*Center for Drug Evaluation and Research* ***2003***

# Report to the Nation

## *Improving Public Health Through Human Drugs*

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

# MISSION

The Center for Drug Evaluation and Research promotes and protects public health by assuring that safe and effective drugs are available to Americans. The *Food and Drug Administration Modernization Act of 1997* affirmed the center's public health protection role, clarified the FDA's mission and called for the FDA to:

1. Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner.
2. Protect the public health by ensuring that human drugs are safe and effective.
3. Participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.
4. Carry out its mission in consultation with experts in science, medicine and public health and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of human drugs.

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

PDF: http://www.fda.gov/cder/reports/rtn/2003/rtn2003.pdf

HTML: http://www.fda.gov/cder/reports/rtn/2003/rtn2003.htm

Slides: http://www.fda.gov/cder/reports/rtn/2003/rtn2003.ppt

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# *Director's Message*

Last year, we at the Center for Drug Evaluation and Research worked hard to meet the challenge of promoting and protecting the public health. We were pleased to welcome our new colleagues involved in the review of therapeutic biologics. The dedication, creativity and expertise of all our professional staff have enabled us to meet our everyday deadlines and embark on new initiatives under the framework of FDA's strategic plan. The strategic plan is very familiar to us because it builds on what we have been doing. The plan outlines a very ambitious effort to achieve five broad priority goals.

### Efficient, science-based risk management

We have long led the world in applying the principles of risk management—assessing public health risks, analyzing methods for reducing them and taking appropriate action. With the expanding complexity of our medical challenges and the need to reduce the health risks facing the public at the lowest cost to society, efficient risk management is more important than ever.

Our approach to efficient risk management requires the use of the most current biomedical, statistical, managerial and economic science. We aim to achieve quicker access to safe and effective new products and reduce public health risks without unnecessary costs by:

- Identifying scientific research gaps along the critical path to drug approval.
- Employing principles and technologies that can reduce avoidable delays and costs in product approvals.
- Overhauling and updating the way medical products are manufactured.
- Implementing an enforcement strategy that combines clear communications to industry backed up by effective civil and criminal enforcement.

### Patient and consumer safety

Too many Americans suffer from preventable adverse events related to pharmaceutical products resulting in human suffering and avoidable medical costs. Consequently, we are enhancing our post-market monitoring, communication and regulatory activities.

In addition, one of the most promising new ways we can improve the system for reporting safety problems is to have direct and secure access to relevant modern electronic health information. By supplementing the current passive reporting systems and partnering with healthcare providers and other government agencies, we will develop more innovative and effective information on the risks associated with regulated products.

We will help speed the implementation of safer systems for medical care through steps such as:

- Bar coding medications in hospitals.
- Implementing 21st-century methods for communicating with health professionals to reduce adverse events.
- Improving our current system for colleting and acting on adverse events related to the products we regulate.

### Better informed consumers

Informed consumers represent our nation's greatest public health asset, because the choices Americans make every day can have a great impact on their own health and the health of the nation.

We are undertaking major new efforts to ensure consumers have the most up-to-date, truthful information on the benefits and risks of regulated products. In this arena, we meet two complementary objectives:

- Ensure the information that sponsors provide about prescription drug products is accurate and allows for their safe use.
- Communicate directly with the public concerning benefits and risks of the products we regulate.

Our goal is a well-informed public, empowered to make better choices to improve their health.

### Counterterrorism

We are working harder and more creatively than ever to speed the availability of the next generation of safer, more effective countermeasures to protect Americans from biological, chemical, nuclear and radiological agents of terrorism. We have two complementary—but necessarily separate—roles in this effort:

- We will help get products developed.
- We will then review marketing approval data on the same products.

### A strong FDA

Our continued ability to carry out our mission of protecting and advancing America's health rests squarely on our most important resource: a talented and dedicated staff. More than ever, we rely on a solid cadre of experienced physicians, toxicologists, chemists, statisticians, mathematicians, project managers and other highly qualified and dedicated professionals. The expertise of our professional staff is essential for making our regulatory decisions balanced and fair. A committee of our scientists oversees an extensive program of training, seminars, case study rounds and guest lectures that helps keep our scientists up-to-date on the latest developments in their disciplines and current industry practices.

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

**Janet Woodcock, M.D.**
Director, January-September 2003
Center for Drug Evaluation and Research
Acting Deputy Commissioner for Operations
Food and Drug Administration

**Steven Galson, M.D., MPH**
Acting Director
Center for Drug Evaluation and Research

# INTRODUCTION

## Who we are

The Center for Drug Evaluation and Research is America's consumer watchdog for medicine. We are part of one of the nation's oldest consumer protection agencies—the Food and Drug Administration. The FDA is an agency of the federal government's Department of Health and Human Services. We are the largest of FDA's five centers, with about 1,800 employees. Approximately half of us are physicians or other kinds of scientists. Many of us have experience and education in such fields as computer science, legal affairs and regulatory matters.

## What we do

Our best-known job is to evaluate new drugs for safety and effectiveness before they can be sold. Our evaluation, called a review, makes sure that the drugs we approve meet our tough standards for safety, effectiveness and quality. We also make sure that you and your doctor will have the information you need to use medicines wisely. Once drugs are on the market, we monitor them for problems.

*Reviewing drugs before marketing.* A drug company seeking to sell a drug in the United States must first test it. We monitor clinical research to ensure that people who volunteer for studies are protected and that the quality and integrity of scientific data are maintained. The company then sends us the evidence from these tests to prove the drug is safe and effective for its intended use. We assemble a team of physicians, statisticians, chemists, pharmacologists and other scientists to review the company's data and proposed use for the drug. If the drug is effective and we are convinced its health benefits outweigh its risks, we approve it for sale. We don't actually test the drug when we review the company's data. By setting clear standards for the evidence we need to approve a drug, we help medical researchers bring new drugs to American consumers more rapidly. We also review drugs that you can buy over the counter without a prescription and generic versions of over-the-counter and prescription drugs.

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

### What is a drug?

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

**However, drugs include more than just medicines.**

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

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

**Some are available in less-expensive generic versions.**

### Prescription drugs

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

- **The disease or condition may be serious and require a doctor's management.**
- **The medicine itself may cause side effects that a doctor needs to monitor.**
- **The same symptoms may be caused by different diseases that only a doctor can diagnose.**
- **The different causes may require different medicines.**
- **Some medicines can be dangerous when used to treat the wrong disease.**

### Over-the-counter drugs

**You can buy OTC 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.**

of patients who depend on a drug. We try to make sure that an adequate supply of drugs is always available.

*Monitoring drug information and advertising.* Accurate and complete information is vital to the safe use of drugs. Drug companies have historically promoted their products directly to physicians. More and more frequently now, they are advertising directly to consumers. While it is primarily the Federal Trade Commission that regulates advertising of over-the-counter drugs, we regulate unapproved products that may be marketed OTC, including their associated promotional materials, to ensure that they meet applicable approval requirements and are not fraudulent. Advertisements for a drug must contain a truthful summary of information about its effectiveness, side effects and circumstances when its use should be avoided. We are monitoring the industry's voluntary program to provide consumers useful information about prescription drugs when they pick up their prescriptions. We are watching this program closely to see that it meets its goals for quantity and quality of information.

*Protecting drug quality.* In addition to setting standards for safety and effectiveness testing, we also set standards for drug quality and manufacturing processes. We work closely with manufacturers to see where streamlining can cut red tape without compromising drug quality. As the pharmaceutical industry has become increasingly global, we are involved in international negotiations with other nations to harmonize standards for drug quality and the data needed to approve a new drug. This harmonization will go a long way toward reducing the number of redundant tests manufacturers do and help ensure drug quality for consumers at home and abroad. 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**

# 2003 HIGHLIGHTS

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

## Drug review

Children and adults with cancer, heart disease and other serious conditions have benefited from our approvals in 2003. We saw improved results from the previous year on overall approvals and decreases in the time it took us to review and approve most applications.

A highlight was the approval of 21 new molecular entities with active ingredients never before marketed in the United States. This number increased from the 2002 total of 17. Priority approvals for products of special medical importance increased from 2002 as well. There were 14 priority NDAs and nine priority NMEs, compared to 11 and seven in 2002, respectively..

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

We increased choices for self-care by approving three medicines for over-the-counter marketing. This included the first switch of a previously prescription-only treatment for frequent heartburn.

Our reviews of generic drugs have been prompt and predictable. We approved 263 generic equivalents for prescription or over-the-counter drugs. These included first-time generic approvals of treatments for depression, seizures and high blood pressure.

## Drug safety and quality

All medicines have risks. With modern, state-of-the-art tools and techniques, we are able to detect rare and unexpected risks rapidly and take corrective action quickly.

We processed and evaluated more than 370,000 adverse drug events and 3,000 reports of medication errors. We proposed a regulation that called for over-the-counter medicines commonly used in hospitals and all prescription medicines to have a bar code. The rule became final in 2004.

We continued to focus on managing risks of marketed medicines, including having a public workshop to gather consumer and scientific input on our proposals for risk management strategies during drug development and after a drug is marketed.

We held several public meetings to discuss our effort to promote modernization of pharmaceutical manufacturing.

### Quality systems

**We are starting down a long road toward making major improvements to our quality systems to improve the way we do our work. We already have some quality systems and subsystems in place, so we will build on those and add new ones.**

**The basic concepts underlying quality systems are quite simple:**

- **Say what you do.**
- **Do what you say.**
- **Prove it.**
- **Improve it.**

### Communications

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

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

**We developed public education campaigns in areas such as antibiotic resistance and buying drugs from outside the United States. Our education program on generic drug quality, specially funded by Congress, has been enormously successful, with many organizations reproducing our materials at no cost to the government.**

### International activities

**We continued our close work with our colleagues in Japan and the European Union on finding ways to make the drug development process more efficient and uniform.**

**We entered new information-sharing agreements with Canada, Switzerland and the European Union.**

# *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 is a slowdown—instead of an 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.

## 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.

The traditional tools used to assess product safety—animal toxicology and outcomes from human studies—have changed little over many decades and have largely not benefited from recent gains in scientific knowledge.

Better tools are needed to identify products that will prove clinically useful and eliminate impending failures more efficiently and earlier in the development process.

