
Center for Drug Evaluation and Research **2004**

Report to the Nation

*Improving
Public Health
Through
Human Drugs*

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

MISSION

The Center for Drug Evaluation and Research promotes and protects public health by 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/2004/rtn2004.pdf>.
- HTML: <http://www.fda.gov/cder/reports/rtn/2004/rtn2004.htm>.
- Slides: <http://www.fda.gov/cder/reports/rtn/2004/rtn2004.ppt>.

Suggested citation: U.S. Food and Drug Administration. *CDER 2004 Report to the Nation: Improving Public Health Through Human Drugs*. Rockville, Maryland. 2005.

CONTENTS

DIRECTOR'S MESSAGE	iii
INTRODUCTION.....	1
HIGHLIGHTS AND INITIATIVES	3
Drug Safety Initiative	4
Critical Path Initiative.....	6
Improving Manufacturing Practices	8
Counterterrorism.....	9
Scientific Research	11
1 DRUG REVIEW.....	13
New Drug and Biologic Review.....	14
New or Expanded Use Review	21
Pediatric Drug Development	24
Pregnancy and Lactation Labeling	26
Over-the-Counter Drug Review	27
Generic Drug Review	28
Assessing Data Quality, Research Risks	31
Electronic Submissions	32
User Fee Program	33
Drug Review Team.....	34
2 DRUG SAFETY AND QUALITY	35
Safety System for Medicines.....	36
Drug Safety Surveillance.....	37
Public Health Advisories in 2004.....	38
MedWatch Outreach and Reporting	39
Medication Error Prevention	41
Drug Recalls	42
Safety-Based Drug Withdrawals	43
Drug Promotion Review	44
Compliance Oversight	46
Product Quality Science	50
3 INTERNATIONAL ACTIVITIES	51
President's Emergency Plan for AIDS Relief	51
4 COMMUNICATIONS.....	55
Ombudsman's Activities	57
Where to Find More Information	58

Graphs and Charts

Critical Path.....	7
Priority NDA & BLA Approvals	14
Priority NME & New BLA Approvals	15
Standard NDA & BLA Approvals	16
Standard NME and New BLA Approvals.....	17
Priority New or Expanded Use Approvals	22
Standard New or Expanded Use Approvals	23
Pediatric Drug Development.....	25
OTC New Approvals & New Uses	27
Generic Drug Approvals	29
Generic Drug Tentative Approvals	29
Generic Drug Applications Received.....	30
Inspections of Clinical Research.....	31
Sources of Risk from Medicine.....	36
Adverse Event Reports.....	37
Drug Recalls.....	42
Safety-Based Withdrawals	43
Letters Issued on Drug Promotion Compliance	45
FDA Inspections of Manufacturing Plants.....	47
Drug Quality Reports	49
Reported Drug Quality Defects.....	49
Modular Structure of Common Technical Document.....	53
Export Certificates Issued	54
Average Monthly Use of CDER Internet Site.....	56
Organizational Chart	Inside back cover

Director's Message

Last year, the staff in the Center for Drug Evaluation and Research worked hard to protect and promote public health. Our highly trained and dedicated staff supports a unique mission to ensure availability of effective pharmaceutical products while maximizing patient safety. The health of millions of Americans and the global leadership of the United States in drug development depends on the quality and timeliness of this critical work. To manage this effort is a solemn honor.

Modern drugs provide unmistakable and significant health benefits. However, as we move into the 21st century with an armamentarium of medicines unimaginable 100 years ago, we are finding that the scientific tools of the 20th century are not adequate to achieve our goals of:

- Developing new medicines efficiently without lowering our standards of safety and effectiveness.
- Identifying and managing issues related to the safe use of approved medicines.

Because we can't solve 21st century problems with 20th century policies and scientific tools, we realize we can't continue with business as usual to develop new medicines, and we are working on several initiatives that hold much promise for:

- Streamlining the path for developing new drugs, including drugs for children, orphan diseases and medical countermeasures to terrorist attacks.
- Improving the science of drug manufacturing.
- Improving our methods for identifying, analyzing and responding to emerging safety issues and communicating those results to physicians and patients.

We believe we can make important contributions to the public health by aggressively following up on these initiatives.

Improving our scientific tools for analysis and prediction

The Critical Path Initiative is our effort to address the fact that developing new medicines has become increasingly expensive and time-consuming, with likelihood of success more uncertain than ever before. We need to work to assure that the promise of ongoing basic science research is translated into efficient assessment of new medicines for patients.

We are proposing collaborative research to improve predictability and efficiency and to get much needed treatments to patients faster. We are seeking development of a versatile applied science toolkit containing such methods as animal- and computer-based predictive models, greater use of biomarkers for assessing safety and effectiveness and new clinical evaluation techniques.

Encouraging innovation in manufacturing

Good manufacturing practices are as important to public health as they are to making best use of government and industry resources. Our overhaul of the pharmaceutical good manufacturing practices encourages manufacturers to modernize their methods, equipment and facilities to eliminate both production inefficiencies and undue risks for consumers. Our improved polices are also making better use of our limited resources through more targeted and effective inspections.

Addressing public concerns about drug safety

Concerns about high-profile products with safety questions should not distort the fact that drugs are safer today than they have ever been before and that millions of Americans each day benefit from them. Nonetheless, too many Americans suffer from unexpected and unpreventable adverse events from the medicines they use. We have undertaken several new initiatives to improve the ways that we detect, analyze and respond to emerging safety signals and then to communicate those signals to patients and health care professionals effectively. A new, independent Drug Safety Oversight Board will oversee the management of important drug safety issues and assist in the timely release of emerging safety information.

Speeding the development of medical countermeasures

We recognize the clear need to facilitate the development of countermeasures to protect Americans from biological, chemical, nuclear and radiological agents of terrorism. To do this, we are working with other parts of the Department of Health and Human Services to provide guidance that will facilitate their development.

We are extremely proud of our work outlined in this report and will continue to work on our initiatives as we look forward to the Agency's 100th anniversary in 2006.

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 but usually considerably less expensive.

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. 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. We also protect drug quality with rigorous manufacturing inspections to ensure compliance with current Good Manufacturing Practice requirements.

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 ninth performance report. Our work in 2004 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 steps to improve the science of drug development.
- Improving manufacturing practices.
- Protecting the homeland with improved medical countermeasures to be used in 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 119 new medicines, including 36 truly new medicines that had not been marketed in any form before in this country. We approved 147 new or expanded uses for already approved medicines. We approved 380 generic versions of existing drugs.
- *User fee performance.* We exceeded our goals for review performance.
- *Drug safety surveillance.* We processed and evaluated more than 400,000 reports of adverse drug events, including more than 20,000 submitted directly from individuals.
- *Drug promotion and advertising.* We issued more than 800 letters to help ensure manufacturers comply with regulations concerning drug promotion.
- *Bar codes on medicines.* We promulgated a regulation that calls for bar codes on over-the-counter medicines commonly used in hospitals and most prescription medicines.
- *Public health advisories.* We issued warnings on non-steroidal anti-inflammatory pain medicines and on antidepressant use in children, adolescents and adults.
- *Manufacturing.* We implemented our initiative that encourages adoption of state-of-the-art manufacturing processes.

Drug Safety Initiative

Americans are rightly concerned about the safety of their drugs. Too many suffer from unexpected and unpreventable adverse events from the medicines they need. Some have worried about “dangerous” drugs, while others have worried that an “overemphasis” on safety will delay developing new therapies.

The most important concern for many Americans, however, has been the gap between the time a safety issue emerges and the time we know enough to make a regulatory decision. Our reforms of our drug safety efforts will:

- Give patients, healthcare professionals and consumers quick and easy access to the most up-to-date and accurate information on medicines.
- Make our drug review, approval and monitoring programs as transparent as possible.

Drug safety has been and will continue to be a top priority for us. A recent internal audit showed that our professional staff spends about one-half its time addressing safety issues. Drug safety involves more than watching for problems once we approve a drug. Other important areas where the evaluation of drug safety takes place include:

- Oversight of clinical trials.
- Evaluation of safety and efficacy of new therapies and new or expanded uses for existing therapies. Because all drugs have risks, our evaluation must balance those risks against expected benefits.
- Regulation of manufacturing, distribution and promotional activities.
- Prevention of medication errors by evaluating proposed proprietary names, labeling and packaging.
- Development of proactive risk management strategies both before and after approval.

Oversight board

The new, independent Drug Safety Oversight Board will oversee the management of drug safety issues and will provide emerging information to doctors and patients about the risks and benefits of medicines. It will:

- Recommend information and updates for placement on the proposed Drug Watch Web page.
- Resolve disagreements over approaches to drug safety issues.
- Assess the need for MedGuides.
- Oversee development and implementation of Centerwide drug safety policies.

Institute of Medicine Study

We have contracted with the IOM to study the effectiveness of the nation’s drug safety system. The study will have an emphasis on 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 IOM is the nation’s foremost body for science-based advice on matters of biomedical science, medicine and health.

Differences of professional opinion

In most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisors, leads to an agreed course of action. Sometimes, however, consensus cannot be reached. We normally document these differences and their resolution in the official file of an action.

An employee may sometimes feel that the normal process was inadequate and the decision made will have a significant negative impact on the public health.

We have implemented a pilot process, coordinated by our ombudsman (page 57), to provide for expeditious review and resolution of these differences by qualified staff not directly involved in the decisions.

Oversight Board members don't directly supervise approvals

The board consists of FDA supervisors, staff and medical experts from other medical agencies in the Department of Health and Human Services and other government departments such as the Department of Veterans Affairs. The board will consult with outside medical experts and representatives of patient and consumer groups. To avoid conflicts of interest, the board members have no direct supervision of approval decisions. Because board members are government employees, they will be able to freely discuss confidential and proprietary information.

New communications channels

We will share drug safety information sooner, more broadly and more conveniently through tailored drug safety information sheets for healthcare professionals and patients.

We expect these new and direct communication channels will enhance knowledge and understanding of safety issues. Emerging or potential safety problems can be discussed even before we have reached conclusions that would prompt a regulatory action.

The new communication channels include:

- *Drug Safety Web site.* Consumers will find a variety of new information on specific drug products, including information sheets for patients and healthcare professionals (described below), the product's regulatory history and its prescribing information. The site is <http://www.fda.gov/cder/drugsafety.htm>.
- *Proposed Drug Watch Web site.* The Drug Safety Oversight Board will place "emerging" drug safety information on this site, such as possible serious side effects of particular drugs, before we have fully determined that the drug was responsible. This information will also include risks that might alter the benefit and risk analysis of a drug, affect patient selection, change monitoring decisions or could otherwise be avoided.
- *Healthcare professional information sheets.* These will be one-page information sheets for all drugs on FDA's Drug Watch and all drugs with Medication Guides. They will contain the most important new information for safe and effective product use, such as known and potential safety issues based on reports of adverse events, new information that may affect prescribing of the drug and the approved indications and benefits of the drug.
- *Patient information sheets.* These one-page information sheets in a consumer friendly format will contain new safety information as well as basic information about how to use the drug for all products on Drug Watch. Ultimately, such sheets will be made available for every new drug that is approved.

Public support for Critical Path

We have heard from patient groups, the drug and biotech industry, and industry groups. They concur with the scientific infrastructure problem and the focus on research, science-based standards and collaboration.

Areas of major concern are:

Clinical trials

- Statistical tools to support innovative trial design.
- Disease modeling and trial simulation.
- Standardization of trial administration.
- Development of consistent electronic data collection, monitoring and reporting.

Biomarkers and endpoints

- Clarification of the process for validating surrogate endpoints.
- Evidence needed to use biomarkers for other purposes, such as patient selection.
- Standards for imaging as a biomarker.

Critical Path Initiative

FDA's March 2004 report, *Innovation or Stagnation?—Challenge and Opportunity on the Critical Path to New Medical Products*, provides our analysis of the "pipeline problem."

There has been a slowdown—instead of the expected acceleration—in innovative medical therapies reaching patients. The medical product development path is becoming increasingly challenging, inefficient and costly. As a consequence, our mission to ensure the availability of safe and effective medical treatments for Americans that take advantage of the latest science is becoming compromised.

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, our report identifies:

- The critical path for product development from design and discovery to commercial marketing.
- The scientific and technical dimensions of the critical path.
- The three types of research that support the critical path.

Personalized medicine

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

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

Instead of a hit-or-miss approach to treating patients where it can take multiple attempts to find the right drug and the right dose, pharmacogenomics holds the promise that doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy and dose from the start.

The field has experienced significant growth over the last few years. The sequencing of the human genome and the advent of new tools and technologies have already opened new possibilities in drug discovery and development.

Research needed to improve development tools

Together with academia, patient groups, industry and other government agencies, we need to embark on an aggressive, collaborative research effort to create a new generation of performance standards and predictive tools. We need tools that will provide better answers about the safety and effectiveness of investigational products, faster and with more certainty.

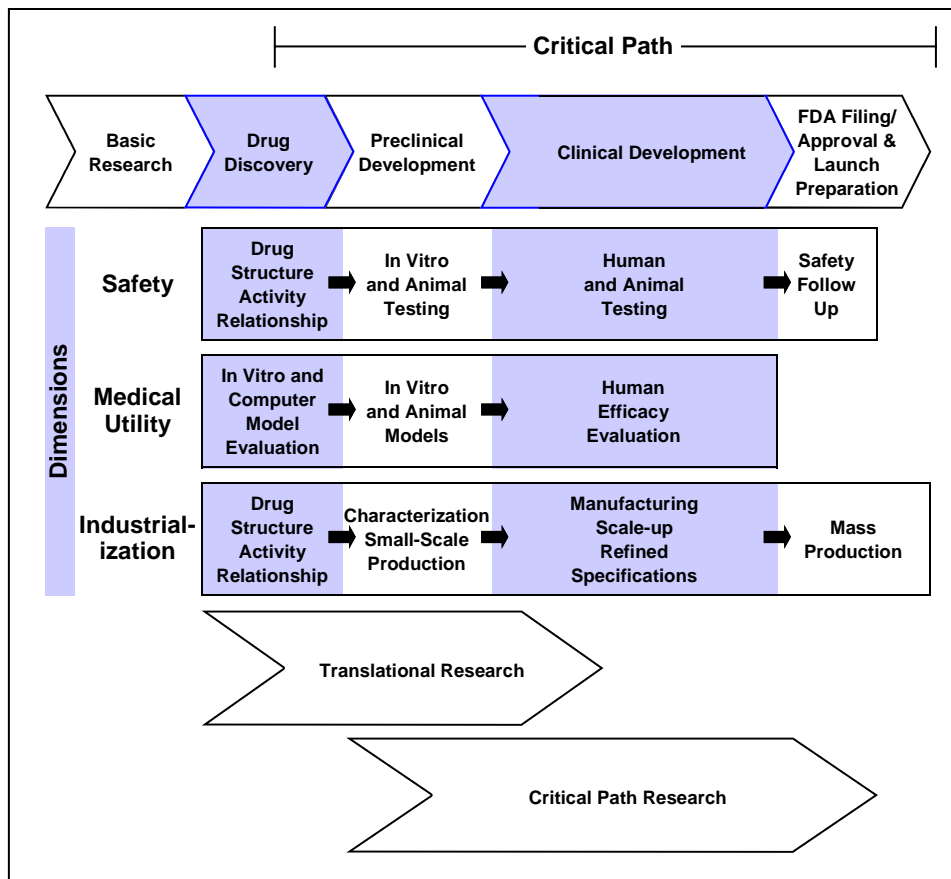
We at FDA are uniquely suited to play a major role in this effort because of:

- Our experience overseeing medical product development, assessment and manufacturing/marketing.
- Our vast clinical and animal databases.
- Our close interactions with all the major players in the critical path process.

