These are available on the Internet at http://www.fda.gov/cder/drug/DrugSafety/drugSafetyConsumer.htm.

Ombudsman's Activities

Our ombudsman serves as a portal for consumers, regulated industry and small businesses to, among other things:

- Comment on our programs and actions.
- Obtain formal and informal dispute resolution.
- Seek general information on product development and regulation.
- Report adverse drug experiences.

Industry, drug and device consultants contacted the office more often than consumers. About one-third of industry contacts related to jurisdictional and drug development assistance. Several people contacted the office to report irregularities and possible fraud in conducting and reporting clinical trials, in manufacture's promotional activities and violations in pharmaceutical manufacturing.

Several hundred people contacted the office to express their opinions urging us to approve some drug therapies and to disapprove or rescind the approval of other drug therapies. Fewer consumers commented in 2005 than in 2004 on direct-to-consumer prescription drug advertising and on advisory committee members.

Examples of cases and allegations our ombudsman handled in 2005 included:

- Unethical conduct of clinical research including institutional review board issues.
- Whistle blowers' informing about pharmaceutical companies in violation of FDA regulations.
- Delay in review or drug development.
- Unfair handling of an issue.
- Backlog in processing Freedom of Information requests.
- Management and employee disagreements.
- Citizen petition delays and advice.
- Incorrect advice provided to industry by our staff.
- Import and export issues.

Internet, e-mail

- More information and a full report on 2005 activities is at http://www.fda.gov/cder/ombud/default.htm.
- You can e-mail our ombudsman at Warren.Rumble@fda.hhs.gov.

Jurisdictional issues

Many times it is not readily apparent where a proposed product will be reviewed and regulated either within the center or between FDA centers.

Our ombudsman is our jurisdiction officer and a member of the steering committee that advises FDA's Office of Combination Products, which coordinates intracenter jurisdictional issues.

Our ombudsman responded to more than 200 informal jurisdiction questions that helped guide product development.

When regulatory assignment is not readily apparent, a sponsor may submit a formal request for designation.

FDA received 41 of these requests in 2005, a large majority of which were combinations of drugs and devices.

Ombudsman's 2005 hot topics

Two hot topics with consumers were the same as in 2004:

- Enforcement against importing prescription medicines from Canada.
- Our non-approval letter for over-the-counter sales of emergency contraception.

Consumers have definitely made the Internet their primary method of communication with us. We received many times more e-mails than telephone contacts. Many consumers requested assistance in reporting drug adverse events.

Others commented on:

- The high cost of medicines.
- Inconsistency in color and shape among generic brands of prescription drugs.
- The necessity to increase the size of OTC labeling.
- High profile market withdrawals (page 43).
- Abuse of oxycodone.
- Politicizing of FDA.

Where to Find More Information

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

Internet site

CDER Internet home page: http://www.fda.gov/cder/

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@fda.hhs.gov.

Regular mail

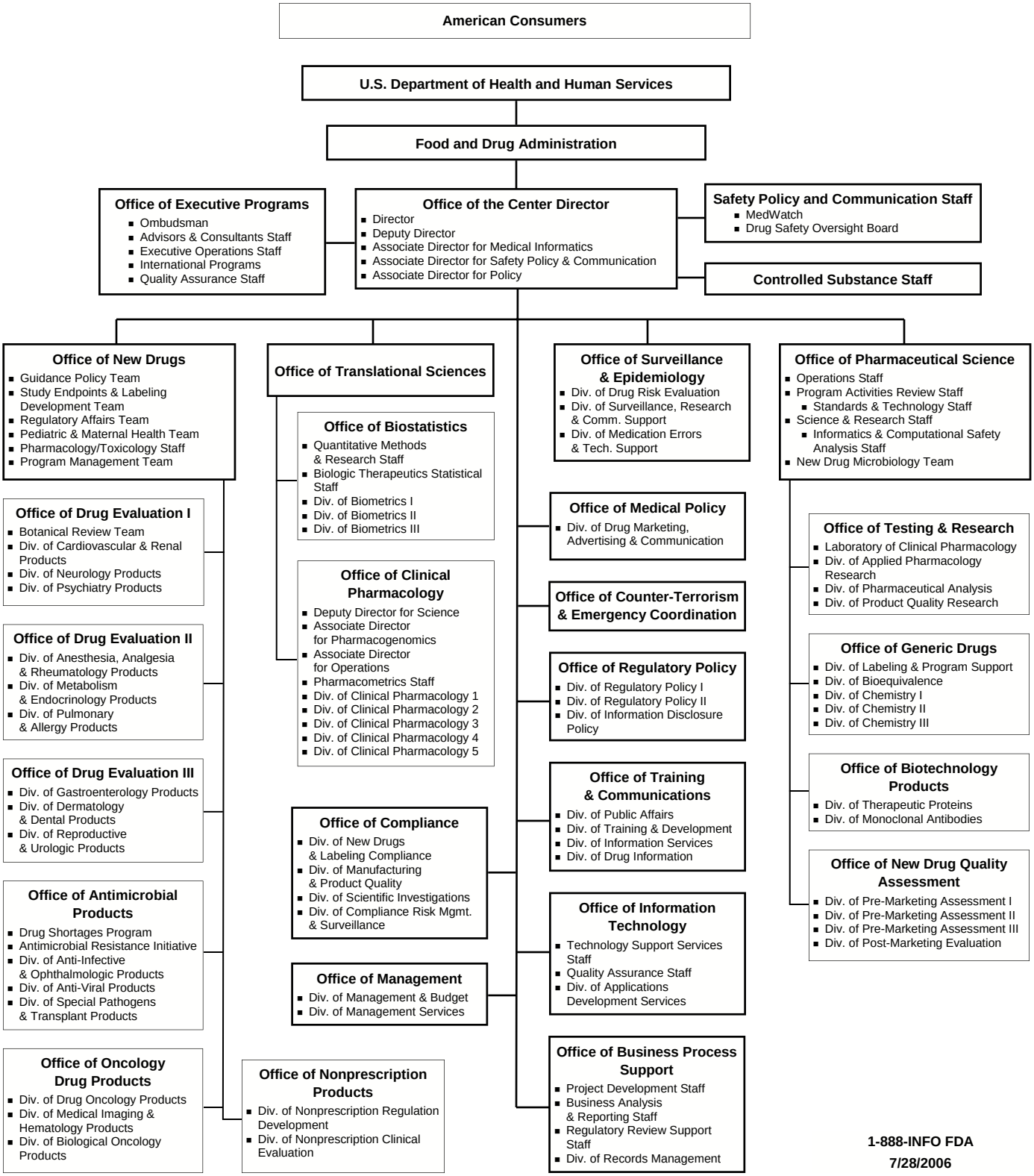
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Information
HFD-240, Room 12B-05
5600 Fishers Lane
Rockville, MD 20857

E-mail notification from us

At http://www.fda.gov/cder/cdernew/listserv.html, you can sign up for these updates from the Center for Drug Evaluation and Research:

- *Website updates.* Daily and weekly lists of new postings.
- *MedWatch.* Immediate notification of new safety information on human health-care products.
- *Drug shortages.* New, medically necessary drug shortages.
- *Consumer news.* New education materials.
- *Small business.* Information for small pharmaceutical companies.

Organizational Structure of the Center for Drug Evaluation and Research



U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research