### Critical path

**An idealized "critical path" encompasses the medical product development process. The critical path begins after basic research provides candidate products for development. These products then face successively more rigorous evaluation steps along the path, including:**

**□ Drug discovery**

**□ Preclinical development**

**□ Clinical development**

**□ Scale-up for mass production**

**□ FDA filing/approval and launch preparation**

**A striking feature of this path is the difficulty, at any point, of predicting ultimate success with a novel candidate. Recent biomedical research breakthroughs have not improved our ability to identify successful candidates.**

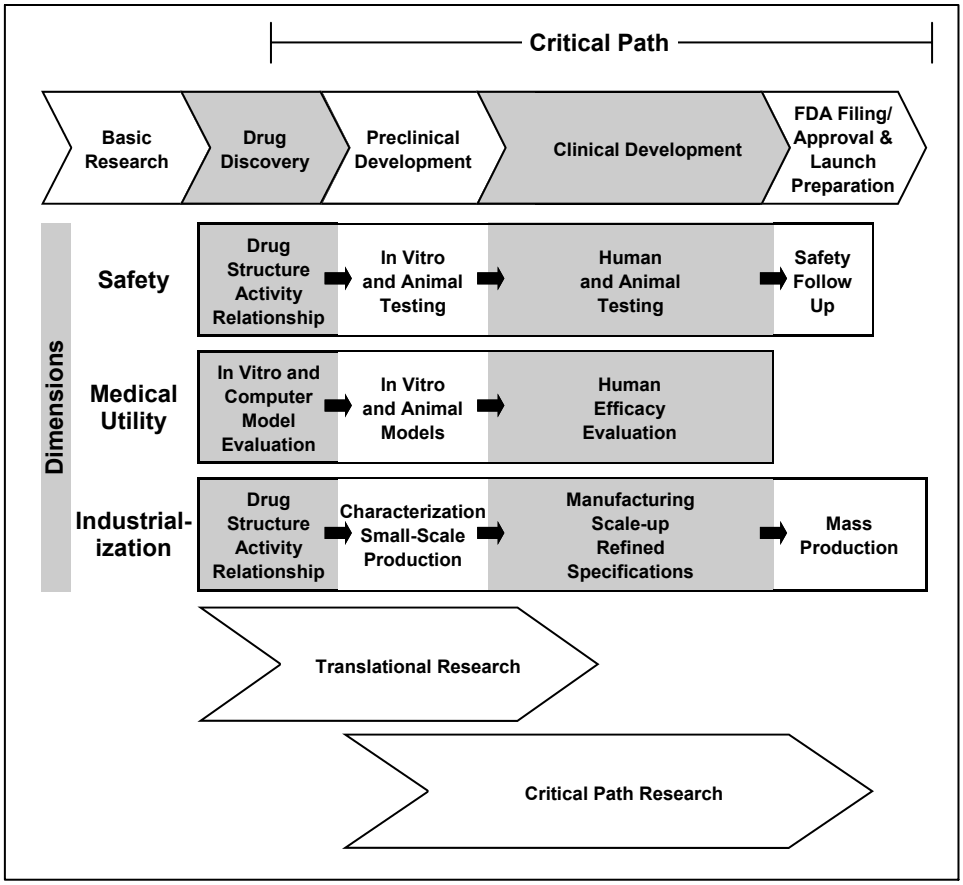
### Critical path research

**These different types of research support medical product development:**

**□ *Basic research* is directed toward a fundamental understanding of biology and disease processes. It provides the foundation for product development.**

**□ *Translational research* is concerned with moving basic discoveries from concept into clinical evaluation and is often product or disease specific.**

**□ *Critical path research* is directed toward improving the medical product development process itself by establishing new evaluation tools.**




The current drug discovery process, based on in-vitro screening techniques and animal models of often poorly understood clinical relevance, is fundamentally unable to identify candidates with a high probability of effectiveness. Reaching a more systemic and dynamic understanding of human disease will require major additional scientific efforts as well as significant advances in bioinformatics.

The challenges involved in successful industrialization are complex, though highly underrated in the scientific community. Problems in physical design, characterization, manufacturing scale-up and quality control routinely derail or delay development programs and keep needed treatments from patients.

## 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 report is available at http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html.

### Research needed to improve development tools

**While the biomedical research community has widened its efforts to include translational research, in our report, we call for a new focus on critical path research.**

**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 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 take a major role in this effort because of our experience overseeing medical product development, assessment and manufacturing/ marketing; our vast clinical and animal databases; and our close interactions with all the major players in the critical path process.**

# *Pharmaceutical cGMP Initiative*

### cGMP initiative goals

**□ Public health protection is strengthened by implementing risk-based approaches that focus both industry and our attention on critical areas for improving product safety and quality**

**□ The regulatory review program and the inspection program operate in a coordinated and synergistic manner**

**□ Regulation and manufacturing standards are applied consistently using state-of-the-art pharmaceutical science**

**□ Innovation in the pharmaceutical manufacturing sector is encouraged**

**□ Our resources are used most effectively and efficiently to address the most significant health risks.**

**More information is at http://www.fda.gov/cder/gmp/index.htm.**

Our regulatory and quality control systems for pharmaceutical products, known as current good manufacturing practices, have become a gold standard for the world; however, the last comprehensive revisions to these regulations took place nearly a quarter of a century ago.

*Pharmaceutical cGMPs for the 21st Century* is a multi-year Agency effort begun in 2002 to enhance the regulation of pharmaceutical manufacturing and product quality.

We evaluated our internal operations under this initiative last year:

- We are developing a quantitative, risk-based site-selection model for use in choosing sites for inspection. This will encourage implementation of risk-based approaches that focus on critical areas. It will ensure a risk-management approach is applied to allocating FDA inspection resources.
- We revised our Preapproval Inspection Compliance Program to give field inspectors more opportunity to use a risk-based approach, allowing greater flexibility in determining whether a preapproval inspection is warranted. The number of categories of drug products that require mandatory inspection have been reduced.

## Guidances to encourage manufacturing improvements

We issued one final and four draft guidances to encourage rapid adoption by industry of modern manufacturing practices. These were:

- A final guidance on the use of electronic records and signatures. which explains the goals of this initiative and removes barriers to scientific and technological advances and encourages the use of risk-based approaches. The guidance clarifies the scope and application of Part 11 of the Code of Federal Regulations and provides for our enforcement discretion in certain areas while we undertake rulemaking to revise Part 11.
- A draft guidance on the aseptic processes used in the manufacture of sterile drugs, emphasizing current science and risk-based approaches. This provides recommendations on how to build quality into products using science-based facilities, equipment and systems design. Sterile drug products are generally of high therapeutic significance, and our proactive efforts to enhance cGMP understanding in this area are intended to promote compliance and ensure a steady supply of these medically necessary products to U.S. consumers.
- A draft guidance on a process for resolving disputes arising over scientific and technical issues related to pharmaceutical current good manufacturing practices.

### cGMP collaborations

**□ A collaboration with two universities to identify the factors that predict manufacturing performance to further refine our pharmaceutical manufacturing risk-based assessment.**

**□ A collaboration with the National Science Foundation's Center for Pharmaceutical Processing Research allowing us to expand our scientific foundation in the area of innovative pharmaceutical manufacturing technology.**

**□ A cooperative research and development agreement with a major pharmaceutical manufacturer to research chemical imaging applications in pharmaceutical manufacturing and quality assurance.**

**□ A memorandum of understanding between us and FDA's field force to set up the Pharmaceutical Inspectorate who will devote most of their time to conducting human drug manufacturing quality inspections.**

- A draft guidance on preparation and use of a comparability protocol for assessing chemistry, manufacturing and control changes to protein drug products and biological products.
- A draft guidance for process analytical technology, a framework for allowing regulatory processes to adopt more readily state-of-the-art technological advances in drug development, production and quality assurance (page 44).

### Counterterrorism Internet resources

**We provides links to the most current information on:**

**□ Drugs to prevent or treat disease caused by terrorism agents including drugs for use against anthrax, plague, radiation emergencies and chemical agents.**

**□ Drug development of counterterrorism products.**

**□ Vaccines.**

**□ Pediatric counterterrorism measures.**

**□ Prescribing and buying countermeasures.**

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

# *Counterterrorism*

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

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

We continue to facilitate development of new drugs and new uses for already approved drugs that could be used as medical countermeasures. We work with other agencies to implement a shelf-life extension program for stockpiled drugs for military use. We gather information on drugs that might be used in response to an attack, including data on manufacturers, bulk suppliers, inventories and lead times for production. We participate in preparedness and response activities to test and establish appropriate communications procedures for emergency situations. We are collaborating with the Centers for Disease Control and Prevention on plans for obtaining post-event outcome data on the use of medical countermeasures.

### Collaborative research on pneumonic plague

**We are collaborating with the National Institute of Allergy and Infectious Diseases and the U.S. Army Medical Research Institute of Infectious Diseases to investigate the use of the antibiotic gentamicin and other antimicrobials for the treatment of pneumonic plague.**

**Natural history, pharmacokinetic and toxicology studies were performed to support planned efficacy studies using a non-human primate model of pneumonic plague.**

### Shelf-life extension for drug stockpiles

**Our laboratories perform shelf-life extension testing for drug products stockpiled by the U.S. military and the Strategic National Stockpile.**

**We published the *Guidance for Federal Agencies and State and Local Governments: Potassium Iodide Tablets Shelf Life Extension* as a draft, and it became final in March 2004.**

## Counterterrorism notable 2003 achievements

- Approved *pyridostigmine bromide tablets* (page 16) as a pretreatment to increase survival after exposure to Soman "nerve gas" poisoning. The product is approved for combat use by U.S. armed forces. This is the first drug approved under the animal efficacy rule.
- Approved lower doses of the *atropine autoinjector (AtroPen)* (page 19) for use in children and adolescents exposed to certain nerve agents and insecticides. The atropine autoinjector was approved for adult use in 1973.
- Approved *insoluble Prussian blue (Radiogardase)* capsules (page 16) to treat people exposed to radiation contamination from harmful levels of cesium-137 or thallium poisoning. The application for this drug was sent in response to the publication of our findings that Prussian blue would be safe and effective for this indication when produced under conditions specified in approved marketing applications. More information is at http://www.fda.gov/cder/drug/infopage/prussian_blue/.
- Published our findings on *intravenous chelators* for treating exposure to radioisotopes. We determined that pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA) are safe and effective, when produced under conditions specified in approved marketing applications, for treatment of contamination with radioactive isotopes of the elements plutonium, americium and curium. We are encouraging manufacturers to use these findings to submit new drug applications.
- Published information on the World Wide Web on how to dissolve and mix *doxycycline tablets* with food or drinks. Following an exposure to inhalational anthrax, parents may receive stockpiled tablets for their children if suspensions are not available. We published these instructions for making palatable doses of the antibiotic to give small children who may not be able to swallow tablets.
- Participated in emergency response activities, including the international Global Mercury smallpox exercise and the U.S. government's Scarlet Cloud anthrax exercise. We also began testing components of our continuity of operations plan to assure that we can maintain vital operations and service.
- Began discussions with CDC on mechanisms to collect and assess outcome information following the use of medical countermeasures in a terrorist event.
- Drafted a guidance for industry that we published in March 2004, *Vaccinia Virus: Developing Drugs to Mitigate Complications from Smallpox Vaccination.*