Critical path dimensions

From the earliest phases of preclinical work to commercialization, developers must manage successfully in these three dimensions:

- *Assessing safety.* Showing that a product is adequately safe for each stage of development.
- *Demonstrating medical utility.* Showing a new product will actually benefit people.
- *Industrialization.* Turning a laboratory concept into a consistent and well-characterized medical product that can be mass produced.



Personalized medicine for cancer

Genomic tests are helping to identify cancers that have a good chance of responding to a particular medication or regimen. This has enabled the development of targeted therapies like trastuzumab for metastatic breast cancer, imatinib mesylate for chronic myeloid leukemia and cetuximab for metastatic colorectal cancer.

The way forward

This initiative is not a fundamental departure for us, but rather builds on our proven best practices for developing industry guidance and expediting the availability of promising medical technologies.

The next steps in this initiative include a series of workshops and meetings, to start development of a National Critical Path Opportunities list and to identify the key priorities.

- The full Critical Path report is available at <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>.
- You can view public comments to our proposal at <http://www.fda.gov/ohrms/dockets/dockets/04n0181/04n0181.htm>.

Improving Manufacturing Practices

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.

Collectively, our policies are known as “current good manufacturing practices” or cGMPs, and our last comprehensive revisions to them took place nearly a quarter of a century ago.

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/>.

Pharmaceutical cGMP initiative final report issued

In 2004, we moved into an implementation phase and issued a final report on:

- Our assessment of our regulations, current manufacturing practices as well the new tools in manufacturing science that will enable a progression to controls based on quality systems and risk management.
- Specific steps we have taken and will take to develop and implement quality systems management and a risk-based product quality regulatory system.

The report is available at http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065734.

Process analytical technologies initiative

A key element of the cGMP initiative is our effort to encourage adoption of state-of-the-art quality control systems in manufacturing. This work is based on the premise that quality cannot be tested into products; it should be built into products by design.

Process analytical technology is a system for design, analysis and control of manufacturing with the goal of ensuring final product quality. It does this through timely measurements—during processing—of critical quality and performance attributes of raw and in-process materials and processes.

Effective use of the most current pharmaceutical science and engineering principles and knowledge—throughout the life cycle of a product—can improve the efficiencies of both the manufacturing and regulatory processes. More information is on [page 50](#).

Emerging technologies in process validation recognized

We revised a long-standing policy document regarding the validation of pharmaceutical manufacturing processes. New to this version is the recognition of the role of emerging advanced engineering principles and control technologies in ensuring batch quality.

For drugs produced using these new principles and technologies, we provide for possible exceptions to the need for manufacturing multiple conformance batches prior to initial marketing.

Counterterrorism

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

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

Medical countermeasure approvals

- The *infant atropine autoinjector (Pediatric AtroPen)* provides an automatic injection of a potentially life-saving nerve agent antidote to children as young as 6 months. Doses and dosage forms of the AtroPen for adults and older children had been approved previously.
- *Pentetate calcium trisodium injection (Calcium DTPA)* and *pentetate zinc trisodium injection (Zinc DTPA)* treat people who have become internally contaminated with certain radioactive isotopes (plutonium, americium or curium). The label includes information on pediatric dosing. These new molecular entities received priority approval and have orphan drug status. A second manufacturer received tentative approvals for these two drugs.
- A second manufacturer of *insoluble Prussian blue (Manoplex)*, to treat people internally contaminated with radioactive cesium-137 or thallium, received tentative approval in 2004. The first approval for insoluble Prussian blue was in 2003, and the product received orphan exclusivity.
- We updated the *ciprofloxacin (Cipro)* label to include human information based on its use to prevent inhalational anthrax during the attacks in 2001. The label previously referenced only animal efficacy data for this indication.
- *Levofloxacin (Levaquin)* is now approved to treat inhalational anthrax (post exposure prophylaxis) in adults. Levaquin is similar to ciprofloxacin, except it can be dosed once daily.
- Fifteen new generic *ciprofloxacin* drug products were approved. Each will be indicated for prevention of inhalational anthrax post-exposure.
- *Penicillin G procaine injectable suspension (Wycillin)* was approved to prevent the occurrence or progression of anthrax disease following exposure to *Bacillus anthracis* (including inhalational anthrax).

Strategic National Stockpile regulatory, policy issues working group

We participated in this internal FDA working group to address issues such as:

- Compounding medical countermeasures during a mass casualty situation.
- Labeling and dispensing medical countermeasures during a mass casualty.
- FDA-shelf-life extension program and re-labeling.
- Cities Readiness Initiative (mass prophylaxis dispensing).
- Availability and vulnerability of products in the stockpile.
- Risk assessment and enforcement discretion.
- Proactive facilities inspections.
- Patient access to life-saving therapies through investigational applications for countermeasures.

Emergency use authorization

Under the 2004 Project BioShield Act, we worked with the Centers for Disease Control and Prevention to identify potential medical countermeasures in the Strategic National Stockpile that we could authorize for emergency use for an unapproved indication.

We also outlined the internal processes and procedures we need to handle an emergency use authorization.

Emergency preparedness

We participated in four emergency response exercises. Threat agents were smallpox, anthrax, radiological contamination from a dirty bomb and cyanide. We also engaged in continuity of operations exercises, including an "at home" test to assure maintenance of vital operations and services in an emergency.

Facilitating medical countermeasure development

- *Plague.* The Centers for Disease Control and Prevention began enrolling patients in an FDA-funded clinical trial to assess the efficacy of the antibiotic gentamicin for endemic plague in two African countries where antimicrobial options for plague are extremely limited. We contributed to protocol design and the formation of a data safety monitoring board to oversee study safety concerns. We are continuing our collaboration with the 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) to treat pneumonic plague in a non-human primate model. Natural history studies, pharmacokinetic and toxicology studies to support efficacy studies and efficacy studies with high-dose and a humanized (lower) dose of gentamicin have been completed and analyzed.
- *Radiological and nuclear threats.* We began another collaboration with the National Institute of Allergy and Infectious Diseases to identify promising new products for use against radiological and nuclear threats. We discuss scientific and regulatory issues with manufacturers of such products and inform them about possible funding sources, both for early development and for procurement by the federal government.

Interagency collaborations

- *Post-event surveillance planning.* Along with the FDA's other medical centers and the CDC, 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 working groups engaged in counter-terrorism efforts. These groups have contributed to gap analyses in medical countermeasures and have authored many of the requirements documents that will be used to prioritize products for development and eventual procurement under BioShield.

Counterterrorism guidances published in 2004

- *Guidance for Federal Agencies and State and Local Governments: Potassium Iodide Tablets Shelf Life Extension.*
- *Draft Guidance for Industry: Vaccinia Virus—Developing Drugs to Mitigate Complications from Smallpox Vaccination.*

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.

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.

Internet resources

We provide links at <http://www.fda.gov/cder/drugprepare/default.htm> to the most current information on:

- Drugs to prevent or treat disease caused by terrorism agents including drugs for use against anthrax, plague, radiation emergencies and chemical agents.
- Drug development of counterterrorism products.
- Vaccines.
- Pediatric counterterrorism measures.
- Prescribing and buying countermeasures.

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

Clinical pharmacology

- We are exploring the utility and value of quantitative drug-disease state models and clinical trial simulation in drug development and regulatory review.
- We issued the final guidance: *Exposure-Response Relationships: Study Design, Data Analysis and Regulatory Applications*
- We cosponsored an open workshop on pharmacogenomics in drug development and regulatory decision-making.
- We published a draft guidance, *Pharmacogenomic Data Submissions*, to provide a better understanding on the current use of pharmacogenomics in drug development and to gain experience in handling and evaluating genotype and gene expression data.
- We are working on a draft guidance for industry on the regulatory pathway for pharmacogenomic drug-device combinations.

Biotechnology research

Our new Office of Biotechnology Products was officially transferred to our center in 2003 from the Center for Biologics Evaluation and Research. The office 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 the determining glove permeability to lindane shampoo and lotion, treatments for lice whose active ingredient is highly toxic.

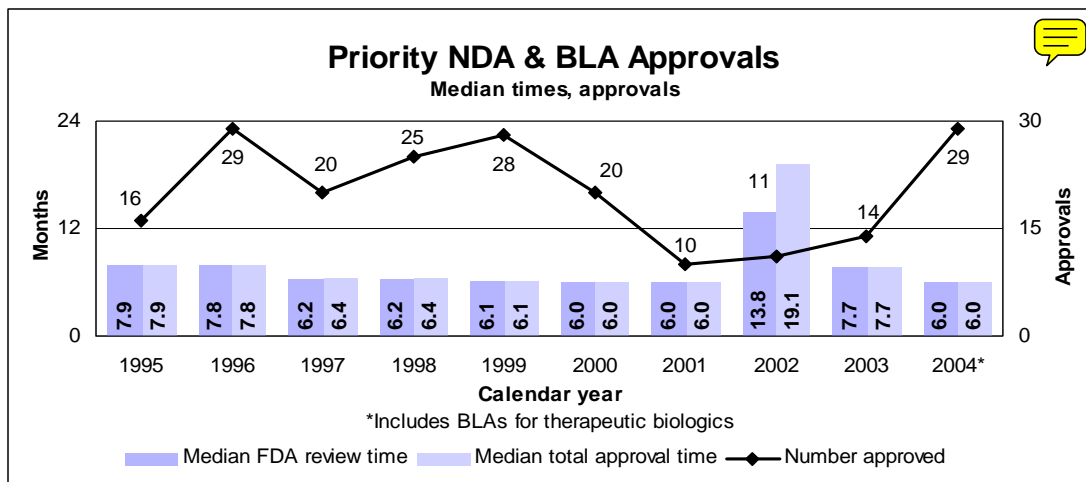
1

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.

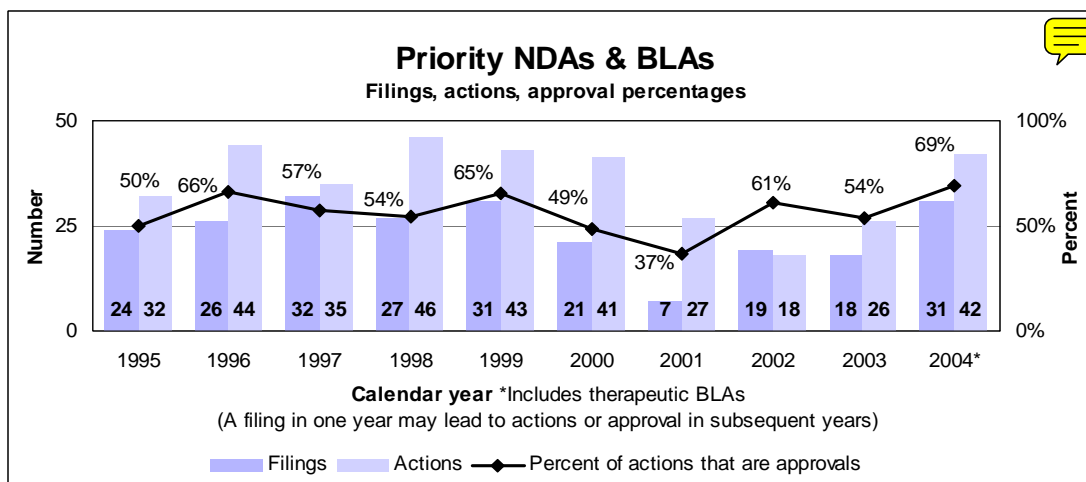
Highlights for 2004 include:

- *119 new medicines.* We approved 113 drugs and six biologics (29 priority and 90 standard reviews).
- *36 truly new medicines.* We approved 31 drugs and five new biologics that had never been marketed before in any form in this country (21 priority and 15 standard reviews).
- *147 new treatment options.* We approved new or expanded uses for 133 already approved drugs and 14 already approved biologics (48 priority and 99 standard reviews).
- *13 medicines for cancer.* Our approvals included seven priority new medicines and six priority new or expanded uses for existing medicines.
- *8 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.
- *15 "orphan" medicines.* Our approvals included 11 new medicines and four new or expanded uses for patient populations of 200,000 or fewer.
- *Medicines for children.* We provided 23 priority reviews of pediatric studies of already approved medicines. These resulted in seven medicines gaining approval for new or expanded uses in children.
- *380 generic drugs.* We gave final approval to 380 generic versions of existing drugs and tentative approval to another 95. We received 635 marketing applications for generic drugs.
- *User fee goals.* We exceeded all our performance goals for the fiscal year 2003 receipt cohort, the latest year for which we have full statistics. We are on track for exceeding all user-fee performance goals for the fiscal year 2004 cohort.
- *730 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.



Priority new drugs and biologics

- 29 total approvals
- 25 drugs
- 4 biologics
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 31 filings
- 42 actions
- 9 orphan approvals (includes 8 NMEs)



New Drug and Biologic Review

Definitions

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.

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.

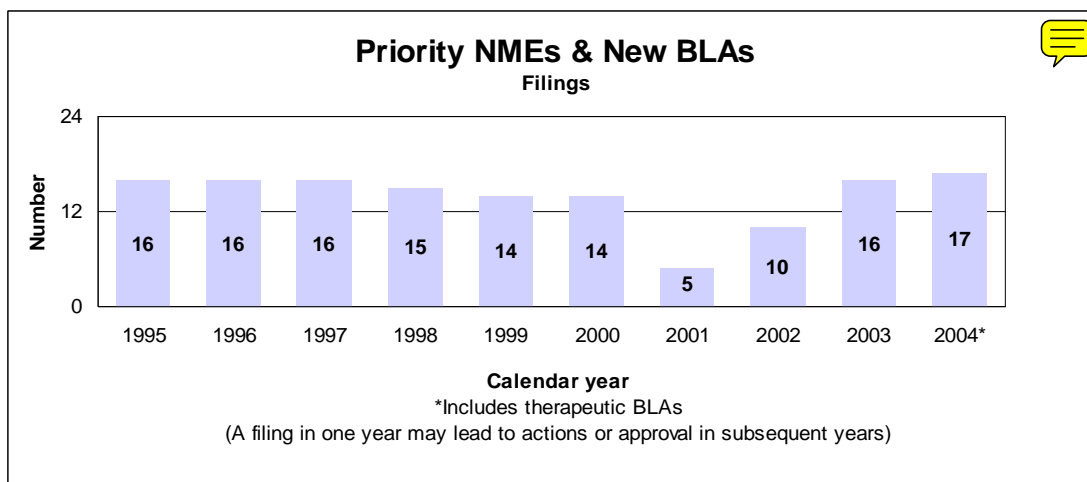
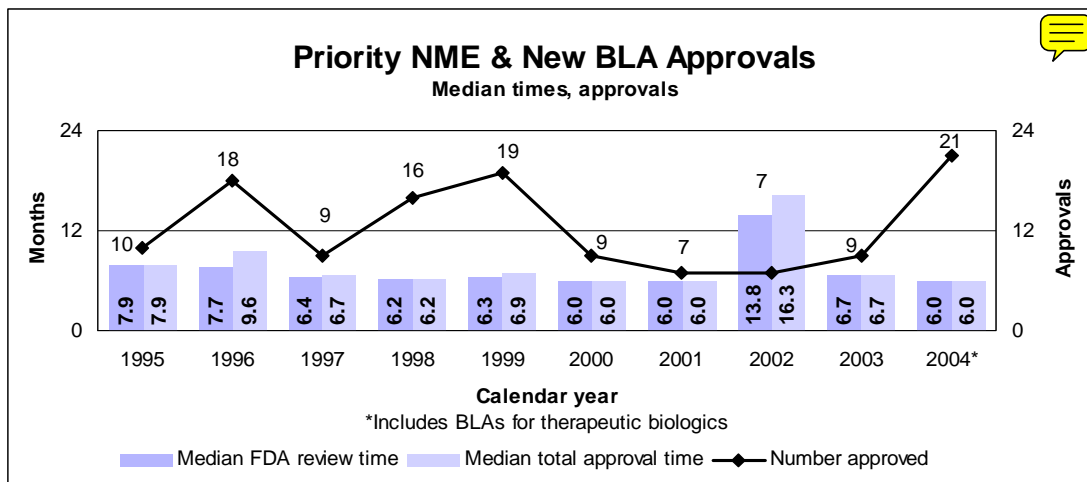
Actions and filings. An application is “filed” when we determine it is complete and accept it for review. We make a filing decision within 60 days of receiving an application. Approval is one of the actions that we can take once an application is filed. Other actions include seeking more information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

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.