### Animal efficacy rule

**Certain human drugs and biologics intended to reduce or prevent serious or life-threatening conditions may be approved based on animal evidence of effectiveness when human efficacy studies are not ethical or feasible. The regulation, also known as Subpart I for drugs (21 CFR Part 314) or Subpart H for biologics (21 CFR Part 601) applies when:**

**□ The pathophysiology of the disease and the mechanisms of action of the drug are reasonably well-understood.**

**□ The efficacy endpoints in the animal trials are clearly related to human benefit.**

**□ The drug effect is demonstrated in more than one well-characterized animal species expected to react with a response predictive for humans; and**

**□ Data allow selection of an effective human dose.**

### Counterterrorism scientific research

**Some medical countermeasures are stockpiled in tablet form that may be difficult to swallow for infants, small children and others. Two examples are doxycycline, for post-exposure prophylaxis for anthrax, and potassium iodide, for use in emergencies involving radioactive iodine.**

**We used the "electronic tongue" instrument to extend our studies of the stability and palatability of these drugs when crushed and mixed with different foods or drinks. We compared the results to those of human taste panels.**

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

# *Scientific Research*

We advance the scientific basis of regulatory practice by developing, evaluating or applying the best, most appropriate and contemporary scientific methods to regulatory testing paradigms. We provide scientific support for reviewer training, regulatory decision making and the development of regulatory policy.

We focus on creating a tighter scientific linkage between non-clinical and clinical studies, enhancing methodology for assuring product quality, building databases for improved drug development and review and providing regulatory support through laboratory testing.

## Linking nonclinical and clinical studies

- We are identifying, evaluating and establishing relvant 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.
- To enhance safety within broad segments of patient populations and enable safe development of new drug classes, we are working on the identification and elucidation of associated serum biomarkers and mechanisms responsible for the development of vascular inflammation in specific organ systems.
- We conduct targeted research on microarrays, a new technology that can identify thousands of genes or proteins rapidly and at the same time. We are evaluating how this technology could improve the interface between drug development and regulatory practice.
- We established scientific research capabilities in the analyses of medicinal plant and herbal products.
- 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.
- 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.
- We are developing a pediatric population pharmacokinetics study design template to facilitate implementation of sparse sample strategies in pediatric drug development.

### 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.**

### 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 on *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications.***

**□ We cosponsored an open workshop pharmacogenomics in drug development and regulatory Decision-making.**

**□ We published a draft guidance for industry, *Pharmacogenomic Data Submissions,* to provide a better understanding on the current use of pharmacogenomics in drug development and 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 in 2003 from the Center for Biologics Evaluation and Research. The office consists of about 80 scientists who are responsible for evaluating therapeutic biotechnology product submissions as well as carrying out scientific research related to biologics regulatory issues.

- 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.
- 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

- 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 propriety information.
- 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.

### Pharmaceutical analysis

**We assure that analytical methods being developed by pharmaceutical companies are suitable for quality assurance and regulatory purposes. We assessed analytical methods for six new drugs and one generic drug.**

**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

**Last year our efforts included:**

**□ Assessment of the safety (cyanide release) and the efficacy (cesium binding) of Prussian blue in support of its approval as a medical countermeasure** **(page 16).**

**□ 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

**Drug approvals for 2003**

- **72 new drugs**
- **21 new molecular entities**
- **6 orphan new drugs**
- **2 orphan new uses for existing drugs**
- **131 new or expanded uses for already approved drugs**
- **3 over-the-counter drugs or Rx-to OTC switches**
- **263 generic equivalents for prescription and over-the counter drugs**

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

We approved 21 new medicines that have never been marketed before in this country, known as new molecular entities. We approved 263 generic versions of existing drugs. We authorized three medicines to be sold over the counter without a prescription, and one of them can be used by children.

We met or exceeded all 10 performance goals for the fiscal year 2002 receipt cohort, the latest year for which we have full statistics. These are goals we agreed to under legislation authorizing us to collect user fees for drug reviews. In addition to surpassing all goals for original new drug applications, we exceeded both goals for new molecular entities.

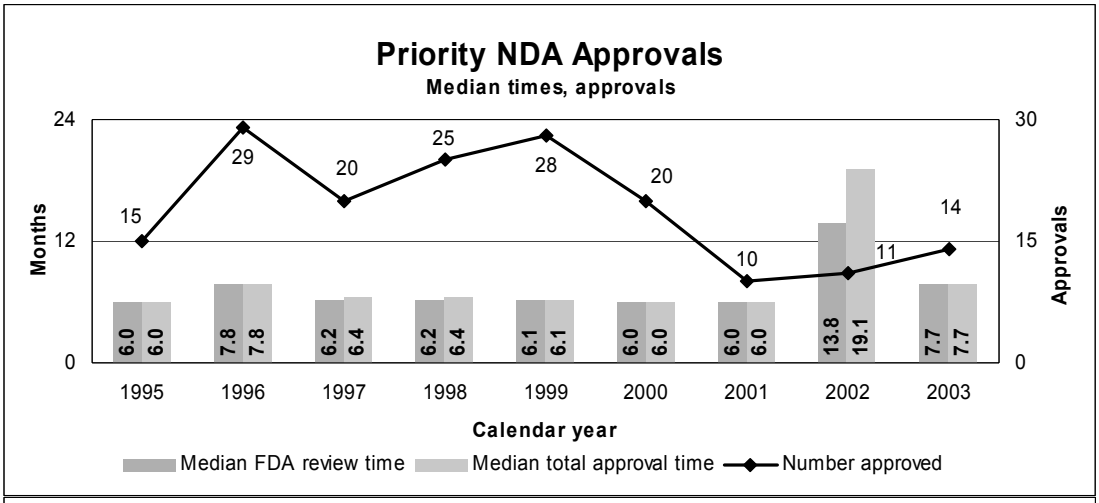
We conducted 728 foreign and domestic inspections that help protect volunteers for clinical trials from research risks and validate the quality and integrity of data submitted to us.

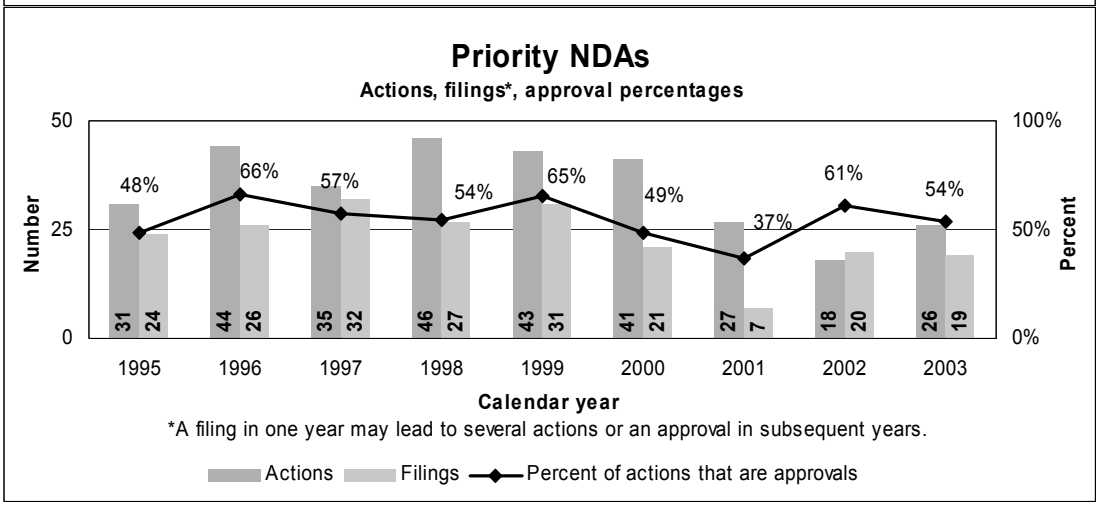
Highlights of new medication options for American consumers include:

- Five cancer treatments.
- Three new drugs for HIV infection, including the first in a class of antiretroviral drugs known as fusion inhibitors.
- Three treatments for infections, including the first in a new class of antibiotics.
- Six orphan new drugs and two orphan new uses to treat patient populations of fewer than 200,000.
- One new drug for treating hepatitis in children and 15 labels with information for treating children.
- Lower doses of estrogen-containing drugs for treating symptoms of menopause.
- Expanded treatment options for children with depression and obsessive compulsive disorder.
- New options for oral contraceptives, including a chewable version and one that reduces menstruations to once every three months.
- The first over-the-counter treatment for frequent heartburn.

**Mission**

**We promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner.**




### Priority new drugs

- **14 approvals (including 9 NMEs)**
- **Median review time: 7.7 months**
- **Median approval time: 7.7 months**
- **26 actions**
- **19 filings**
- **5 orphan approvals (including 3 NMEs)**

### Priority approval, review times down in 2003

**The median total approval and review times for priority NDAs were 7.7 months each, and the times for priority NMEs were 6.7 months each.**

**The much higher times shown in 2002 were caused by the approval of a number of older applications coupled with a decrease in the number of new applications received.**

# *New Drug Review*

## *Definitions*

*Review and approval times.* Review time represents the time that we spend examining the application. Approval time represents our review time plus industry's response time to our requests for additional information.

*Median times.* Our charts show review and approval times as "medians." The value for the median time is the number that falls in the middle of the group after the numbers are ranked in order. It provides a truer picture of our performance than average time, which can be unduly influenced by a few very long or short times. Our guide to understanding median approval time statistics is available at http://www.fda.gov/cder/present/MedianAPtime/index.htm.

*New molecular entities.* NMEs contain an active substance that has never before been approved for marketing in any form in the United States. Because of high interest in truly new medicines, we report NMEs separately; however, the charts for NDAs include the NMEs as well.

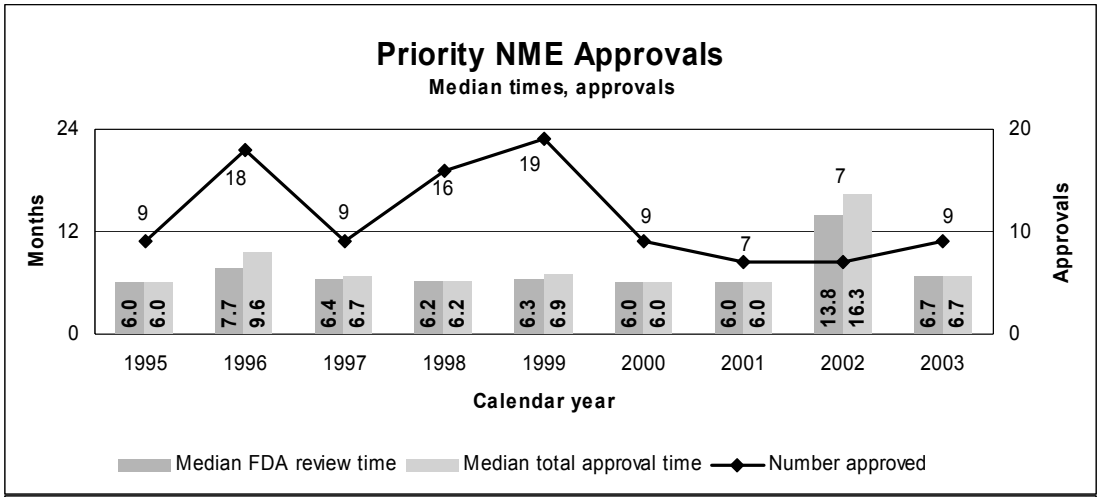
### Priority new drugs

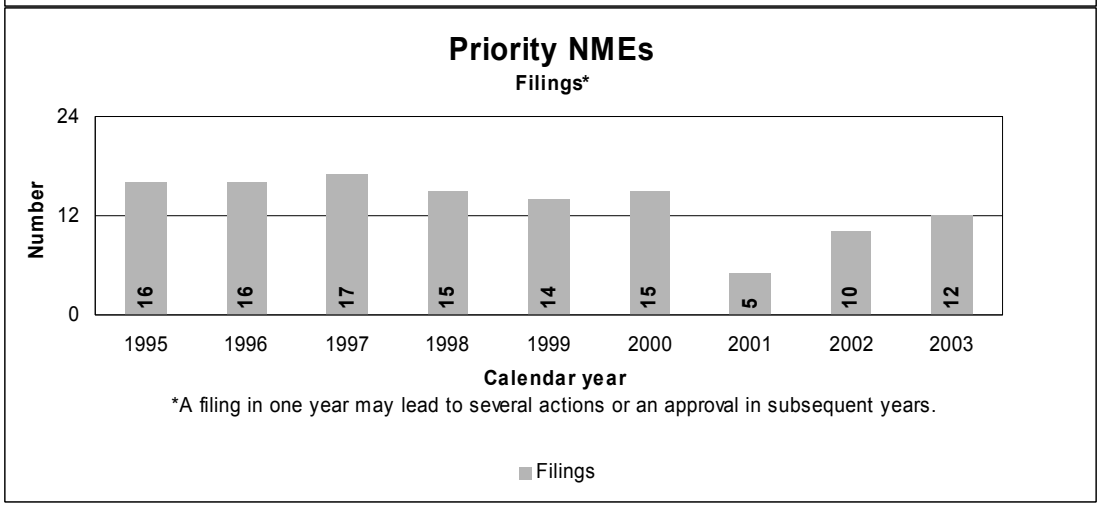
(N=NME)

- **Abarelix (Plenaxis) (N)**
- **Aprepitant (Emend) (N)**
- **Atazanavir sulfate (Reyataz) (N)**
- **Bortezomib (Velcade) (N)**
- **Daptomycin (Cubicin) (N)**
- **Enfuvirtide (Fuzeon) (N)**
- **Gefitinib (Iressa) (N)**
- **Imatinib mesylate (Gleevec)**

### Priority new molecular entities

- **9 approvals**
- **Median review time: 6.7 months**
- **Median approval time: 6.7 months**
- **12 filings**
- **3 orphan approvals**




### Priority new drugs (cont.) (N=NME)

- **Olanzapine and fluoxetine hydrochloride (Symbyax)**
- **Pegvisomant (Somavert) (N)**
- **Prussian blue (Radiogardase) (N)**
- **Pyridostigmine bromide (Pyridostigmine Bromide)**
- **Ribavirin (Rebetol)**
- **Sterile talc powder (Sterile Talc Powder)**

*Priority new drugs.* These drugs represent significant improvements compared with marketed products. We have a goal of reviewing 90 percent of these applications within six months.

*Standard new drugs.* These drugs have therapeutic qualities similar to those of already marketed products. We have a goal of reviewing 90 percent of these applications within 10 months.

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

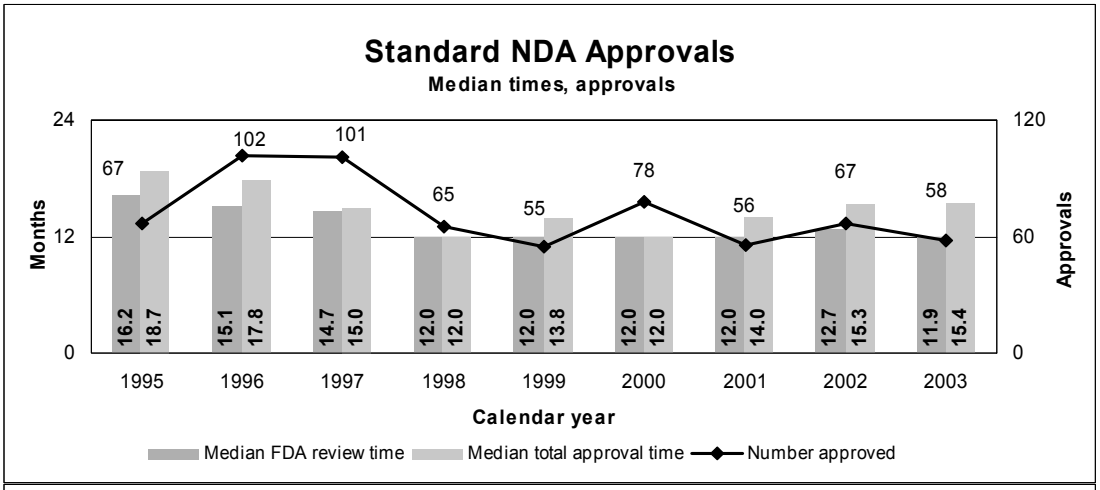
*Orphan drugs.* We administer a program that provides incentives to develop drugs for use in patient populations of 200,000 or fewer. Sponsors of orphan drugs receive inducements that include seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance from FDA and grants of up to $200,000 per year.

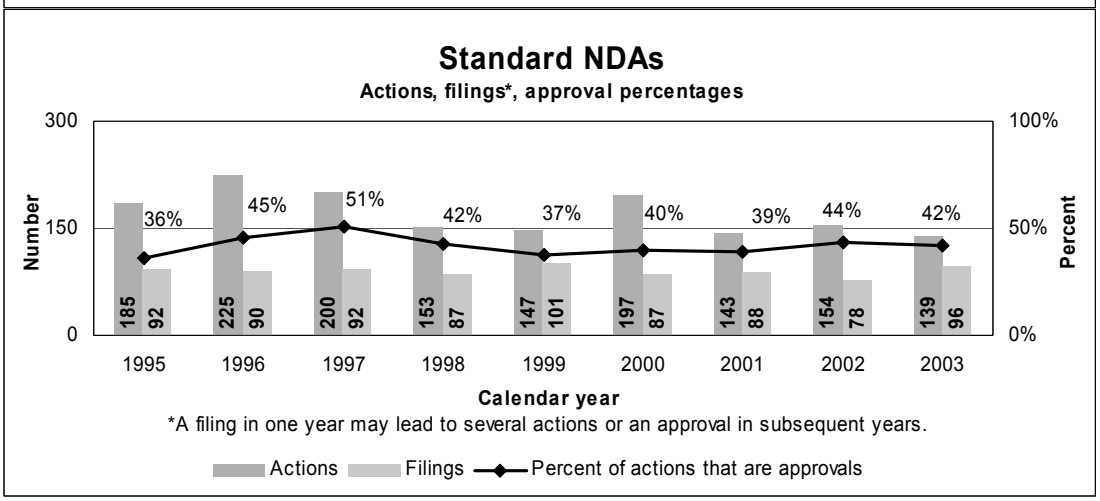
### Accelerated approval

**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.**




### Standard new drugs

- **58 approvals (including 12 NMEs)**
- **Median review time: 11.9 months**
- **Median approval time: 15.4 months**
- **139 actions**
- **96 filings**
- **1 orphan approval**

### New molecular entities

- **Abarelix (Plenaxis)**
- **Alfuzosin hydrochloride (Uroxatral)**
- **Aprepitant (Emend)**
- **Atazanavir sulfate (Reyataz)**
- **Bortezomib (Velcade)**
- **Daptomycin (Cubicin)**
- **Emtricitabine (Emtriva)**
- **Enfuvirtide (Fuzeon)**
- **Epinastine hydrochloride (ELESTAT)**
- **Gefitinib (Iressa)**