Priority new molecular entities and new biologics

- 21 total approvals
- 17 NMEs
- 4 new BLAs
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 17 filings
- 8 orphan approvals



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 a biologic that has never been approved for marketing in the United States.

Definitions (cont.)

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.

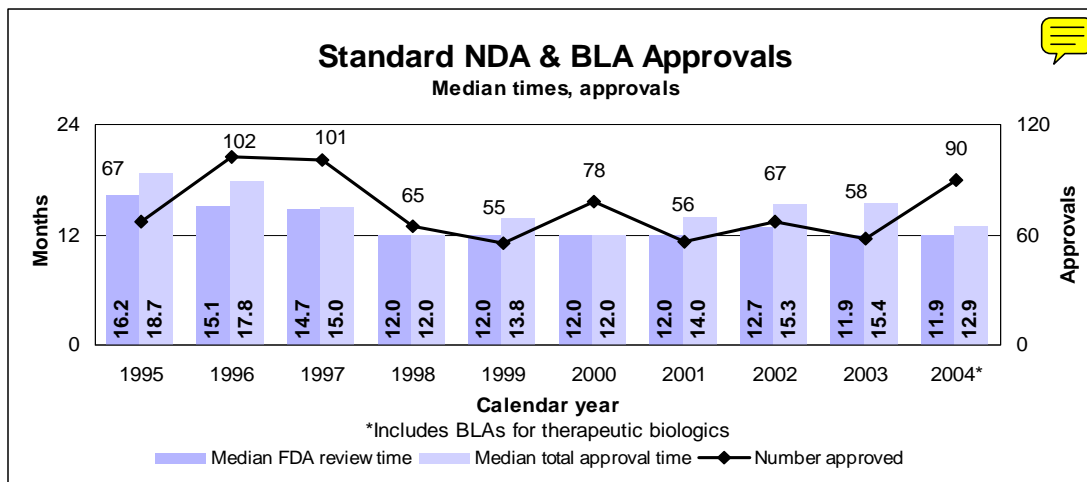
Accelerated approval. This program helps make products for serious or life-threatening diseases available earlier in the development process. We base our approval on a promising effect of the drug that can be observed significantly sooner than a long-term clinical benefit. Sponsors perform additional 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.

2002 data. The higher review and approval times in 2002 resulted from the approval of some older applications and a decrease in applications filed.

Approval totals

- 119 drugs and biologics
- 113 drugs
- 6 biologics
- 36 truly new medicines
- 31 NMEs
- 5 new BLAs
- 15 orphan approvals
- 11 NDAs (includes 9 NMEs)
- 4 new or expanded uses



Standard drugs and biologics

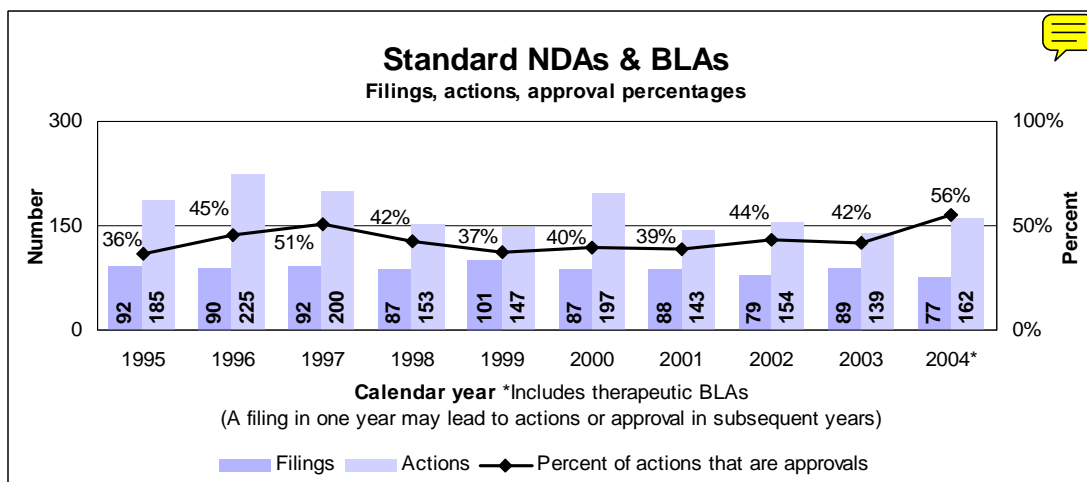
- 90 total approvals
- 88 drugs
- 2 biologics
- Median review time: 11.9 months
- Median approval time: 12.9 months
- 77 filings
- 162 actions
- 2 orphan approvals (including 1 NME)

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>.



Notable 2004 New Approvals

Last year’s approvals benefited people with diabetes, neurological disorders, infections, cancer, heart disease and other disorders.

People with diabetes

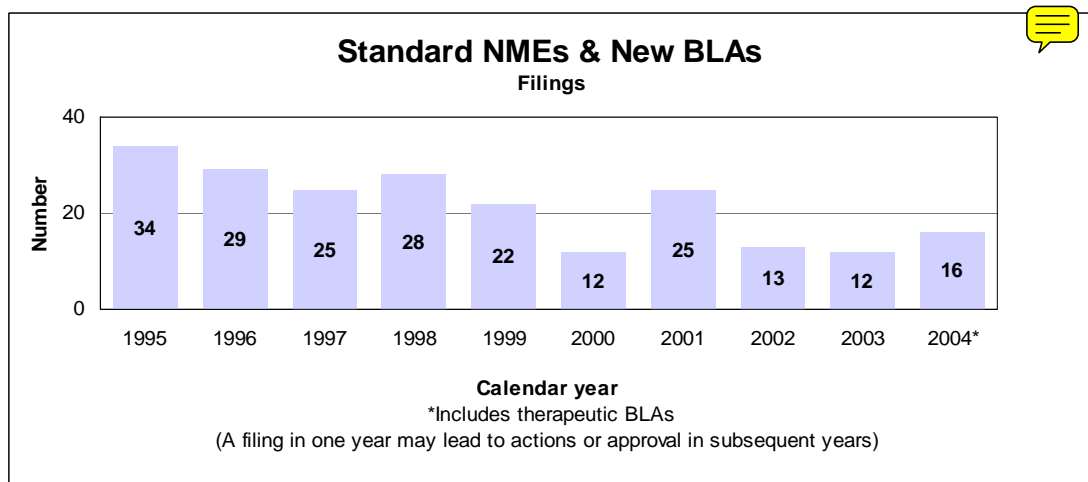
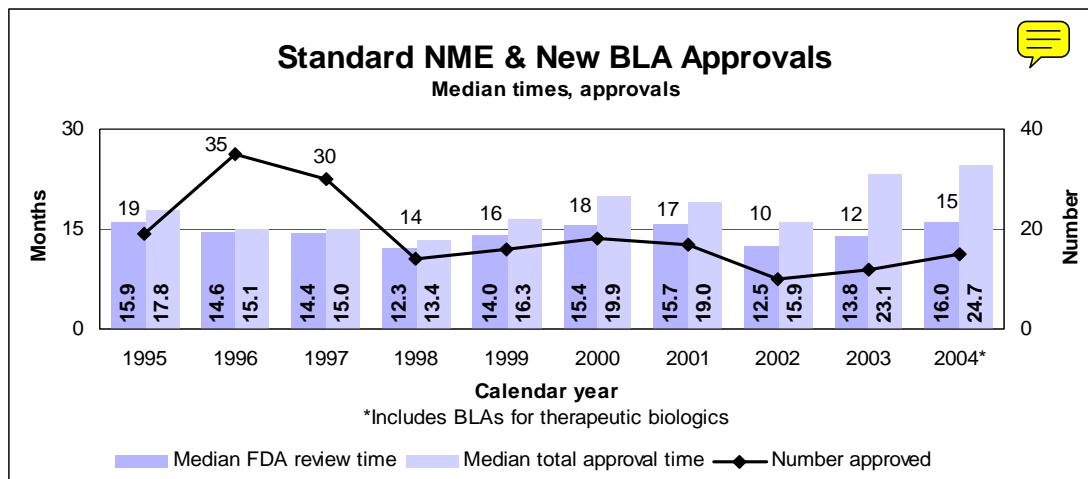
Insulin glulisine (Apidra) is a rapid-acting, synthetic insulin that starts working faster than regular insulin but does not work as long. It is approved for adults and is used with a longer-acting insulin or by itself in an insulin pump to maintain proper blood sugar control. (NME)

People with depression

Duloxetine hydrochloride (Cymbalta) treats depression. It belongs to a class of medicines called serotonin and norepinephrine reuptake inhibitors. The label carries our warning (page 38) about suicidal thoughts or actions in children, adolescents and adults. (NME)

Standard new molecular entities and new biologics

- 15 total approvals
- 14 NMEs
- 1 new BLA
- Median review time: 16.0 months
- Median approval time: 24.7 months
- 16 filings
- 1 orphan approval



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.

People with neurological disorders

Apomorphine hydrochloride (Apokyn) treats loss of control of body movements in people with advanced Parkinson's disease. (NME, priority, orphan)

Natalizumab (Tysabri), which received accelerated approval in November 2004, represented a new approach to treating patients with relapsing forms of multiple sclerosis. In February 2005, however, we issued a public health advisory to inform patients and health care providers about natalizumab's suspended marketing while we and the manufacturer evaluate serious adverse events reported with its use. (biologic, priority)

People with pain

Ziconotide (Prialt) helps in the management of severe chronic pain in people who are intolerant of or refractory to other treatment. It is used with an implanted pump that injects the drug into the space around the spinal cord. (NME, priority)

Pregabalin (Lyrica) helps manage pain associated with diabetic peripheral neuropathy. (NME, priority)

Additional statistics

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

Data updated

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

NMEs

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

- Acamprosate calcium (P)
- Apomorphine hydrochloride (P, O)
- Azacitidine (P, O)
- Cinacalcet hydrochloride (P, O)
- Clofarabine (P, O)
- Darifenacin hydrobromide (S)
- Duloxetine hydrochloride (S)
- Erlotinib hydrochloride (P)
- Eszopiclone (S)
- Gadobenate dimeglumine (S)
- Human secretin (P)
- Hyaluronidase (P)
- Iloprost (P, O)
- Insulin glulisine (S)
- Lanthanum carbonate (S)

Notable 2004 new drug approvals (continued)

People with cancer

Azacitidine (Vidaza) treats patients with myelodysplastic syndrome, a group of conditions caused by a problem in the blood-forming cells of bone marrow. (NME, priority, orphan)

Bevacizumab (Avastin) is used with intravenous 5-FU based chemotherapy as a first-line treatment for patients with cancer of the colon or rectum that has spread to other areas of the body. (biologic, priority)

Cetuximab (Erbix) treats a type of cancer of the colon or rectum that has spread to other areas of the body and is known as EGFR-expressing metastatic colorectal carcinoma. It is the first monoclonal antibody approved to treat this type of cancer and is given intravenously in combination with irinotecan, another drug approved to fight colorectal cancer, or alone if patients cannot tolerate irinotecan. (biologic, priority)

Clofarabine (Clolar) treats 1- to 21-year-old patients with acute lymphoblastic leukemia that has relapsed after at least two treatments or is unresponsive to treatment. Also known as ALL, the disease is responsible for 80 percent of the acute leukemias of childhood. (NME, priority, orphan)

Erlotinib hydrochloride (Tarceva) treats non small-cell lung cancer that has spread within the lung or other parts of the body after failure of at least one prior chemotherapy regimen. (NME, priority)

Palifermin (Kepivance) is used to reduce the chances of developing mucositis, a severe injury to the cells lining the mouth, and to shorten the time with severe mucositis in patients with cancer who receive high doses of chemotherapy and radiation therapy followed by stem cell rescue. It is a modified version of a naturally occurring human growth factor that helps maintain the normal structure of the skin and gastrointestinal surface. (biologic, priority)

Pemetrexed (Alimta) in combination with cisplatin treats patients with malignant pleural mesothelioma. It is an orphan drug and the first approved for cancer of the mesothelium, a membrane that covers and protects most of the internal organs of the body. The disease is rare and usually associated with a history of asbestos exposure. (NME, priority, orphan)

People with alcoholism

Acamprosate calcium (Campral) helps patients with alcoholism stay alcohol-free after they have stopped drinking. (NME, priority)

NMEs (cont.)

- L-Glutamine (S, O)
- Omega-3-acid ethyl esters (S)
- Ovine hyaluronidase (P)
- Pegaptanib sodium (P)
- Pemetrexed disodium (P, O)
- Pentetate calcium trisodium (P, O)
- Pentetate zinc trisodium (P, O)
- Pregabalin (P)
- Rifaximin (S)
- Solifenacin succinate (S)
- Telithromycin (S)
- Tinidazole (S)
- Tiotropium bromide (S)
- Trospium chloride (S)
- Trypan blue (P)
- Ziconotide (P)

New BLAs

- Bevacizumab (P)
- Cetuximab (P)
- Natalizumab (P)
- Palifermin (P)
- Technetium 99m Tc fanolesomab (S)

Other NDA priority approvals (T=tentative)

- Acetylcysteine
- Desloratadine
- Emtricitabine; tenofovir disoproxil fumarate
- Insoluble Prussian blue (T)
- Nitazoxanide
- Pentetate calcium trisodium (T)
- Pentetate zinc trisodium (T)
- Saquinavir mesylate

Notable 2004 new drug approvals (continued)

Infectious diseases

Nitazoxanide (Alinia) treats diarrhea caused by parasites. For diarrhea caused by *Giardia lamblia*, an oral suspension can be used for patients 1 year of age and older and tablets can be used for patients older than 12. The oral suspension can also treat diarrhea caused by *Cryptosporidium parvum* in patients 1 to 11 years of age. (priority)

Rifaximin (Xifaxan) is a nonsystemic antibiotic used to treat traveler's diarrhea caused by *Escherichia coli*. The drug does not enter the bloodstream. (NME)

Tinidazole (Tindamax) treats infections caused by parasites in both adults and pediatric patients older than 3 years of age. It treats trichomoniasis, a sexually transmitted disease, and the intestinal infections, giardiasis and amebiasis. (NME)

Telithromycin (Ketek) is an antibiotic to treat certain respiratory infections in adults 18 years of age and older. (NME)

People with lung disease

Tiotropium bromide (Spiriva HandiHaler) is for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. (NME)

People with pulmonary hypertension

Iloprost (Ventavis) treats pulmonary arterial hypertension, high blood pressure in the artery that carries oxygen-poor blood from the heart to the lungs. The inhaled drug helps dilate blood vessels in the lungs. (NME, priority, orphan)

People with macular degeneration

Pegaptanib sodium (Macugen) slows vision loss in people with the eye disease known as neovascular (wet) age-related macular degeneration. The drug is a selective vascular endothelial growth factor antagonist and is among the first treatments to target the underlying biology of this disease. (NME, priority)

People with end-stage kidney disease

Lanthanum carbonate (Fosrenol) is used to reduce the buildup of phosphates in patients with end-stage kidney disease. Fosrenol mixes with phosphates from food in the stomach to stop the phosphates from passing into the body. While small amounts of phosphates are needed by all cells in the body for them to work the right way, normal kidneys remove excess phosphate that can weaken bones. (NME)

People with HIV infection

Saquinavir mesylate (Invirase) and the combination of *emtricitabine* and *tenofovir disoproxil fumarate (Truvada)*, in combination with other antiretroviral agents, treat adults with HIV. (both priority)

Children with allergies, hives

Desloratadine (Clarinex Syrup), a new pediatric formulation, treats allergy symptoms and hives in children from 6 months old to 2 years old. (priority)

Counterterrorism treatments

For NME and new drug tentative approvals see [page 9](#).

Notable 2004 new drug approvals (continued)

People with other disorders

Acetylcysteine (Acetadote) prevents or lessens injury to the liver when administered within 8 to 10 hours after swallowing a potentially liver-damaging quantity of acetaminophen. (*priority, orphan*)

Cinacalcet hydrochloride (Sensipar) treats patients with high levels of parathyroid hormone in their blood due to chronic kidney disease that requires dialysis or with high levels of calcium in their blood due to cancer of the parathyroid gland. (*NME, priority, orphan*)

Darifenacin hydrobromide (Enablex), *solifenacin succinate (VESIcare)* and *trospium chloride (Sanctura)* treat an overactive bladder. (*NMEs*)

Eszopiclone (Lunesta) treats insomnia. (*NME*)

L-glutamine (NutreStore) treats short bowel syndrome in patients receiving specialized nutritional support when used with a recombinant human growth hormone approved for this indication. *The manufacturer discontinued this product.* (*NME, orphan*)

Omega-3-acid ethyl esters (Omacor) are used along with diet to lower very high triglyceride levels in adults. Elevated blood levels of triglycerides appear to increase the risk of developing heart disease. (*NME*)

Diagnostic and treatment aids

Gadobenate dimeglumine (Multihance) is a contrast agent used in magnetic resonance imaging of the central nervous system. (*NME*)

Human secretin (ChiRhoStim) can be used to stimulate the pancreas as an aid in the diagnosis of pancreatic disease. (*NME, priority*)

Hyaluronidase (Amphadase) and *Ovine hyaluronidase (Vitrase)* help to increase the absorption and dispersion of other injected drugs. (*NME, priority*)

Technetium 99m Tc fanolesomab (NeutroSpec) helps in the imaging of patients with equivocal signs and symptoms of appendicitis who are 5 years of age or older. It is a kit to prepare a radiolabeled monoclonal antibody. (*biologic*)

Trypan blue (VisionBlue) helps in eye surgery by staining the part of the eye that holds the lens in place. (*NME, priority*)

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.”

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.

Notable 2004 new or expanded use approvals

People with cancer

Docetaxel (Taxotere), in combination with the steroid prednisone, treats advanced metastatic prostate cancer. This is the first drug for hormone refractory prostate cancer that has shown a survival benefit. The drug’s uses were also expanded for use in combination with other chemotherapy for treatment of patients with operable node positive breast cancer. *(priority)*

Gemcitabine hydrochloride (Gemzar), in combination with the cancer chemotherapy paclitaxel, is a first-line treatment for patients with breast cancer that has spread and who have had a failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. *(priority)*

Interferon gamma-1b (Actimmune), a treatment to reduce the frequency and severity of serious infections in people with chronic granulomatous disease, now has safety and efficacy data for pediatric patients. *(biologic, priority)*

Letrozole (Femara) can now be used with other chemotherapy for the extended treatment of early breast cancer in postmenopausal women who have received five years of tamoxifen therapy. *(priority)*

Oxaliplatin (Eloxatin), in combination with other chemotherapy, can now be used to treat patients previously untreated for advanced cancer of the colon and rectum. *(priority)*

Tositumomab and *iodine I 131 tositumomab (Bexxar)* can now treat patients with relapsed or refractory, low grade, follicular or transformed CD20 positive non-Hodgkin’s lymphoma who have not received rituximab. *(biologic, priority)*

People with diabetes

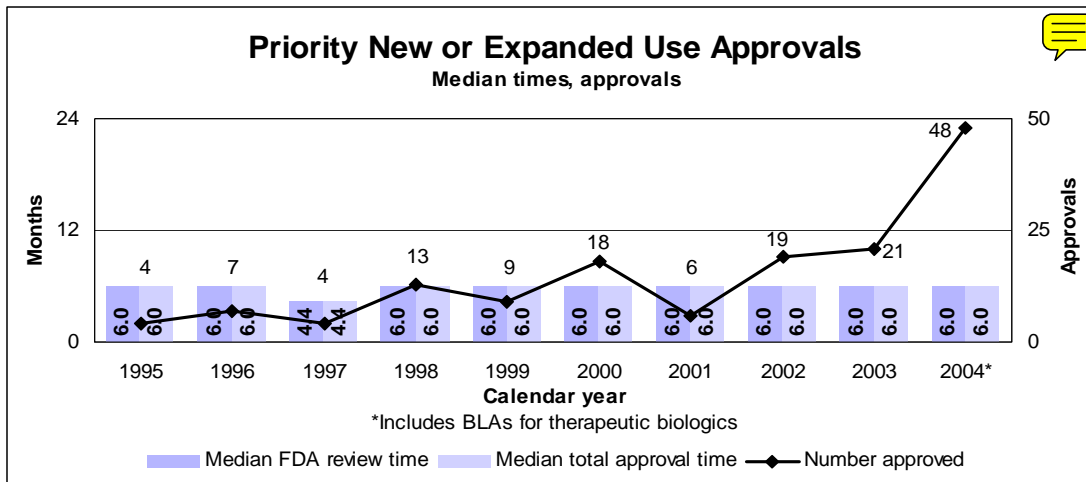
Duloxetine hydrochloride (Cymbalta), a treatment for depression ([page 16](#)), can now be used for the management of neuropathic pain associated with diabetic peripheral neuropathy. It carries our warning ([page 38](#)) about suicidal thoughts or actions in children, adolescents and adults. *(priority)*

Counterterrorism treatment

See [page 9](#) for the expanded use of *Penicillin G procaine* to prevent the occurrence or progression of anthrax disease following exposure to *Bacillus anthracis* (including inhalational anthrax). *(priority)*

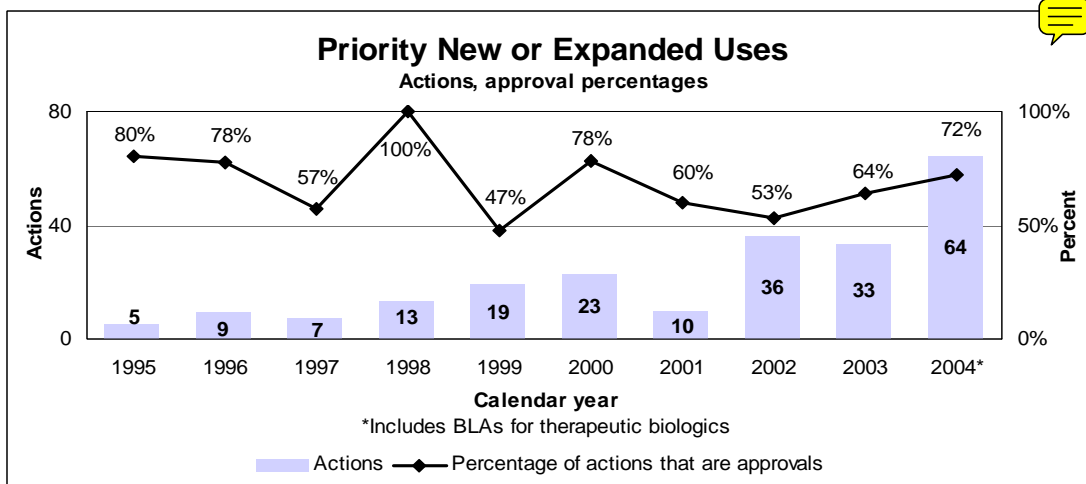
Pediatric new or expanded uses

See [page 25](#) for the drugs with new or expanded uses in children approved under priority review required by the Best Pharmaceuticals for Children Act.



Priority new or expanded uses (efficacy supplements)

- 48 total approvals
- 46 drugs
- 2 biologics
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 64 actions
- 23 pediatric approvals (page 25)
- 2 orphan approvals



25 priority approvals

[number of approvals]

(See page 25 for 23 pediatric priority approvals)

- Docetaxel [2]
- Duloxetine [1]
- Gatifloxacin [2]
- Gemcitabine hydrochloride [1]
- Icodextrin [1]
- Interferon gamma-1b [1] (biologic)
- Leflunomide [1]

Notable 2004 new or expanded use approvals (cont.)

People on artificial feeding

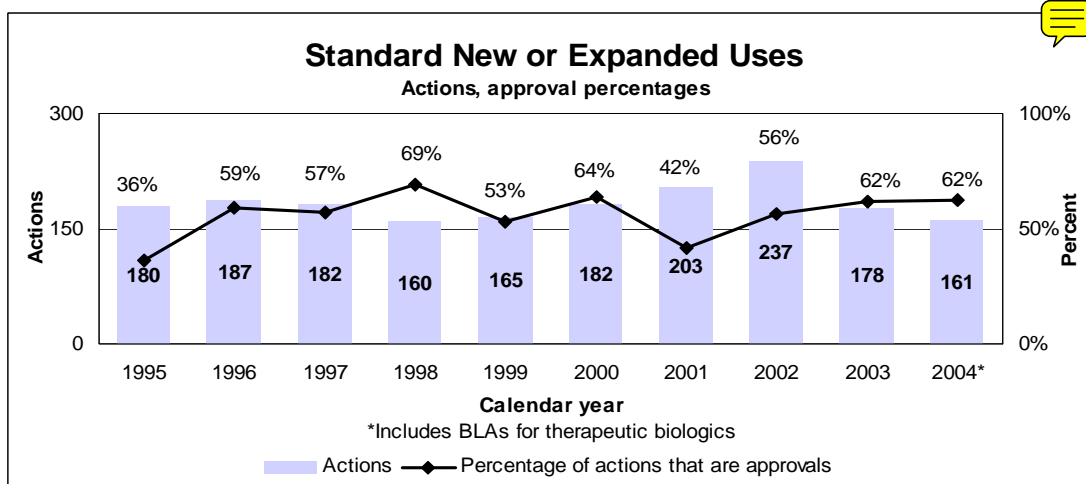
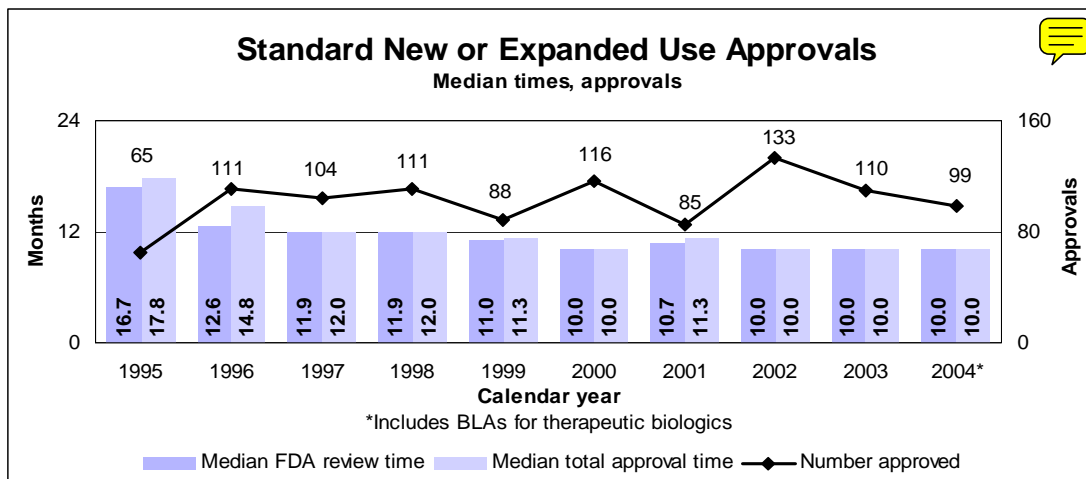
Multi-vitamin infusion without vitamin K (MVI-12) is used to prevent vitamin deficiency and complications from blood clots in people receiving home parenteral nutrition who also receive warfarin-type blood thinning therapy. (priority, orphan)

People on dialysis

Icodextrin (Extraneal Peritoneal Dialysis Solution), used for continuous ambulatory peritoneal dialysis or automated peritoneal dialysis for the management of chronic renal failure, is an improvement over normal solutions in certain patients. (priority)

Standard new or expanded uses (efficacy supplements)

- 99 total approvals
- 87 drugs
- 12 biologics
- Median review time: 10.0 months
- Median approval time: 10.0 months
- 161 actions
- 2 orphan approvals



25 priority approvals (cont.)

[number of approvals]

- Letrozole [1]
- Levofloxacin [5]
- Linezolid [3]
- Moxifloxacin hydrochloride [2]
- Multi-vitamin infusion without vitamin K [1]
- Oxaliplatin [1]
- Rofecoxib [2]
- Tositumomab and iodine I 131 tositumomab [1] (biologic)

Antimicrobial Resistance

Drug-resistant bacteria continue to be a major threat to the public health.

In an effort to help protect public health, we provided priority reviews of new or expanded uses for four antibiotics to treat community acquired pneumonia due to multi-drug resistant *Streptococcus pneumoniae*. The antibiotics are *Gatifloxacin* (Tequin), *Levofloxacin* (Levaquin), *Linezolid* (Zyvox) and *Moxifloxacin hydrochloride* (Avelox). Linezolid was also approved to treat hospital-acquired pneumonia caused by *Streptococcus pneumoniae*, including multi-drug resistant strains.

Education campaign

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.

Approval totals

- 147 drugs and biologics
- 133 drugs
- 14 biologics

Some conditions with approved pediatric labeling

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

Pediatric Drug Development

The Best Pharmaceuticals for Children Act of 2002 renewed our authority to grant six months of additional marketing exclusivity to manufacturers who conduct and submit pediatric studies in response to our written requests. In calendar year 2004, we approved 25 pediatric labeling changes as a result of the exclusivity provision.

NME approval. We provided a priority review and orphan status to one new molecular entity—*clofarabine (Clolar)*—for use in children (page 18).

Exclusivity. As of April 30, 2005, we had received 374 proposed pediatric study requests from manufacturers, issued 300 written requests, made 121 exclusivity determinations, granted exclusivity to 111 drugs and added new pediatric information to 90 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. As a result of this pediatric testing we now have 10 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. The failure to produce drugs in dosage forms that can be taken by young children—such as liquids or chewable tablets—can also deny them access to important medications.