### Internet resources for drug review statistics

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

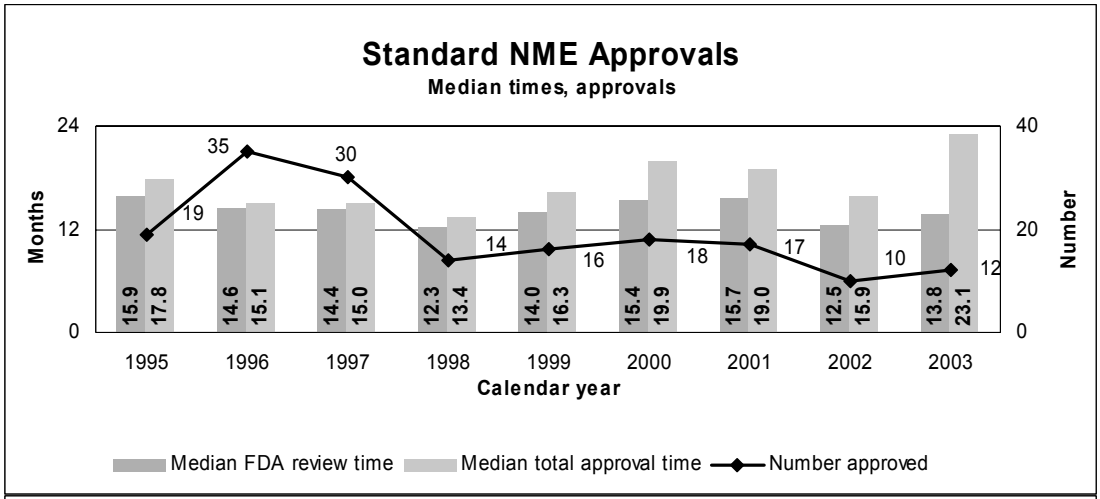
## Notable 2003 new drug approvals

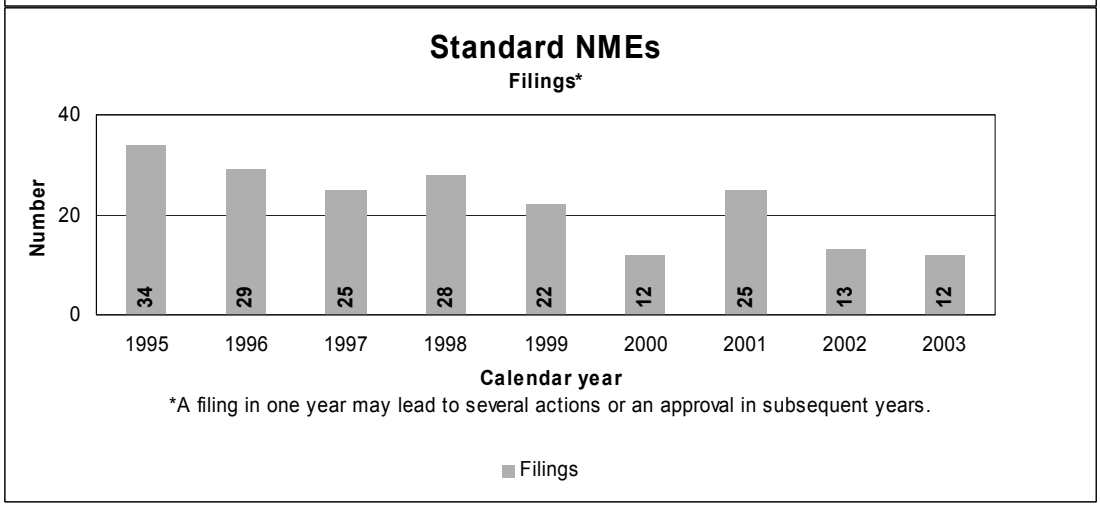
Last year's approvals benefited people with cancer, HIV infection, heart disease and other disorders.

### *People with cancer*

*Abarelix (Plenaxis)* is a palliative treatment for advanced prostate cancer for patients who cannot take other hormone therapies and who have refused surgical castration. Abarelix lowers the male hormone testosterone, which is involved in most prostate cancer growth. A study of 81 men showed they could avoid surgical castration by undergoing at least 12 weeks of treatment with the drug. Some also experienced other benefits, including decreased pain and relief from urinary problems. The drug is marketed under a risk management program because of an increased risk of serious and potentially life-threatening allergic reactions. (NME, P)

*Aprepitant (Emend)* is used in combination with other anti-nausea and anti-vomiting drugs for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. (NME, P)




### Standard new molecular entities

- 12 approvals
- Median review time: 13.8 months
- Median approval time: 23.1 months
- 13 filings
- 1 orphan approval

### New molecular entities (cont.)

- Gemifloxacin mesylate (Factive)
- Ibandronate sodium (Boniva)
- Memantine hydrochloride (Namenda)
- Miglustat (Zavesca)
- Palonosetron hydrochloride (Aloxi)
- Pegvisomant (Somavert)
- Prussian blue (Radiogardase)
- Rosuvastatin calcium (Crestor)
- Sertaconazole nitrate (Ertaczo)
- Tadalafil (Cialis)
- Vardenafil hydrochloride (Levitra)

## Notable 2003 new drug approvals (continued)

*Gefitinib (Iressa)* is a single-agent treatment for patients with advanced non-small cell lung cancer, whose cancer has continued to progress despite treatment with platinum-based chemotherapy and docetaxel. Gefitinib, which received accelerated approval, was developed to block growth stimulatory signals in cancer cells. (NME, P)

*Imatinib mesylate (Gleevec)* received regular approval as a treatment for refractory chronic myeloid leukemia, a rare life threatening form of cancer-affecting about 40,000 people in the United States. The drug was originally approved under the accelerated approval program in 2001. (NDA, P)

*Palonosetron hydrochloride (Aloxi)* is an injectable drug for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. (NME, S)

### Orphan new drug approvals

(N=NME)

- Bortezomib (Velcade) (N)
- Miglustat (Zavesca) (N)
- Pegvisomant (Somavert) (N)
- Prussian blue (Radiogardase) (N)
- Ribavirin (Rebetol)
- Sterile talc powder (Sterile Talc Powder)

## Notable 2003 new drug approvals (continued)

*Bortezomib (Velcade),* an orphan drug, is indicated for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. (Orphan, NME, P)

*Sterile talc powder (Sterile Talc Powder),* an orphan drug, is indicated for administering intrapleurally via chest-tube as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients. The pleura is a thin, transparent membrane that covers the lungs and also lines the inside of the chest wall. Normally, only a thin layer of fluid separates the two layers of the pleura. An excessive amount of fluid, called pleural effusion, may accumulate for many reasons, including heart failure, cirrhosis, pneumonia and cancer. (Orphan, NDA, P)

### *People with HIV infection*

*Atazanavir sulfate (Reyataz)* is a protease inhibitor to be used in combination with other anti-retroviral agents for the treatment of adult patients with HIV infection. This drug is the first protease inhibitor that only can be taken once daily. It has a low "pill burden" of two pills each day. Protease inhibitors block the protease enzyme that HIV needs in order to make new viruses. When protease is blocked, HIV makes copies of itself that cannot infect new cells. (NME, P)

*Emtricitabine (Emtriva)* is indicated for the treatment of HIV infection in adults. The drug belongs to the class of anti-HIV agents known as nucleoside reverse transcriptase inhibitors that, when used in combination with other anti-HIV drugs, can block the replication of HIV in a person's blood. (NME, S)

*Enfuvirtide (Fuzeon)* is an injectable drug indicated for the use in combination with other antiretroviral agents for the treatment of HIV infection in treatment-experienced patients who show evidence of HIV replication despite ongoing antiretroviral therapy. The first member of a new class of medications called fusion inhibitors, the drug received accelerated approval. Enfuvirtide interferes with the entry of HIV into cells by inhibiting fusion of viral and cellular membranes. (NME, P)

### *People with heart disease*

*Rosuvastatin calcium (Crestor)* is an adjunct to diet to lower elevated cholesterol levels, a risk factor for heart disease. It belongs to the class of drugs called HMG-CoA reductase inhibitors, also known as statins. (NME, S)

### Counterterrorism treatments

***Insoluble Prussian blue (Radiogardase),* an orphan drug, can be used to treat people exposed to radiation contamination due to harmful levels of cesium-137 or thallium poisoning. The drug works by increasing the rate of elimination of these substances from the body. More information is at http://www.fda.gov/cder/drug/infopage/prussian_blue/. (Orphan, NME, P)**

***Pyridostigmine bromide tablets (Pyridostigmine Bromide)* are used as a pretreatment to increase survival after exposure to Soman "nerve gas" poisoning. The product is approved for combat use by U.S. armed forces. This application, sponsored by the U.S. Army, is the first drug approved under the animal efficacy rule (page 8). That 2002 regulation allows for use of animal data for evidence of a drug's effectiveness when the drug cannot be ethically or feasible tested in humans. (NDA, P)**

### Drugs@FDA

**Drugs@FDA is a Web site where you can find official information about FDA approved brand name and generic drugs. Use Drugs@FDA to search for:**

- **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."**

## Notable 2003 new drug approvals (continued)

### *Infectious diseases*

*Daptomycin (Cubicin)* injection treats complicated skin and skin structure infections. These are serious infections, usually occurring in hospitalized patients and include major abscesses, post-surgical skin wound infections and infected ulcers. Daptomycin is the first approved product in a new class of antibiotics called cyclic lipopeptide antibacterial agents. The drug binds to bacterial membranes and rapidly upsets electrical balance. This leads to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. (NME, P)

*Gemifloxacin mesylate (Factive)* is indicated for the treatment of community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis. Gemifloxacin, a synthetic broad-spectrum antibacterial agent for oral administration, is related to the fluoroquinolone class of antibiotics. (NME, S)

*Sertaconazole nitrate (Ertaczo)* cream is indicated for the topical treatment of athlete's foot (interdigital tinea pedis) in immunocompetent patients 12 years of age and older. Sertaconazole belongs to the imidazole class of antifungals. (NME, S)

### *People with metabolic disorders*

*Miglustat (Zavesca),* an orphan drug, is indicated for the treatment of mild to moderate Type I Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option due to constraints such as allergy, hypersensitivity or poor venous access. Type 1 Gaucher disease is an inborn error of metabolism that results in disease because of a defect in an enzyme needed to break down the chemical glucocerebroside. The enzyme defect leads to the progressive accumulation of glucocerebroside in the spleen, liver and lymph nodes. Miglustat reduces the body's formation of glucocerebroside to a level that allows the residual activity of the deficient enzyme to be more effective. (Orphan, NME, S)

*Pegvisomant (Somavert),* an orphan drug, is for the treatment of acromegaly in patients who have an inadequate response to existing therapies or for whom these therapies are not appropriate. Acromegaly is a potentially life-threatening disease caused by an excess of growth hormone. The drug is the first in a new class called growth hormone receptor antagonists. Acromegaly causes changes in facial features and enlarged hands, feet and jaw as well as headaches, profuse sweating, swelling and joint disorders. If untreated, patients with acromegaly often have a shortened life span because of heart and respiratory diseases, diabetes mellitus and cancer. (Orphan, NME, P)

### BLA approval statistics

**This report will begin incorporating statistics on consolidated therapeutic biologic license approvals (BLAs) in 2004.**

**The Center for Biologics Evaluation and Research is reporting these statistics for 2003.**

**During the period Sept. 1 to Dec. 31, 2003, when we had official approval authority for therapeutic biologics, we approved one BLA:**

□ ***Efalizumab (Raptiva)* is a treatment for adult patients 18 years or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.**

### Therapeutic biologic reviews consolidated

**The review staff and review of some new biologic products were transferred to our center in 2003.**

**This will enhance the efficiency and consistency of reviewing clinically similar products.**

**Medicines transferred include monoclonal antibodies, cytokines, growth factors, enzymes and other therapeutic immunotherapies.**

## Notable 2003 new drug approvals (continued)

### Women

***Ibandronate sodium (Boniva),* indicated for the treatment and prevention of postmenopausal osteoporosis, is a bisphosphonate that inhibits bone resorption. (NME, S)**

***Estradiol (Estrasorb)* topical emulsion is an estrogen therapy product in a topical form. The drug treats moderate to severe symptoms of hot flashes and night sweats associated with menopause. Current estrogen products available for treatment include oral pills, transdermal patches and a vaginal ring. (NDA, S)**

### *People with allergic conjunctivitis*

*Epinastine hydrochloride (ELESTAT)* ophthalmic solution is an antihistamine indicated for the prevention of itching associated with allergic conjunctivitis. (NME, S)

### *People with bipolar disorder*

*Olanzapine and fluoxetine hydrochloride (Symbyax)* is a combination of two psychotropic agents and is indicated for the treatment of depressive episodes associated with bipolar disorder. Olanzapine belongs to the thienobenzodiazepine class of drugs, and fluoxetine hydrochloride is a selective serotonin reuptake inhibitor. (NDA, P)

### *Older people*

*Memantine hydrochloride (Namenda)* is the first drug approved for the treatment of patients with moderate to severe Alzheimer's disease. Previous treatments have been studied in patients with mild to moderate disease. The drug is an N-methyl-D-asparate (NMDA) antagonist and is thought to work by blocking the action of the chemical glutamate. Although memantine hydrochloride helps treat the symptoms of Alzheimer's disease, there is no evidence that it modifies the underlying pathology of the disease. (NME, S)

### *Children*

*Ribavirin (Rebetol)* oral solution, an orphan drug, is to be used as part of combination therapy with interferon alpha-2b recombinant (Intron A) for the treatment of chronic hepatitis C among previously untreated pediatric patients at least 3 years of age or older. The drug, a nucleoside analog, was first approved in capsule form in 1998. (Orphan, NDA, P)

### *Men*

*Tadalafil (Cialis)* and *vardenafil (Levitra)* are oral medications to treat erectile dysfunction in men. These are the second and third oral products approved for this condition. (Both NME, S)

*Alfuzosin hydrochloride (Uroxatral)* is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. The drug is an alpha-blocker and may help to relax the muscles in the prostate and the bladder, which may lessen the symptoms of BPH and improve urine flow. (NME, S)

### Women (cont.)

**A combination of a *progestin (norethindrone) and an estrogen (ethinyl estradiol) (Ovcon 35)* is an oral, spearmint-flavored contraceptive tablet that can be chewed or swallowed. This dosage form provides one more alternative to the many types of oral contraceptives currently on the market. (NDA, S)**

**A combination of a *progestin (levonorgestrel) and an estrogen (ethinyl estradiol) (Seasonale)* provides a new 91-day oral contraceptive regimen. Tablets containing the active hormones are taken for 12 weeks, followed by one week of inactive tablets. Conventional oral contraceptive use is based on a 28-day regimen (21 days of active tablets followed by seven days of inactive tablets). Under this drug's dosing regimen, the number of expected menstrual periods is reduced from one a month to about one every three months. (NDA, S)**

# *New or Expanded Use Review*

Applications for a new or expanded use, often representing important new treatment options, are formally called "efficacy supplements" to the original new drug application.

We have a goal of reviewing standard supplements in 10 months and priority supplements in six months. The new and expanded use review statistics on this page include figures for both priority and standard applications.

## Notable 2003 new or expanded use approvals

*Carvedilol (Coreg)* is approved for the treatment of patients with left ventricular dysfunction following myocardial infarction.

*Conjugated estrogens and medroxyprogesterone acetate (Prempro)* and *conjugated estrogens (Premarin)* are available in lower strength doses for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

*Eplerenone (Inspra)* tablets improve the survival of congestive heart failure patients who are stablized following an acute heart attack. The drug is the first member of the aldosterone receptor blocker class of drugs to receive approval for this indication.

*Fondaparinux sodium (Arixtra)* injection, used to prevent blood clots, is approved for extended prevention therapy in patients undergoing hip fracture surgery. In a clinical trial that compared 326 patients receiving the drug to 330 patients receiving placebo, blood clots occurred in 1.4 percent of those who received the drug compared to 35 percent of those who received placebo. During the three-week period of treatment, major bleeding rates were 2.4 percent for those administered the drug and 0.6 percent for those administered placebo.

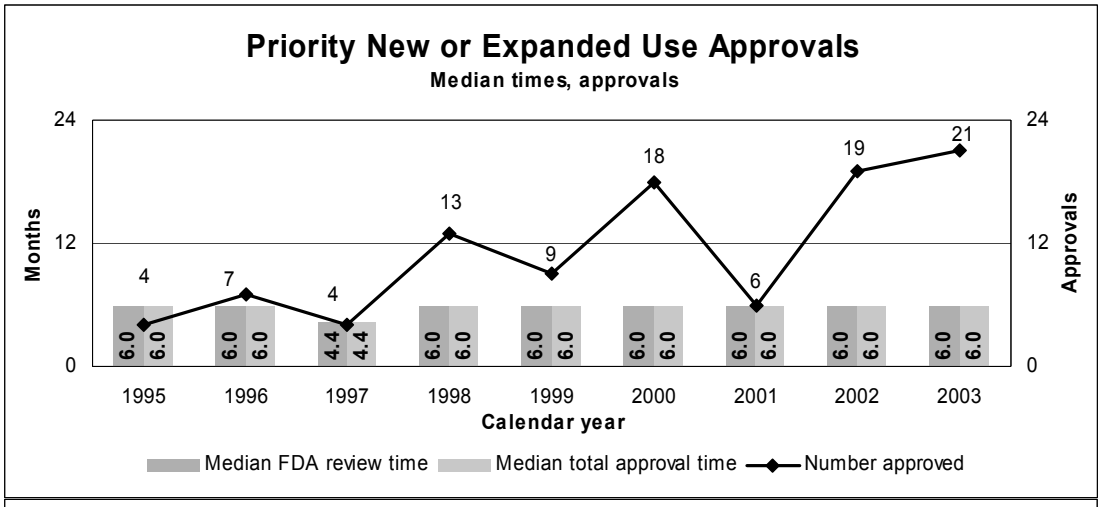
*Leflunomide (Arava)* tablets, a treatment for rheumatoid arthritis, had revised labeling to support the addition of a claim for improved physical function.

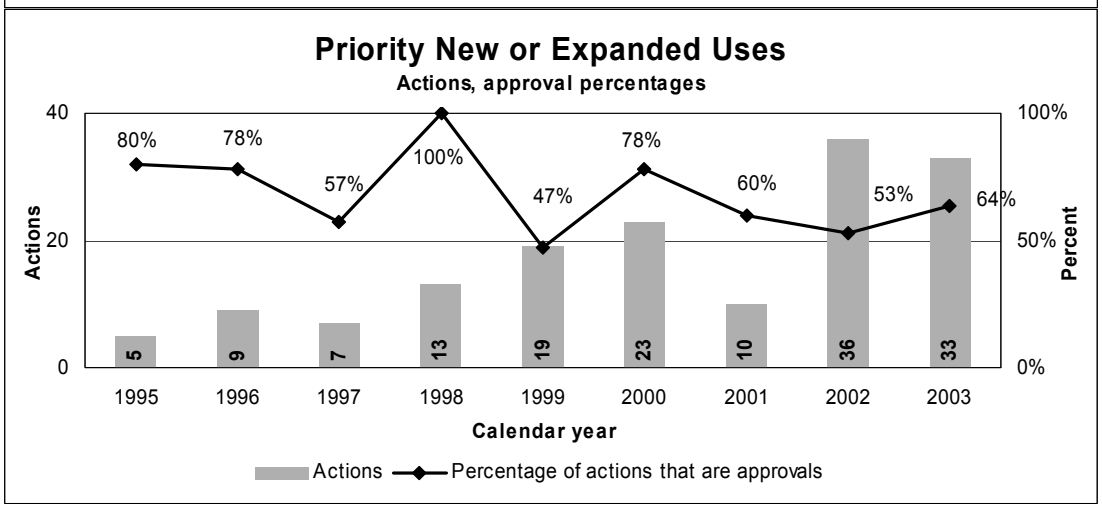
*Losartan potassium (Cozaar)* has a new use to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy. The indications section of the label further notes that there is evidence that this benefit does not apply to black patients.

*Polifeprosan 20 with carmustine implant (Gliadel Wafer)* had its indication expanded to include patients with malignant glioma undergoing primary surgical resection.

### Counterterroism treatment

***Atropine (AtroPen)* autoinjector is now approved for use in children and adolescents exposed to certain nerve agents or insecticides. The atropine autoinjector, approved since 1973 for use in adults, includes information to support two lower-strength autoinjectors (0.5 mg and 1 mg) and a revised package insert for use in both adult and pediatric populations.**




**Priority new or expanded uses (efficacy supplements)**

- **21 approvals**
- **Median review time: 6.0 months**
- **Median approval time: 6.0 months**
- **33 actions**
- **2 orphan new uses**
- **5 priority reviews of pediatric labeling additions**

**Priority new or expanded use reviews**

- **Atovaquone and proguanil hydrochloride (Malarone)**
- **Atropine (AtroPen)**
- **Busulfan (Busulfex)**
- **Carvedilol (Coreg)**
- **Divalproex sodium (Depakote ER)**
- **Eplerenone (Inspra)**
- **Fentanyl (Duragesic)**

## Notable 2003 new or expanded approvals (continued)

S*irolimus (Rapamune),* first approved in 2000 for helping prevent organ rejection in transplant patients, will allow new kidney transplant patients at low to moderate immunologic risk of organ rejection to stop taking cyclosporine two to four months after transplantation. This is the first approval of a cyclosporine-sparing regimen for new kidney transplant patients.