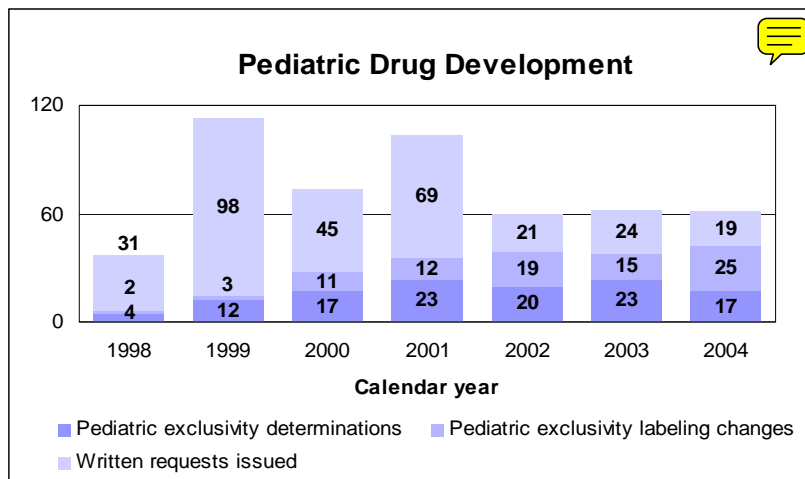
Off-patent drugs. The law also established a publicly funded contracting process to study drugs that lack patent protection or market exclusivity, referred to as “off-patent.” In consultation with FDA and other pediatric experts, the National Institutes of Health has published four lists of off-patent drugs for which additional pediatric studies are needed. We have issued and forwarded 11 written requests—four in 2004—for these off-patent drugs. We also forwarded five written requests 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. We have posted 49 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 and presentation of these reports to a pediatric advisory committee. As of February 2005, reports for 34 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

This 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.



2004 pediatric drug statistics

- 19 written requests issued
- 25 pediatric exclusivity labeling changes granted
- 17 exclusivity determinations made

Priority pediatric labeling changes

An efficacy supplement may change labeling to reflect new information about pediatric use, even if there are no new or expanded uses.

Consistent with the Best Pharmaceuticals for Children Act, we gave priority reviews to these pediatric supplements [number of approvals]

- Anagrelide hydrochloride [1]
- Benazepril hydrochloride [1]
- Dorzolamide hydrochloride [1]
- Glyburide and metformin hydrochloride [1]
- Irinotecan hydrochloride [1]
- Lansoprazole [2]
- Tolterodine [1]
- Venlafaxine hydrochloride [2]
- Zolmitriptan [1]

Notable 2004 pediatric new or expanded uses

The Best Pharmaceuticals for Children Act requires us to provide priority reviews to pediatric supplements for drugs submitted under the law. Reviews of 10 supplements for seven drugs resulted in new or expanded medication opportunities for children [number of approvals]:

- *Ciprofloxacin (Cipro)* can treat complicated urinary tract infections and pyelonephritis for pediatric patients 1 to 17 years of age. [4]
- *Fenoldopam mesylate (Corlopam)* is for in-hospital, short-term (up to 4 hours) reduction in blood pressure in pediatric patients. [1]
- *Lansoprazole (Prevacid)* can be used to treat symptomatic gastroesophageal reflux disease, nonerosive esophagitis and erosive esophagitis in pediatric patients between 12 and 17 years of age. [1]
- *Methylphenidate (Concerta)* extended-release tablets (previously approved for pediatric patients 6 to 12 years of age) can be used in adolescents with attention deficit hyperactivity disorder. Labeling has been expanded to include a 72 mg dose. [1]
- *Nelfinavir mesylate (Viracept)* in combination with other antiretroviral agents can be used to treat HIV-1 infection in pediatric patients from 2 to 13 years of age. [3]
- *Paricalcitol (Zemlar)* can be used in pediatric patients with end-stage kidney disease. [1]
- *Sodium ferric gluconate complex in sucrose (Ferrlecit)* can be used to treat iron deficiency anemia in pediatric patients age 6 years and older who are undergoing chronic hemodialysis and receiving supplemental erythropoietin therapy. [1]

Pediatric study information in labeling

We work with sponsors to put more information on pediatric studies into their labels even when the studies did not show efficacy for the indication studied.

Internet resources

Our Web site for up-to-date pediatric labeling changes 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 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.

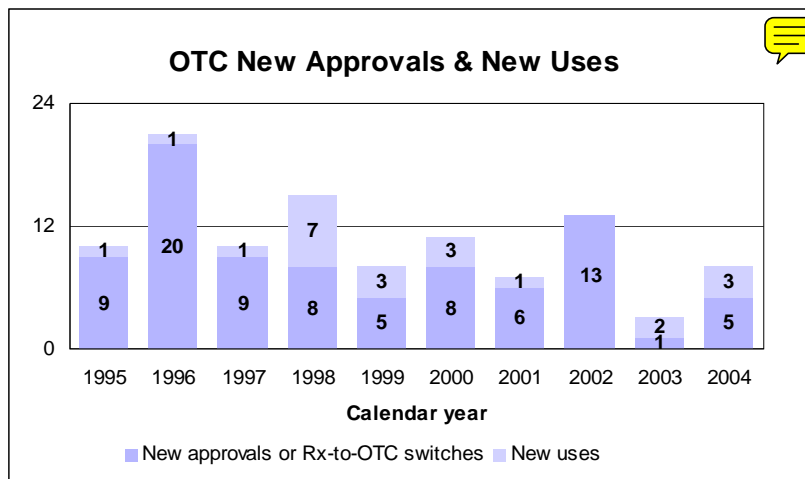
How we regulate OTC drugs

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 statistics

- 5 approvals for first-time OTC sale
- 3 new uses

Over-the-Counter Drug Review

We approved five drugs for first-time over-the-counter sale:

- *Guaiifenesin 600 mg/pseudoephedrine hydrochloride 60 mg tablets and guaiifenesin 1200 mg/pseudoephedrine 120 mg tablets (Mucinex-D Extended Release)* for use as an expectorant and nasal decongestant in adults and children 12 years and older.
- *Guaiifenesin 600 mg/dextromethorphan 30 mg tablets and guaiifenesin 1200 mg/dextromethorphan 60 mg tablets (Mucinex-DM)* for use as an expectorant and cough suppressant in adults and children 12 years and older.
- *Ibuprofen 100 mg/pseudoephedrine hydrochloride 15 mg/chlorpheniramine maleate 1 mg per 5 mL (Children's Advil Allergy & Sinus Elixir)* for the relief of symptoms of allergic rhinitis and the common cold in children 6 years and older.
- *Ibuprofen 100 mg per 5 mL oral suspension (Children's Elixsure IB)* for the relief of minor aches and pains and fever in children 2 years of age and older.
- *Ranitidine hydrochloride 150 mg (Zantac 150 Tablets)* for prevention and relief of heartburn in adults.

We also approved three new uses for existing OTC products, all of which can be used in children 12 years and older:

- *Loratadine 5 mg/pseudoephedrine hydrochloride 120 mg (Claritin-D 12 Hr. Extended Release Tablets)* and *loratadine 10 mg/pseudoephedrine hydrochloride 240 mg (Claritin-D 24 Hr. Extended Release Tablets)* for the nasal congestion due to the common cold in adults and adolescents 12 years and older.
- *Miconazole nitrate (Monistat 1 Combination Pack)* for anytime use in the treatment of vaginal yeast infections in adults and adolescents 12 years and older.

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 380 generic drug products in 2004, 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 15.7 months.

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

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 and in the same time 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.

Generic drug Web site

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

Notable 2004 generic drug approvals

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

- *Fluconazole (Diflucan)* in several dosage forms for use as an antifungal agent.
- *Benazepril hydrochloride (Lotensin)* used to treat high blood pressure.
- *Ciprofloxacin (Cipro)* for antibiotic use, particularly as an agent to treat anthrax exposure.
- *Ribavirin (Rebetol)* used in combination with interferon alpha 2-A for several indications, including the treatment of chronic hepatitis C.
- *Metformin hydrochloride extended release tablets (Glucophage XR)* used to treat Type 2 diabetes mellitus.

Our approval of generic versions of these drugs could 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 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_info/default.htm.

Improving manufacturing practices

Our strategic initiative, Pharmaceutical cGMPs for the 21st Century, also applies to generic drugs (see [page 8](#) and [page 50](#)).

Generic drugs

- 380 generic drug approvals
- Median approval time: 15.7 months
- 95 tentative approvals
- 635 receipts

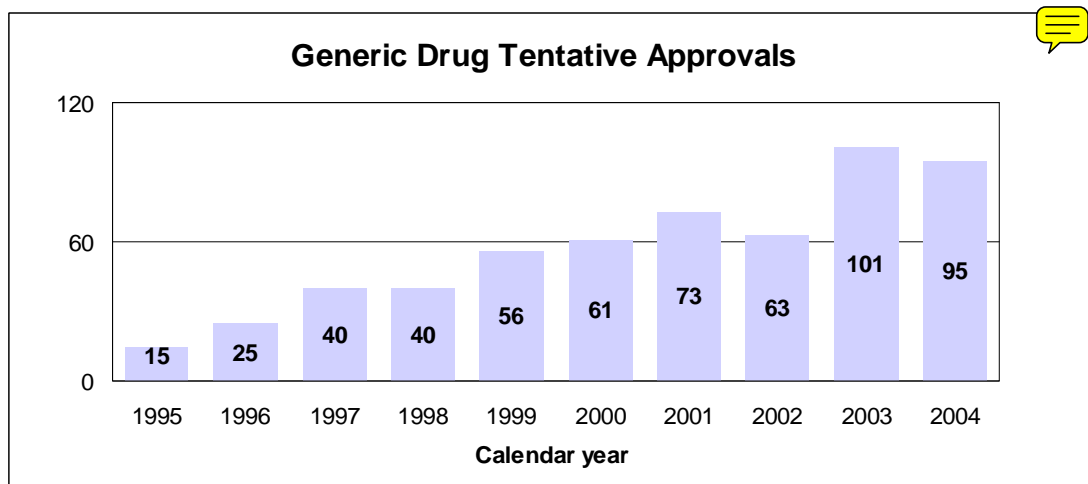
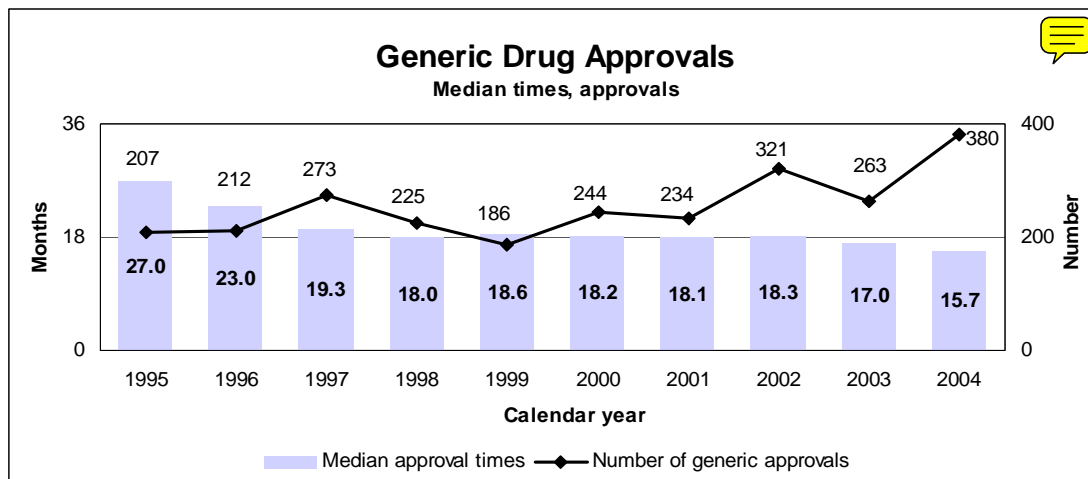
Scientific basis for generic drug review

We continue to articulate the scientific underpinnings of our review process and to work to define 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 professionals on how our approval assures that generic drugs are safe, effective and high quality products.



Tentative vs. full approval

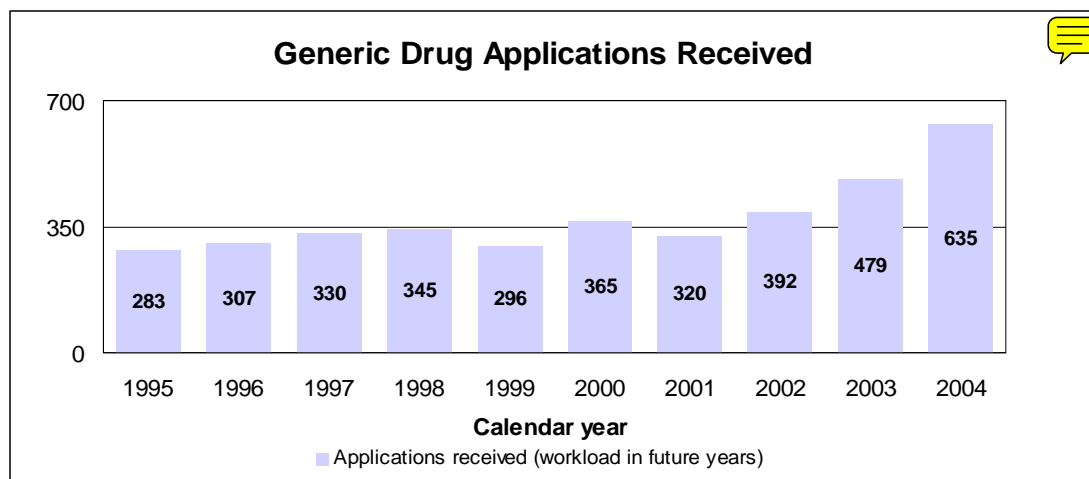
The only difference between a full approval and a tentative approval is that the final approval of these applications is delayed due to existing patent or exclusivity on the innovator drug product. These and other legal issues continue to be a challenge to the generic drug review program.

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 2004's approvals represent conversions of tentative approvals granted in 2003 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).



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.

We are taking steps aimed at improving the content and completeness of generic drug applications and assuring that the applications contain the needed information to be evaluated successfully in one cycle. These steps include:

- Enhanced communication with individual 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 submission of applications in an electronic format for greater efficiency ([page 32](#)).

Electronic submissions

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

Increased generic drug review staff

We have constituted a third chemistry review division for generic drugs. We are augmenting our clinical review staff to further speed our review of generic drug applications.

Reducing legal 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.

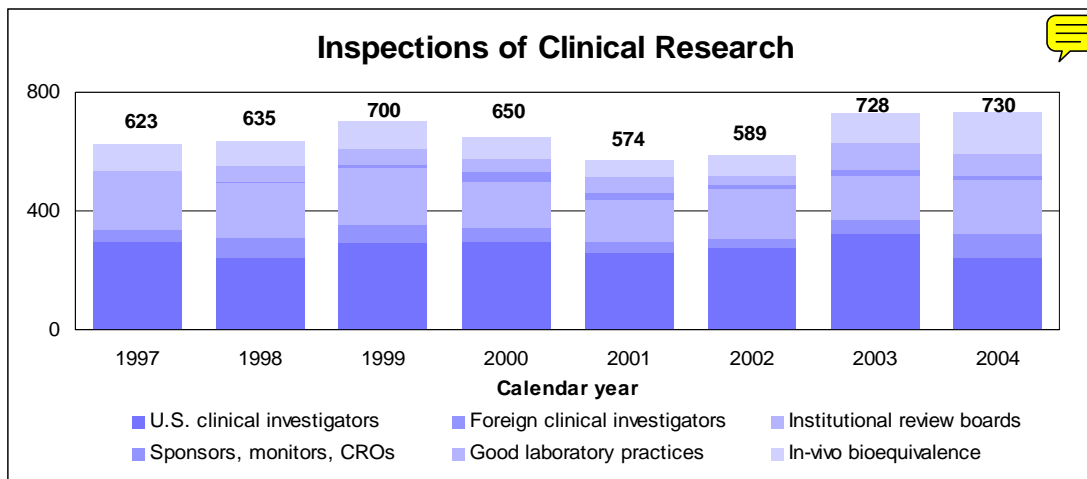
Inspections for data quality, research risks in 2004

We conducted a total of 730 inspections in 2004:

- 242 U.S. clinical investigators
- 82 foreign clinical investigators
- 178 institutional review boards
- 18 sponsors, monitors or contract research organizations
- 74 good laboratory practices
- 136 *in-vivo* bioequivalence

2004 top 5 deficiencies in inspections of clinical investigators

- 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 (see “How we approve generic drugs,” [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 vulnerable populations, such as children, the mentally impaired and prisoners.

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

International inspections of clinical research

We have conducted 592 inspections of clinical research in 55 countries from 1980 to 2004.

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 53](#)) 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. 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.
- *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 41](#)).

We continue to receive electronic submissions using the specifications of the electronic Common Technical Document ([page 53](#)).

Internet resources

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

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 2003 receipt cohort.
- We are on track for exceeding all user-fee performance goals for the fiscal year 2004 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 (page 34) review letter. In fiscal year 2004, we met our goals for all 14 reviewable unit submissions for seven different products.
- *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>.

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).

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

Drug Review Team

Scientific training for reviewers

Our systematic, internal training program is based on core competencies, learning pathways and individual development plans. In 2004:

- We presented 51 scientific seminars and scientific rounds.
- We offered a strong and innovative curriculum of 28 scientific courses.
- We brought in 45 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.

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—differ from others because they are intended to affect the germs instead of patients. Another group of microbiologists evaluates the manufacturing processes and tests for sterile products, such as those used intravenously.
- *Pharmacologists and toxicologists* evaluate the effects of the drug on laboratory animals in short-term and long-term studies, including the potential based on animal studies for drugs to induce birth defects or cancer in humans.
- *Physicians* evaluate the results of the clinical trials, including the drug's adverse and therapeutic effects, and determine if the product's benefits outweigh its known risks at the doses proposed.
- *Project managers* orchestrate and coordinate the drug review team's interactions, efforts and reviews. They also serve as the regulatory expert for the review team and as the primary contact for the drug industry.
- *Statisticians* evaluate the designs and results for each important clinical study.

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: Pharmacogenetics
- 2001: QT prolongation

2

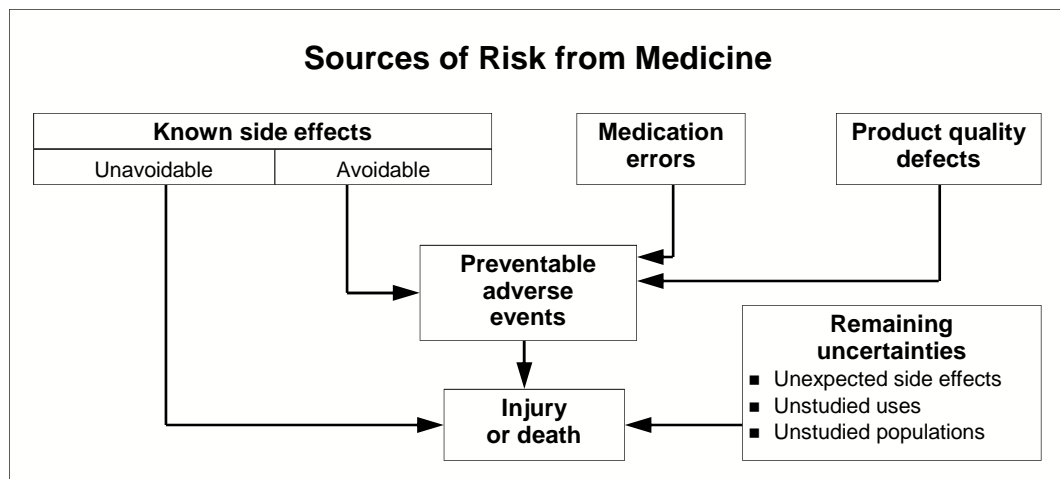
DRUG SAFETY AND QUALITY

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 2004 include:

- Processing and evaluating more than 400,000 reports of adverse drug events, including more than 20,000 submitted directly from individuals.
- Reviewing about more than 35,000 reports of medication errors.
- Issuing more than 800 letters to help ensure manufacturers comply with regulations concerning drug promotion. Included in the total were more than 200 concerning direct-to-consumer advertising.
- Evaluating more than 3,000 reports concerning problems that occur in the manufacturing, processing, packing, labeling, storage or distribution of drugs.
- Promulgating a regulation that calls for bar codes on over-the-counter medicines commonly used in hospitals and most prescription medicines.
- Issuing Public Health Advisories on non-steroidal anti-inflammatory pain medicines and on antidepressant use in children, adolescents and adults.
- Approving Medication Guides for two drugs.
- Implementing our initiative to encourage adoption of state-of-the-art manufacturing processes.



Knowledge gaps in current safety system

- Detection of differences in the frequency of events occurring both in those who take a drug and those who don't take the drug.
- Time-dependent events.
- Adverse events that occur more frequently in populations not normally studied in trials such as those who are very sick or on multiple drugs.
- Adverse events that occur more frequently with off-label use.
- A tendency for medical errors or abuse.

Approaches to resolving knowledge gaps

- Use emerging electronic medical record systems for surveillance.
- Randomized trials or registries conducted in practice settings after marketing.
- More surveillance systems in specialized settings such as emergency rooms or nursing homes.

Safety System for Medicines

Our current system for evaluating drug safety provides:

- Extensive premarket testing with rigorous review, including evaluation of remaining uncertainties.
- Risk management strategies before and after approval.
- Voluntary adverse event reporting systems with additional population-based information.
- Proposed user-friendly communication through an improved drug label compatible with e-prescribing and electronic decision support.

Capacities of current 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 risks.
- Identification of rare serious adverse events that occur after marketing.

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. These include unexpected side effects, long-term effects and unstudied uses and populations. For example, a rare event occurring in 1 in 10,000 persons won't be identified in normal premarket testing.

Adverse event reporting

In 2004, we received 422,889 reports of suspected drug-related adverse events:

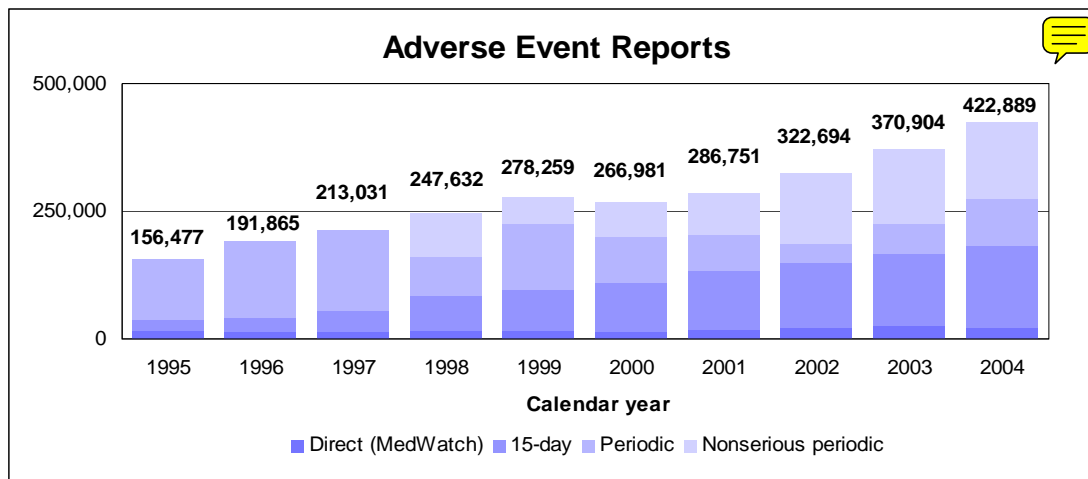
- 21,493 MedWatch reports directly from individuals.
- 162,107 manufacturer 15-day (expedited) reports.
- 89,960 serious manufacturer periodic reports.
- 149,329 nonserious manufacturer periodic reports.

Chart data available

Data for this chart and others is available as comments in the [PDF version](#) of the report.

AERS on Internet

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



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.

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 and the required reports from manufacturers. These reports often form the basis of "signals" that there may be a potential for serious, unrecognized, drug-associated events. When a signal is detected, further testing of the hypothesis is undertaken using various epidemiological and analytic databases, studies and other instruments and resources. AERS offers paper and electronic submission options, international compatibility and pharmacovigilance screening.

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 submission 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 2004, our field investigators inspected 68 domestic and 10 foreign firms to assess compliance with our regulations for adverse event reporting. We sent 10 firms official notification that they had significant uncorrected deficiencies. We were able to work with other firms to obtain voluntary correction of deficiencies identified by our monitoring.

Public Health Advisories in 2004

Non-steroidal anti-inflammatory pain medicines

In December, we issued a Public Health Advisory recommending limited use of non-steroidal anti-inflammatory drug products, including those known as COX-2 selective agents. This was an interim measure pending our further review of data about the increased risk of heart disease. Shortly after the advisory, the manufacturer of one withdrew it voluntarily from the market. In 2005, after further review and a public meeting, we withdrew another and required a boxed warning about heart disease risks on all prescription NSAIDs (page 43). We concluded that over-the-counter NSAIDs are safe for short-term pain relief when used as directed on the package labeling.

Antidepressant use in children, adolescents and adults

We asked manufacturers of all antidepressant drugs to include in their labeling a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents and additional information about the results of pediatric studies.

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 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>.

Data mining

We continued 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. In particular, the software developed under the agreement was piloted in a small group of users.

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 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 healthcare professional and consumer subscribers to our e-mail notification service increased to more than 50,000. We also have 160 MedWatch Partner organizations. In 2004, these individuals and groups received:

- 50 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 or to decide whether to use or to continue to use the product.

In 2004, we approved Medication Guides for two drugs:

- *Abacavir sulfate* and *lamivudine* combination (*Epzicom*).
- *Amiodarone* (*Cordarone*) and seven generic versions.

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

Drugs with special safety restrictions

Controls on 12 prescription drugs include limiting distribution to specific facilities; limiting prescription to physicians with special training or expertise; or requiring certain medical tests with their use. They should not be bought over the Internet.

As of June 23, 2005, these drugs are:

- Abarelix
- Alosetron
- Bosentan
- Clozapine
- Dofetilide
- Fentanyl citrate
- Isotretinoin
- Mifepristone
- Sodium oxybate
- Somatropin (rDNA origin)
- Thalidomide
- Trovafloxacin mesylate or atrofloxacin mesylate injection

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

User fees support risk assessment, minimization

In recent years, about half of all new medicines 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 best able to identify and counter adverse side effects that did not appear during the clinical trials.

Risk management guidances published

We published three risk management draft guidances for industry in 2004:

- *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—finalized in 2005—fulfill our commitment to the risk management performance goals that are part of the 2002 reauthorization of the Prescription Drug User Fee Act. The guidances are based on three concept papers released in 2003, on input from a subsequent public workshop and on comments received on the draft guidances.

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.

DailyMed update

We are collaborating on a multi-agency effort to improve patient safety through accessible medication information. Called DailyMed and scheduled to launch in fall 2005, the project will enable 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.

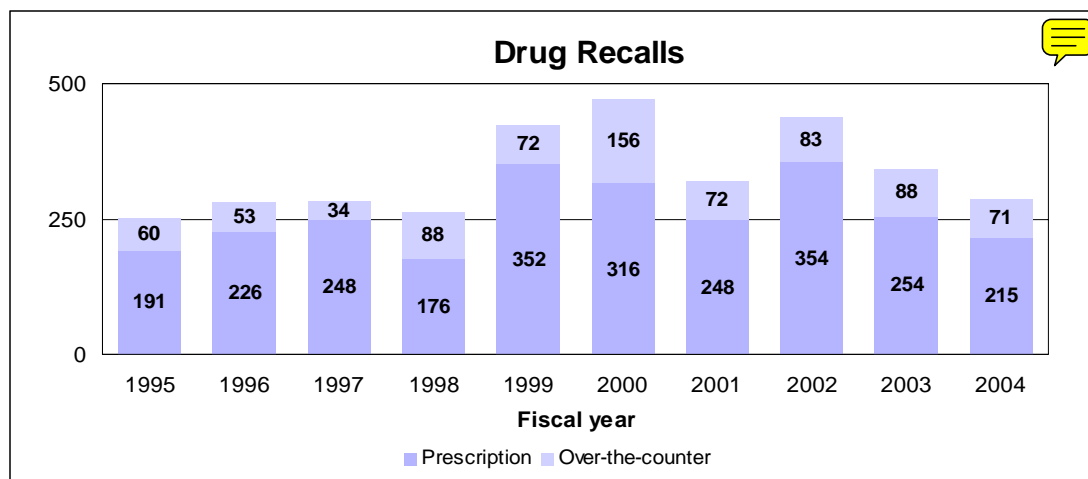
Proposed rule to revise prescription drug labeling

We continued to work on a final rule, based on comments from the public, to our proposal in 2001 to improve professional labeling so that it better communicates essential information about prescription drugs to health care providers.

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@cderr.fda.gov.



Drug recalls in fiscal year 2004

- 215 prescription drugs
- 71 over-the-counter drugs

Recent safety-based NME withdrawals

Drug name
(FY received/
CY approved/
CY withdrawn)
approved use/
reason withdrawn

- **Azaribine**
(1970/1975/1976)
psoriasis treatment/
stroke
- **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/
flank pain syndrome
- **Encainide**
(1984/1986/1991)
irregular heartbeat/
fatal arrhythmia
- **Temafloxacin**
(1990/1992/1992)
antibiotic/kidney failure

Drug Recalls

Top 10 reasons for drug recalls in fiscal year 2004

- cGMP deviations
- Subpotency
- Stability data does not support expiration date
- Generic drug or new drug application discrepancies
- Dissolution failure
- Label mix-ups
- Content uniformity failure
- Presence of foreign substance
- pH failures
- Microbial contamination of non-sterile products

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.

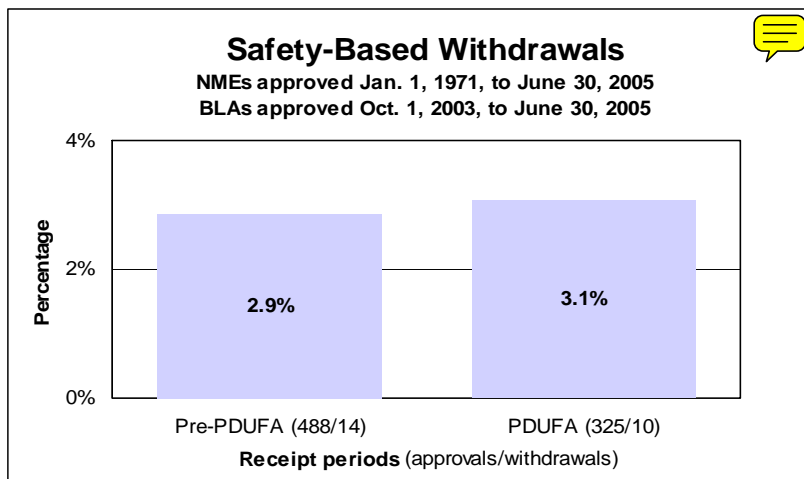
Manufacturers or distributors usually implement voluntary recalls in order to carry out their responsibilities to protect the public health when they need to remove a marketed drug product that presents a risk of injury to consumers or to correct a defective drug product. A voluntary recall of a drug 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.