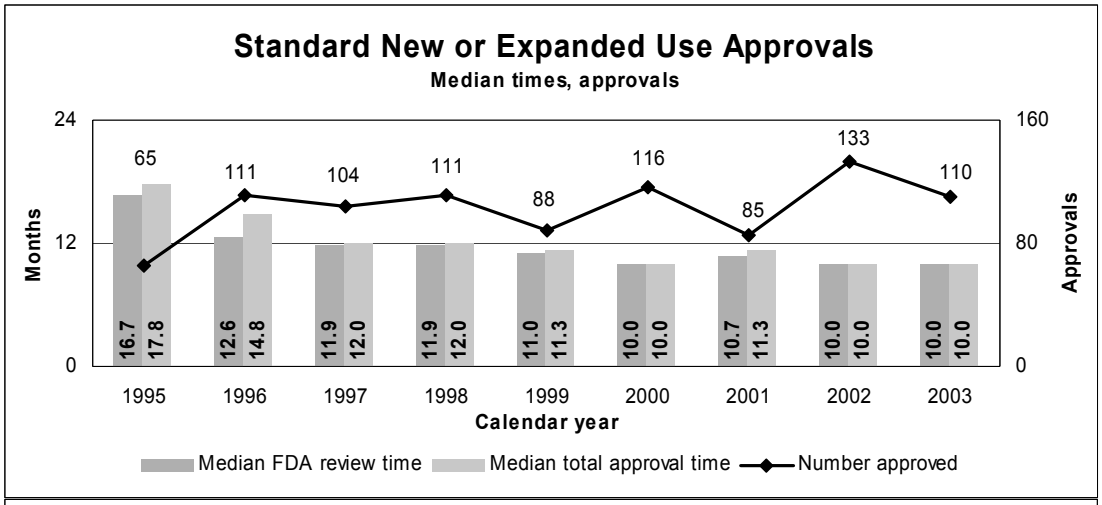
*Valacyclovir hydrochloride (Valtrex)*, a treatment for herpes infections first approved in 1995, reduces the risk of heterosexual transmission of genital herpes to susceptible partners with healthy immune systems when used as suppressive therapy in combination with safer sex practices.

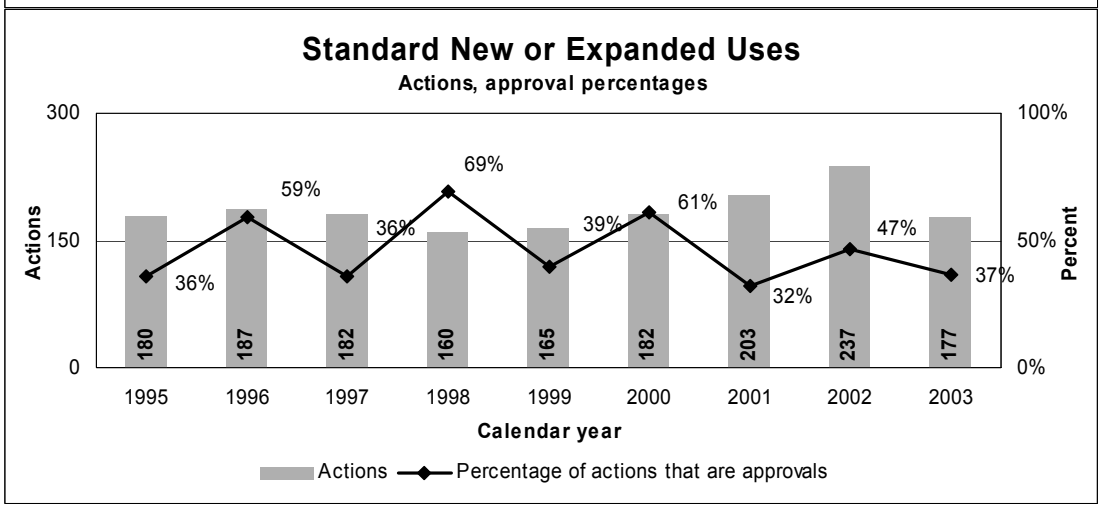
**Priority new or expanded use reviews** (cont.)

- **Fondaparinux sodium (Arixtra)**
- **Fosinopril sodium (Monopril)**
- **Imatinib mesylate (Gleevec) [2 approvals]**
- **Leflunomide (Arava)**
- **Losartan potassium (Cozaar)**
- **Orlistat (Xenical)**
- **Polifeprosan 20 with carmustine implant (Gliadel Wafer)**
- **Porfimer sodium (Photofrin)**

**Standard new or expanded uses (efficacy supplements)**

- **110 approvals**
- **Median review time: 10.0 months**
- **Median approval time: 10.0 months**
- **177 actions**




## Notable 2003 new or expanded approvals (continued)

### *Orphan approvals*

*Porfimer sodium (Photofrin)*, a cancer treatment first approved in 1995, is now approved for the ablation of precancerous lesions in Barrett's esophagus patients who do not undergo surgery to remove the esophagus. The drug is a photosensitizing agent that can kill cells, including cancer cells, when they are exposed to a particular type of light. A small number of people with Barrett's esophagus develop pre-cancerous lesions that progress to an often deadly type of cancer of the esophagus called esophageal adenocarcinoma.

*Somatropin rDNA origin (Zorbtive)*, a human growth hormone (hGH) produced by recombinant DNA technology, treats short bowel syndrome in patients receiving specialized nutritional support. In human clinical studies, the administration of growth hormone has been shown to enhance the transmucosal transport of water, electrolytes and nutrients.

# *Notable pediatric new or expanded uses*

*Atovaquone and proguanil hydrochloride (Malarone Pediatric Tablets)* can be used for the treatment of *Plasmodium falciparum* malaria in pediatric patients weighing 11 pounds to 24.2 pounds.

*Budesonide (Pulmicort)* is approved for use in asthma patients 6 to 12 months; safety information from the study supports the finding that use of the drug in this population may result in systemic effects such as growth suppression.

*Busulfan (Busulfex)* injection, a treatmnent for leukemia, incorporates new pediatric information on dosing, pharmacokinetics and safety.

*Divalproex (Depakote ER)* is now approved for use in pediatric patients for epilepsy.

*Fentanyl (Duragesic)* transdermal system is approved to treat pain in opioid-tolerant pediatric patients 2 years of age and older. The label contains new warning that the drug should only be administered to children if they are opioid-tolerant and 2 years or older.

*Fluticasone propionate (Flonase* and *Cutivate).* A new study with Flonase nasal spray revealed no significant effect on growth as compared to placebo. Cutivate ointment is only indicated for use in adults; in a pediatric study a lower than normal adrenal function was observed.

*Fluoxetine hydrochloride (Prozac)* was approved to treat children and adolescents 7 to 17 years old for depression (major depressive disorder) and obsessive compulsive disorder. The studies revealed a decrease in both height and weight gain as compared to placebo.

*Fosinopril sodium (Monopril)* incorporates pediatric labeling changes in clinical pharmacology, precautions, adverse reactions, overdosage, and dosage and administration sections of the labeling.

*Imatinib mesylate (Gleevec)* is approved for pediatric patients with Ph+ chronic phase chronic phase chronic myeloid leukemia whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. The clinical benefit for pediatric patients was extrapolated from adult data.

*Lisinopril (Prinivil and Zestril)* is labeled for treatment of hypertension in patients 6 to 16 years of age; information on the preparation of a suspension is provided.

*Orlistat (Xenical)* has revised labeling to provide for use in the management of obesity in adolescent patients aged 12 to 16 years.

### 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 mandate in the Best Pharmaceuticals for Children Act, these pediatric supplements received priority reviews last year:**

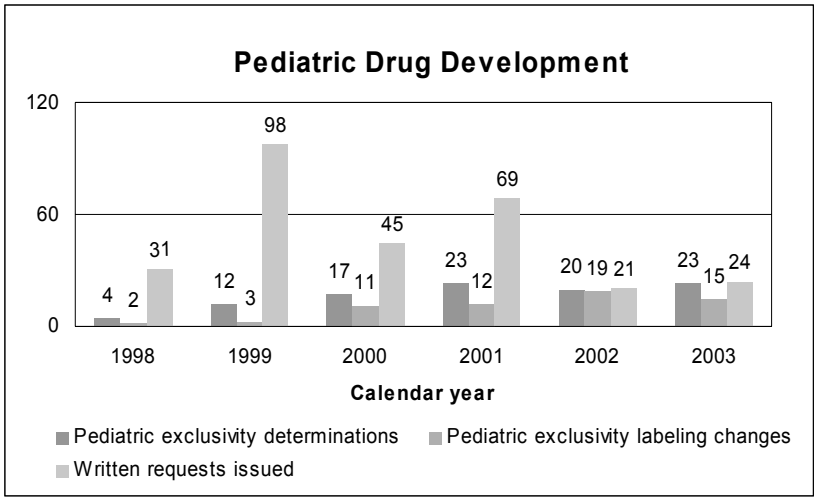
- **Atovaquone/ proguanil**
- **Fentanyl**
- **Fexofenadine hydrochloride (2 approvals)**
- **Fexofenadine hydrochloride and pseudoephedrine hydrochloride**
- **Fludarabine phosphate**
- **Fluticasone**
- **Fosinopril**

### Pediatric Research Equity Act of 2003

**This law gives FDA the authority to require pediatric studies of new drugs and biologics when such studies are needed to ensure the safe and effective use of these products in children.**

### Internet resources

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




### 2003 pediatric drug statistics

- **23 exclusivity determinations made**
- **15 pediatric exclusivity labeling changes granted**
- **24 written requests issued**

# *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. Last year, we approved 15 pediatric labeling changes as a result of the exclusivity provision. Also, we approved one new molecular entity for use in children (page 18).

As of March 31, 2004, we had received 346 proposed pediatric study requests from manufacturers, issued 284 written requests, made 109 exclusivity determinations and added new pediatric information to 71 labels.

Approximately one-fourth of the new pediatric labels have important dosing or safety information. Important differences in clearance and metabolism of products are being discovered. This is important because underdosing leads to ineffective treatment and overdosing poses a greater risk of adverse reactions. Pediatric safety signals that have been identified include effects on growth, school behavior and suppression of the adrenal gland. As a result of this pediatric testing we now have eight drugs with new pediatric formulations and six drugs with recipes in their label that 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.