Recent safety-based NME 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/
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

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.

Record of safety-based market withdrawals

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.

Beginning with this report, our pre-PDUFA and PDUFA periods are based on when we received an application rather than when we approved it. The receipt date more accurately reflects whether we reviewed an application under user fee performance goals (page 33). Starting with Oct. 1, 2003, our chart includes our approvals of new therapeutic biologics. PDUFA-era applications exempt from user fees are also counted.

One safety-based withdrawal in 2004

In September, the manufacturer of rofecoxib voluntarily withdrew the COX-2 selective non-steroidal anti-inflammatory pain reliever because it was found to increase the risk of heart disease.

Further analysis and a public meeting led us in 2005 to require boxed safety warnings on all prescription NSAIDs and the safety withdrawal of valdecoxib, a COX-2 selective NSAID, because of an increased risk of serious skin reactions.

Discontinuations determined to be safety withdrawals

We considered the 2003 marketing discontinuation of levomethadyl a safety-based withdrawal. The manufacturer of the treatment for managing opiate dependence discontinued its sale based on reports of cardiac arrhythmias and cardiac arrest and the availability of safer alternatives.

We determined the 1999 marketing discontinuation of etretinate to be a safety withdrawal because it poses a greater risk of birth defects than acitretin, the active metabolite of etretinate used in its replacement product.

Recent safety-based NME withdrawals (cont.)

- **Alosetron**
[Remarketed in 2002 with
restricted distribution]
(1999/2000/2000)
irritable bowel syndrome/
ischemic colitis, severe
constipation
- **Cerivastatin**
(1996/1997/2001)
cholesterol reduction/
muscle damage leading
to kidney failure
- **Rapacuronium**
(1998/1999/2001)
anesthetic/severe
breathing difficulty
- **Etretinate**
(1985/1986/1999)
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

Drug Promotion Review

The information about a drug available to physicians and consumers is just as important to its safe use as drug quality. We promote and protect the health of Americans by ensuring that drug advertisements and other promotional materials are truthful and balanced. We operate a comprehensive program of education, surveillance and enforcement about drug advertising and promotion.

Research on direct-to-consumer advertising

We published the final report of our two national telephone patient surveys and one physician survey in November 2004 (<http://www.fda.gov/cder/ddmac/researchka.htm>). Our main objective in the studies was to assess the variety of ways direct-to-consumer advertising could influence the doctor-patient relationship. The three surveys found both positive and negative effects:

- *Disease awareness increased.* By and large, consumer ads seem to increase awareness of conditions and treatments, motivate questions to ask a healthcare provider and help patients ask better questions.
- *No increase in doctor visits.* Our data provided no evidence of increased visits as a result of consumer advertising, and few patients reported that advertising motivated physician visits. On the contrary, most people reported that health reasons prompted their visits.

It is clear, however, that direct-to-consumer advertising also has effects that may not be positive:

- *Physicians feel some pressure to prescribe.* Although few physicians report excessive pressure to prescribe requested drugs from patients who have seen advertisements, nearly half report feeling at least a little pressure to prescribe.
- *Patients, physicians say efficacy overstated.* Both patients and doctors indicate that consumer directed advertisements overstate drug efficacy and do not present a fair balance of benefit and risk information.
- *Patients rate brief summary modestly understandable.* Patients gave only modest ratings to the understandability of the “brief summary” that is included in print advertisements. This is information meant to provide a more complete picture of the advertised product’s risks.
- *Patients find recent ads less useful than previously.* Patients also expressed some negative opinions about direct-to-consumer advertising. Perhaps more importantly, fewer patients in the 2002 survey than in the survey conducted three years earlier indicated that advertising was useful in their interaction with their doctor and in their healthcare decision making.

Studies of brief summary

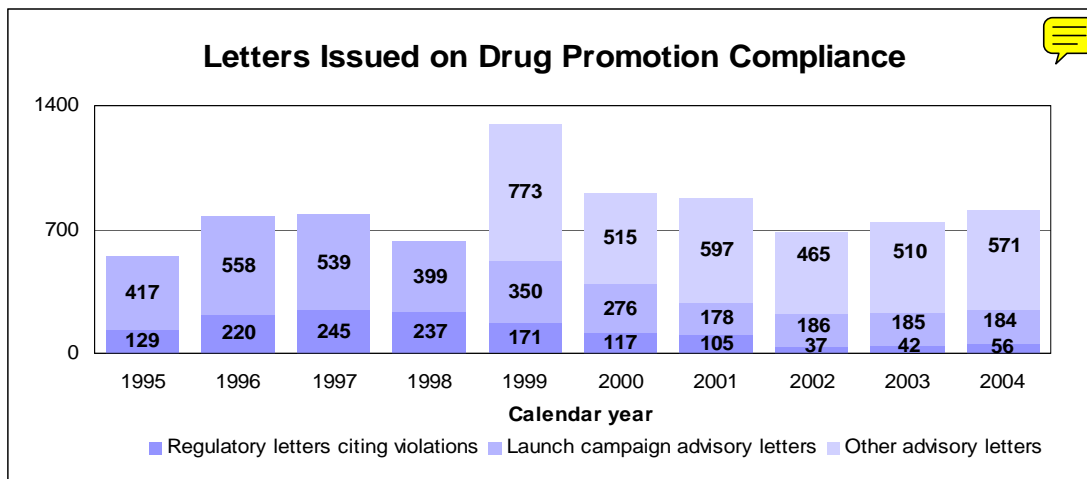
We are conducting three studies to help find the best way or ways to present information in the “brief summary”—the page of risk information in a print ad:

- *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 2005.
- *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.

811 total letters issued on drug promotion activities

In 2004, we issued 811 letters concerning drug promotion. These were:

- 56 letters citing violations of regulations for prescription drug promotion.
- 184 advisory letters concerning launch campaigns.
- 571 other types of advisory, closure or acknowledgement letters.



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 56 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.

Launch campaign advisory letters. When requested, we review advertisements and other promotional materials before drug companies launch marketing campaigns that introduce new drugs or campaigns that introduce new indications or dosages for approved drugs. In 2004, we issued 184 advisory letters to companies regarding their promotional materials for launch campaigns.

Other advisory letters. We issued 423 other advisory letters to the industry regarding proposed promotional pieces, both professional and consumer directed. We also issued 148 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

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 a different treatment that is more appropriate for the patient than the advertised drug. But physicians and others are concerned that consumers may not always get a balanced view of the benefits and risks of a product.

217 letters issued on direct-to-consumer advertising

In 2004, 217 or 27 percent of the 811 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 of letters addressing promotion have been:

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

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.

Sampling criteria

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

Protection of federal funds

Federal law prohibits the expenditure of federal funds for drug products determined to be less than effective for their labeled indications.

Under an intra-agency agreement between the Centers for Medicare and Medicaid Services and FDA, we identify drugs that are not eligible for CMS's Drug Reimbursement Program.

These include dietary supplements and drugs still on the market that have been identified as less-than-effective in *Federal Register* notices.

This process has saved American taxpayers millions of dollars and has made those funds available for reimbursement of eligible drug products.

1,375 preapproval inspections

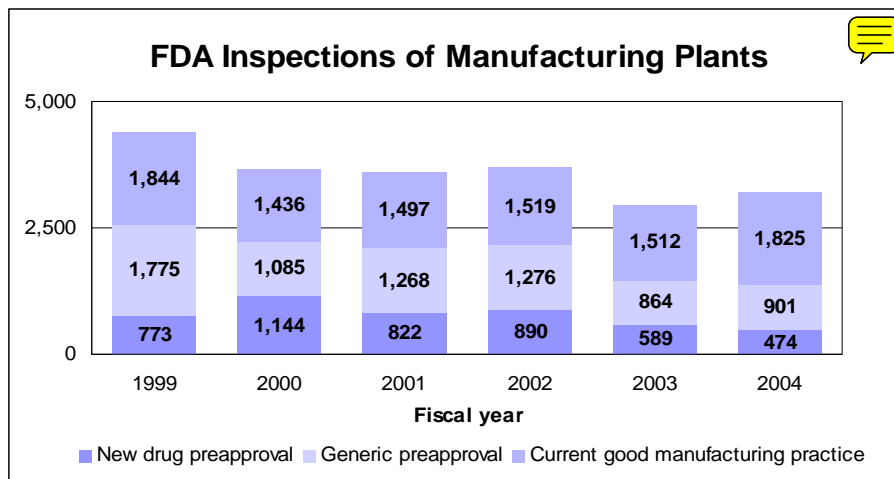
During fiscal year 2004, FDA evaluated:

- 474 plants in support of new drug applications.
- 901 domestic firms in support of generic drug applications.

1,825 good manufacturing practice inspections

There were 1,825 good manufacturing practice inspections in fiscal year 2004.

- We approved 45 field recommendations for regulatory action. These included 40 warning letters, three injunctions and two seizures.
- We reviewed 184 foreign establishment inspection reports, resulting in one warning letter, one import alert and several regulatory meetings.



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.

Compounded drugs

We generally defer to state authorities regarding the regulation of traditional pharmacy compounding—on-site compounding of reasonable quantities of drugs following a valid prescription for an individual patient from a licensed practitioner.

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 seizures of violative products.

Medical gas inspections

We reviewed 171 medical gas inspections and approved issuing one warning letter.

Regulation of OTC promotional statements

Information that accompanies or is displayed with an over-the-counter drug is critical to its safe use.

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

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

We also monitor promotional materials associated with over-the-counter drugs marketed without an approved application or pursuant to a monograph, including fraudulent drugs, and take enforcement actions against these products.

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.

Drug importation

International commerce in pharmaceuticals provides challenges, particularly in counterfeit drugs and counterterrorist activities. We work to:

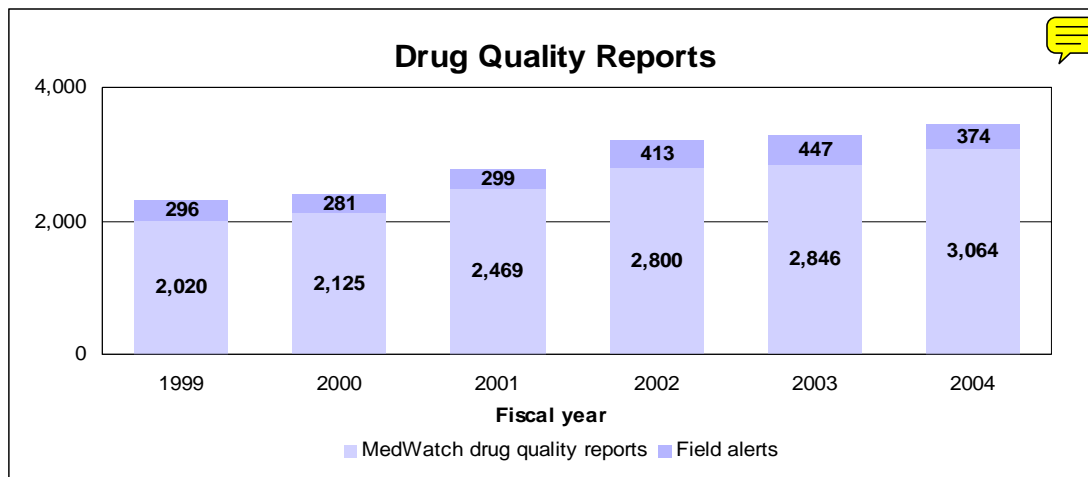
- *Implement law.* With FDA's field force, we implement legal requirements establishing which drugs may be imported by manufacturers, distributors and consumers.

- *Block counterfeits.* We take steps to ensure that imported drugs are not counterfeit or mislabeled 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 developing and implement anti-counterfeiting technology that will trace a drug product through the U.S. drug distribution system.

Drug quality reports

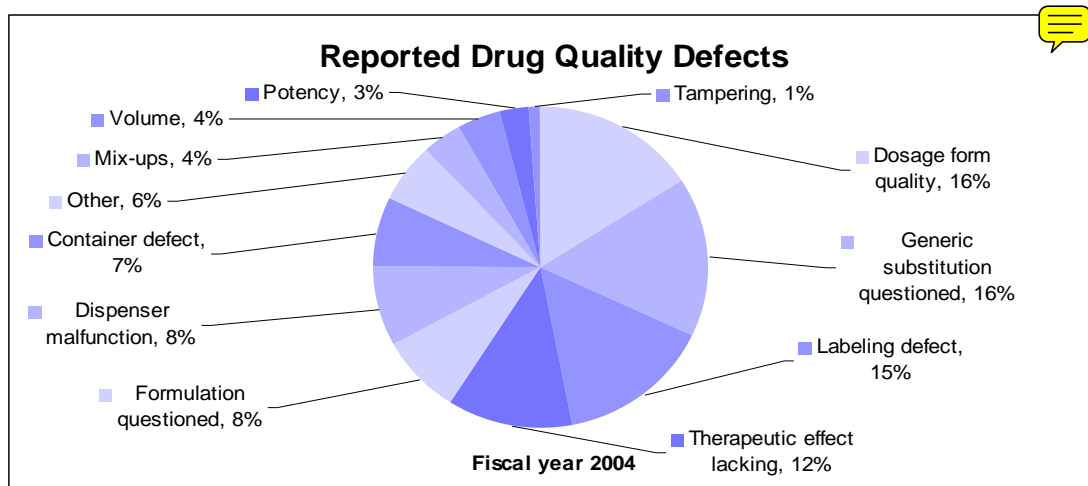
- 374 field alerts
- 3,064 MedWatch reports



Types of reports

■ *Drug Quality Reporting System.* Through MedWatch (page 38), 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

Encouraging innovation, state-of-the-art manufacturing

We have implemented an initiative to encourage manufacturers to be innovative and to apply state-of-the-art quality assurance methodologies to their manufacturing processes. The Process Analytical Technologies Initiative is part of our efforts to ensure the continued availability of the highest quality pharmaceuticals to the American public.

We developed the initiative—a key element in our Pharmaceutical cGMPs for the 21st Century (page 8)—with these essential precepts in mind:

- Testing products *after* manufacturing is not sufficient to guarantee product quality.
- Monitoring and controlling product quality *during* manufacturing provides a much higher degree of quality assurance.

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.

Final guidance establishes scientific tools, regulatory scheme

Our final guidance on process analytical technologies, issued in 2004, includes biotechnology products and establishes a framework that both facilitates innovation and enables risk-based regulatory decisions. The framework has two components:

- A set of scientific principles and tools supporting innovation.
- A strategy for regulatory implementation that will accommodate innovation.

The regulatory implementation strategy includes creation of a process analytical technologies team approach to our review of the chemistry manufacturing and controls section of an application and to inspections of current good manufacturing practices. It includes specialized, joint training and certification of reviewers and inspectors.

To review applications using these new technologies, we bring together the appropriate experts in analytical and physical chemistry, pharmaceutical science, regulatory compliance and chemical engineering to provide a comprehensive assessment of the manufacturing process.

Process analytical technologies Web site

Our effort to facilitate the introduction of new technologies to the manufacturing sector of the pharmaceutical industry has its own Web page at <http://www.fda.gov/cder/OPS/PAT.htm>.

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 53).

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

3

INTERNATIONAL ACTIVITIES

President's Emergency Plan for AIDS Relief

The president's \$15 billion plan for AIDS relief around the world was announced in 2003 and 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.

In May 2004, we announced we would implement a new, expedited review process to ensure that the United States could provide safe, effective drugs to developing countries. That same month, we published a draft guidance encouraging manufacturers to submit applications for fixed-dose combination and co-packaged versions of previously approved antiretroviral therapies. In June 2004, we traveled to South Africa and India to discuss the new guidance with generic drug manufacturers.

Through our commitment to expedited review, we hope to make safe, effective and affordable quality drugs available quickly for patients with HIV or AIDS in the undeveloped world. 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 existing patents or exclusivity prevent the product from being sold in the United States.

We are committed to ensuring that only quality drug products reach the affected nations as quickly as possible. Because we lack information about most clinical laboratories and manufacturing sites associated with the products seeking approval under the emergency plan, our involvement also includes:

- Outreach activities.
- Expedited application review and manufacturer assistance.
- Inspections.
- Post-marketing monitoring.

3-drug regimen eligible 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.

Generic drugs eligible for purchase under president's plan

As of July 22, 2005, we had tentatively approved these generic drugs:

- Efavirenz
- Lamivudine
- Nevirapine
- Stavudine
- Zidovudine

Information-Sharing Agreements

Because of enhanced cooperation among regulators around the world, FDA has entered new international agreements in which we play a critical implementation role. We have a growing list 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.

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 Agency for the Evaluation of Medicinals

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 mutually beneficial direction. An agreement with Canada provides for the exchange of information about pending approvals, post-marketing surveillance and enforcement actions. Exchanges of emerging compliance issues and site-specific information have already begun.

Switzerland

The working arrangement with Switzerland began several years ago and important progress has been made in the past year. 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. Successful joint inspections have helped foster mutual confidence and improve communications.

Pharmaceutical Inspection Cooperation Scheme

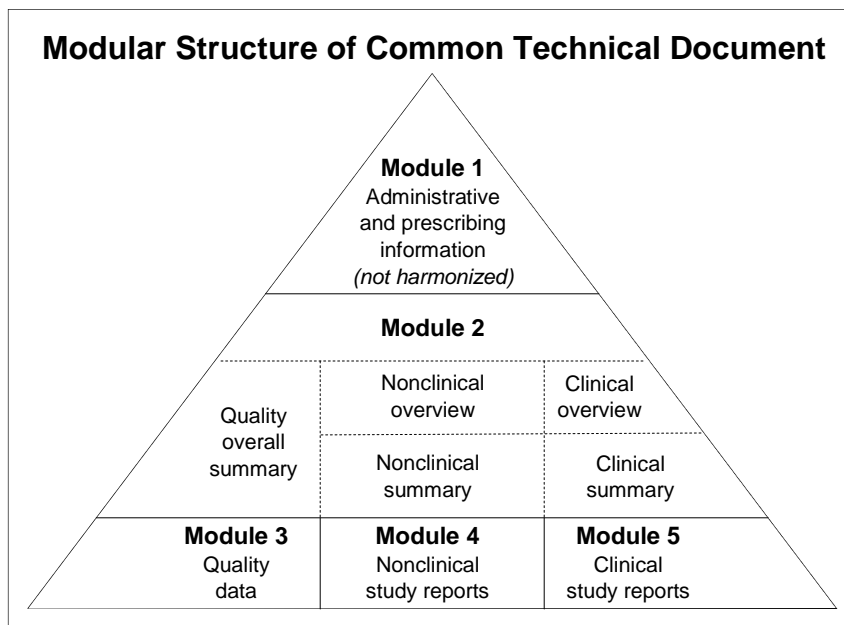
As part of our initiative to improve manufacturing practices (page 8), FDA announced it would seek membership in the Pharmaceutical Inspection Cooperation Scheme.

This is an international organization dedicated to drug regulatory harmonization and collaboration in the area of good manufacturing practices.

Membership would formalize a working relationship that has been in effect for many years and that will offer greater opportunities for expanding international cooperation in drug quality regulation.

Internet resources

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



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 8, 2005, we had:

49 final guidances

- 13 safety
- 3 joint safety/efficacy
- 15 efficacy
- 18 quality

8 draft guidances

- 2 safety
- 1 joint safety/efficacy
- 3 efficacy
- 2 quality

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.

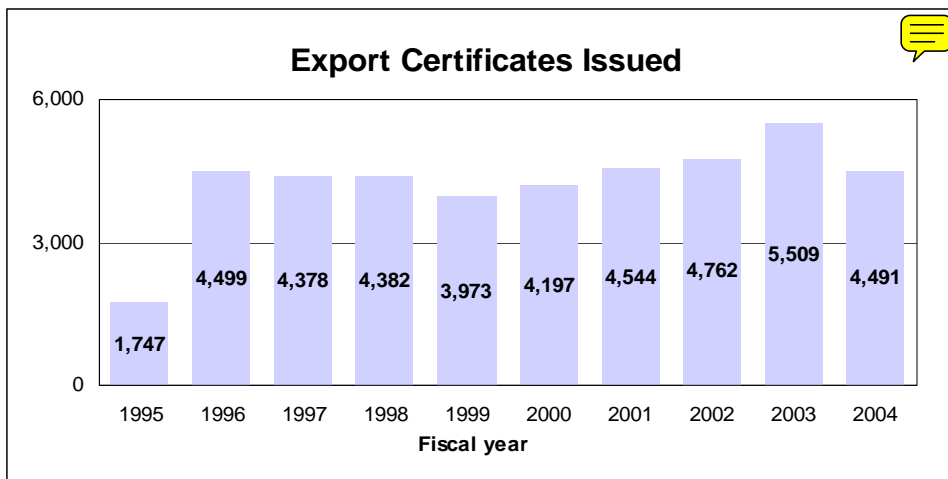
Specifications for electronic submission of the CTD, known as the eCTD, were completed in 2002.

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.



Export Certificates

We promote goodwill and cooperation between the United States and foreign governments through the Export Certificate Program. These certificates enable American manufacturers to export their products to foreign customers and foreign governments. The demand for certificates by foreign governments remains high due to expanding world trade, ongoing international harmonization initiatives and international development agreements.

The certificates attest that the drug products are subject to inspection by the FDA and are manufactured in compliance with current good manufacturing practices. Export certificates verify that drug products being exported:

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

4

COMMUNICATIONS

In 2004, we met 29 times with outside expert advisors in public discussions of difficult scientific and public health issues. We received more than 12 million visits and more than 205 million hits on our Internet information site, which has nearly 100,000 pages and documents, seven databases and 400,000 hyperlinks. Drugs@FDA ([page 20](#)) is the most visited content page 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 workshops to both present information and gather a wide variety of viewpoints on major scientific and regulatory issues, including:

- Radioactive drugs for certain research uses.
- Developing follow-on protein products.
- Targeting safe and effective diabetes prevention and treatment, a joint symposium with the National Institutes of Health.
- Structured product labeling.
- Electronic Common Technical Document.

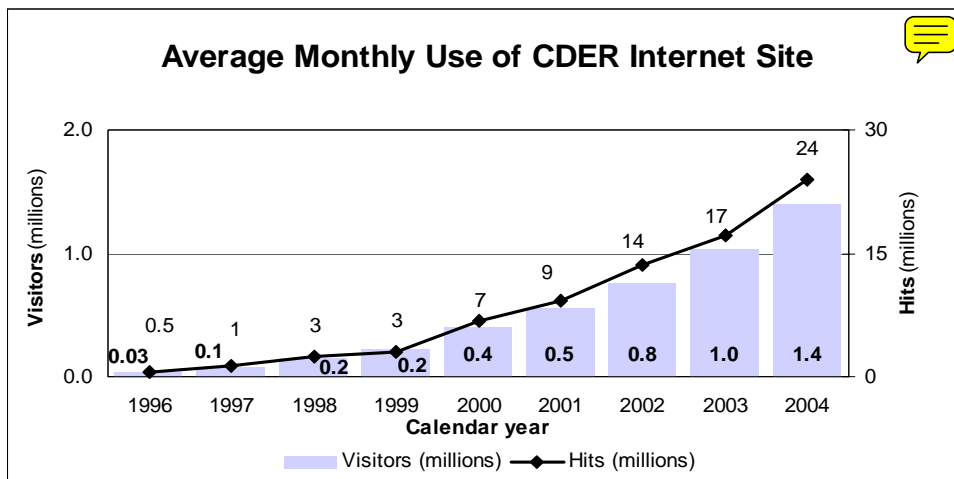
Transparency of policies, decisions

- *Regulations.* We published five final regulations, and we sought public comment on another four proposed regulations.
- *Guidances.* We published 25 guidances for industry that explain our position on best practices in scientific and technical areas. We published another 25 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 22 documents last year.
- *Freedom of Information requests.* We responded to 6,807 requests under the Freedom of Information Act.

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



Public education programs

Our programs educate and empower consumers to make wise choices about their medications. Our messages, which reached millions of Americans last year, include science-based 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/consumerinfo/DPAdefault.htm>.

Consumer, industry outreach

- *Trade press.* We responded to about 2,500 telephone and e-mail requests from the specialized press covering the pharmaceutical industry.
- *Exhibits.* We exhibited at 30 conferences, reaching an estimated audience of more than 100,000 consumers, educators and health care professionals.
- *Videoconferencing.* We held about 150 domestic and foreign videoconferences for academia, industry and associations.
- *General information requests.* We answered more than 32,000 telephone inquiries, 31,000 e-mails and 1,700 letters from consumers, health professionals and industry. We respond to phone calls and e-mail within 48 hours and letters within 30 days.
- *CDER Live!* We produced one satellite television broadcast and Web transmission for a largely pharmaceutical audience estimated at about 5,000 viewers. The first part of the program featured a discussion of the broad science-based issues that form the basis of the pharmaceutical cGMP initiative; the second part presented a discussion of electronic signatures and records.

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>.

Ombudsman's Activities

Our ombudsman serves as a portal for consumers, regulated industry and small business 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.

Several people reported irregularities and possible fraud in conducting and reporting clinical trials, misleading or false promotional activities and violations in pharmaceutical manufacturing.

Several hundred people contacted the office to express their opinions on advisory committee members, direct-to-consumer prescription drug advertising, pending decisions on specific therapies and unwanted e-mail promotion by on-line pharmacies.

Further, numerous consumers have commented on the association of certain antidepressants with suicide, suicidal ideation and addiction.

Examples of cases and allegations our ombudsman handles include:

- Review and drug development delay.
- Unfair handling of an issue.
- Freedom of Information request backlog.
- Docket posting dispute.
- User-fee dispute.

Dispute resolution

Our ombudsman is the initial contact for dispute resolution under our pilot program, that gives our reviewers a forum to discuss and resolve differing professional opinions (<http://www.fda.gov/cder/mapp/4151.2.pdf>).

Sponsors and investigators can contact the ombudsman for informal dispute resolution on procedural issues regarding our reviews at any stage of a product's development.

Outreach

We conducted outreach to explain the ombudsman's functions including product jurisdiction and dispute resolution at several venues. Our ombudsman is a member of the Coalition of Federal Ombudsmen and the American Association of Ombudsmen.

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 67 of these requests in 2004, a majority of which were combinations of drugs and devices.

Ombudsman's 2004 hot topics

- Enforcement against importing prescription medicines from Canada.
- Our non-approval letter for over-the-counter sales of emergency contraception.
- Drug safety monitoring and related testimony before Congress.

Of the approximately 1,950 people who contacted us, more than half were by e-mail. Approximately 250 of these were forwarded to our "druginfo" account ([page 58](#)). We received approximately 800 specific issue contacts by telephone.

E-mail contact

ombudsman@cder.fda.gov

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@cder.fda.gov.

Regular mail

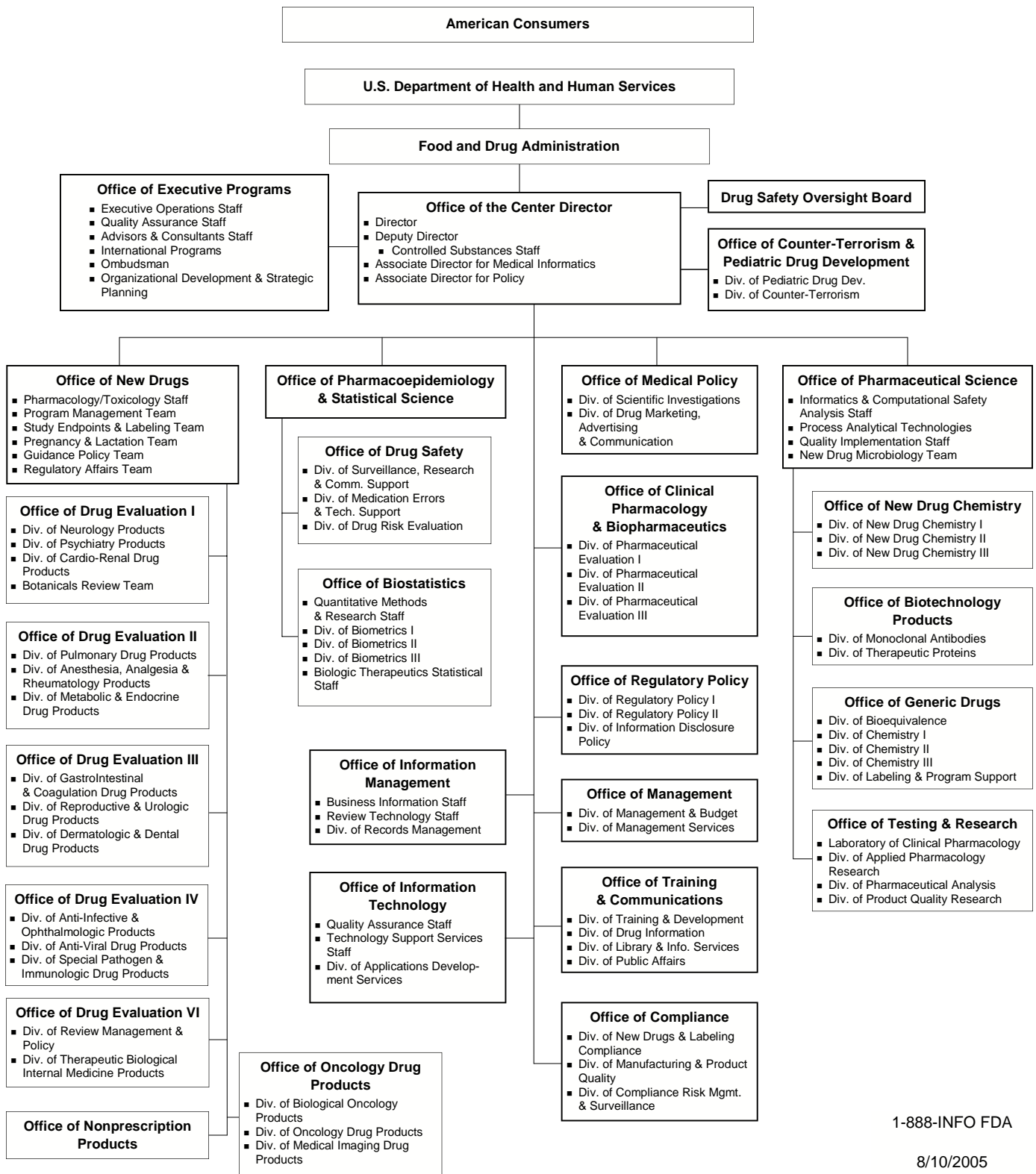
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Information
HFD-240, Room 12B-05
5600 Fishers Lane
Rockville, MD 20857

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*. Medical safety alerts
- *Drug shortages*. New, medically important 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