The BPCA 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 three lists of off-patent drugs for which additional pediatric studies are needed. We have issued and forwarded seven written requests for these off-patent drugs to NIH for study through their contracting process. In addition, we have forwarded four written requests for on-patent drugs, which were declined by sponsors, to the Foundation for the National Institutes of Health for study.

### FDA commissioner's office oversees pediatric issues

**The Best Pharmaceuticals for Children Act of 2002 mandated the creation of the Office of Pediatric Therapeutics, which began operations in October 2002 in the Commissioner's office.**

**This office oversees all pediatric issues within FDA including institutional review board referrals to FDA, safety issues, ethical issues and pediatric trial oversight.**

**The office is also responsible for the new Pediatric Advisory Committee that was authorized as part of the Pediatric Research Equity Act.**

### Conditions with approved pediatric labeling

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

# User Fee Program

Americans deserve timely access to potentially lifesaving new drugs as soon as possible once they are proven safe and effective. The *Prescription Drug User Fee Act of 1992* received its third five-year extension in 2002, known as PDUFA III. This reauthorization will help 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.

### User fee performance

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

**□ We met or exceeded all our performance goals for the fiscal year 2002 receipt cohort.**

**□ We are on track for meeting or exceeding all user-fee performance goals for fiscal year 2003.**

PDUFA III maintains the high review performance goals of PDUFA II and includes increased consultations with drug sponsors and provided for earlier feedback on their submissions. Although our resources from PDUFA III are higher than from PDUFA II, our total resources for new drug review have not increased as much as we expected.

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

We are concerned about the safety of new medicines following approval. In recent years, 50 percent of all new drugs worldwide have been launched in the United States, and American patients have had access to 78 percent of the world's new drugs within the first year of their introduction.

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

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

### Internet resources for user fees

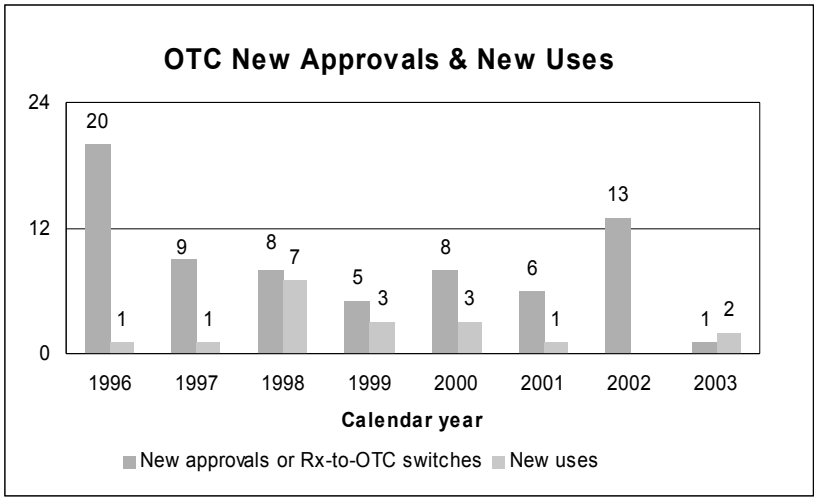
**Our user fee Web site has links to more documents and information including our user fee performance report to Congress.**

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

# End-of-Phase-2A-Meeting Pilot

Making better use of data collected early in drug development could help sponsors avoid some pitfalls that lead to either an extra cycle of review or Phase 4 commitments. We are undertaking a pilot program to discuss this early data with drug sponsors voluntarily at an End-of-Phase-2A meeting.

We think this will improve dose selection and study design for subsequent clinical trials. More information is available in a concept paper we issued in October 2003 (http://www.fda.gov/ohrms/dockets/ac/03/briefing/3998B1_01_Topic%201-Part%20A.pdf).




**Over-the-counter drug statistics**

- **1 new Rx-to-OTC switch**
- **2 new uses**

# *Over-the-Counter Drug Review*

We approved one new Rx-to-OTC switch. We approved two supplemental applications for existing OTC products, one of which can be used by children. The approvals are:

- *Omeprazole magnesium (Prilosec OTC)* is the first OTC treatment for frequent heartburn in consumers 18 years of age and older. This previously prescription-only drug stops acid production at its source in the stomach. It works differently than the other two classes of OTC heartburn treatments: antacids and acid reducers.
- *Famotidine (Pepcid AC)* prevents and temporarily relieves heartburn in consumers 12 years of age and older. This approval was for a higher OTC dose.
- *Loratadine hydrochloride (Claritin Hives Relief)* temporarily relieves itching due to hives for adults and children 6 years and older. This antihistamine was first approved OTC for the temporary relief of allergy symptoms in 2002. This approval was a new use to be marketed under the brand name Claritin Hives Relief.

## 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.

The campaign focuses on OTC drug products that contain acetaminophen and non-steroidal anti-inflammatory agents, which include products such as aspirin, ibuprofen, naproxen sodium and ketoprofen.

Many OTC medicines sold for different uses have the same active ingredients. To minimize the risks of an accidental overdose, we are trying to educate consumers to avoid taking multiple medications that contain the same active ingredient at the same time.

You can learn more about this educational campaign at our Web site: http://www.fda.gov/cder/drug/analgesics/.

**How we regulate OTC drugs**

**We publish monographs that establish acceptable ingredients, doses, formulations and consumer labeling for OTC drugs.**

**Products that conform to a final monograph may be marketed without prior FDA clearance.**

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

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

**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.**

# Generic Drug Review

We approved 263 generic drug products in 2003, 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 for generic drugs was 17 months.

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

### Generic drug Web site

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

## Notable 2003 generic drug approvals

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

- *Paroxetine* (Paxil) used to treat depression.
- *Gabapentin* (Neurontin) used to treat certain kinds of seizures.
- *Mirtazapine* (Remeron) used to treat depression.
- *Quinapril* (Accupril) used to treat hypertension.

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

### *Tentative vs. full approval*

We also issued 101 tentative approvals. While full approvals decreased from 321 to 263, the tentative approvals increased from 63 to 101. The review of an application that is tentatively approved requires the same amount of work as a review that results in a 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.

While tentative approvals represent a full workload for us, they are only displayed in the chart on the next page once they are converted to full approvals. For example, some of the 263 approvals in 2003 represent conversions of tentative approvals granted in 2003 or previous years.

### Electronic submissions

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

**More information electronic submissions is on page 29.**

### 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.**

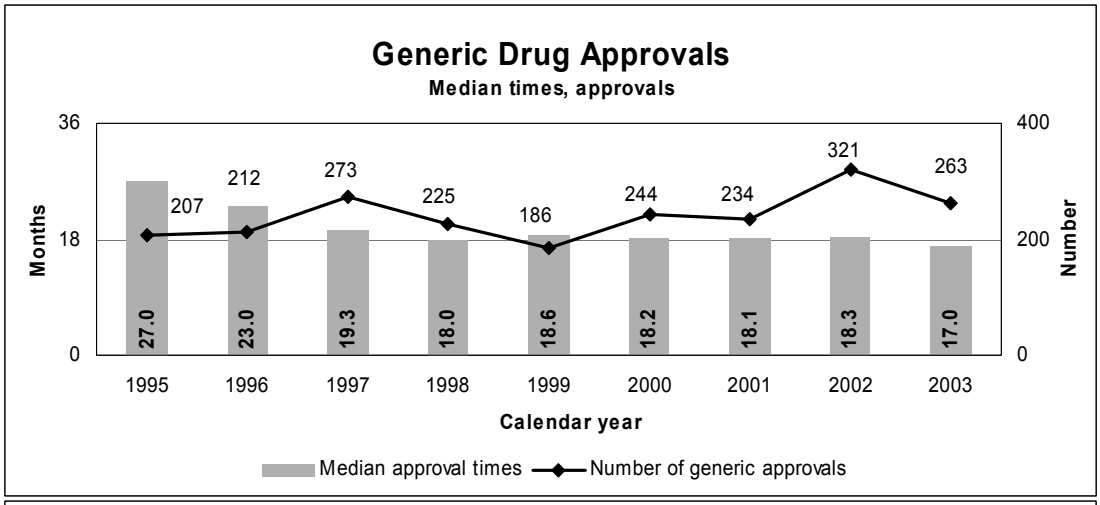
**For many products such as tablets and capsules, the generics must show *bioequivalence* to the brand-name reference listed drug. This means that the generic version must deliver the same amount of active ingredient into a patient's bloodstream and in the same time as the brand-name reference listed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

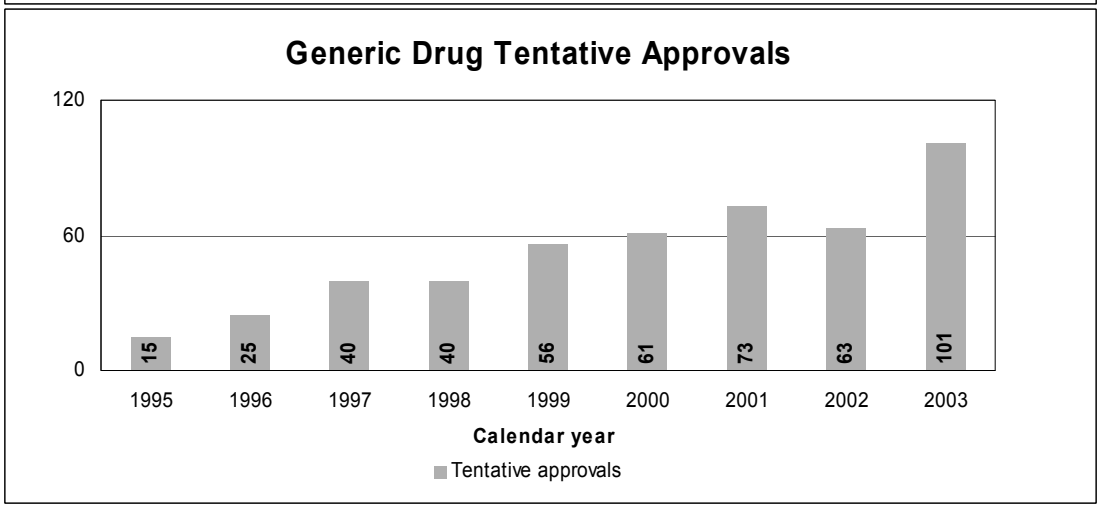
**The rate and extent of absorption is called *bioavailability*. The bioavailability of the generic drug is then compared to that of the brand-name. This comparison is bioequivalence.**

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

### Generic drug statistics

- **263 generic drug approvals**
- **Median approval time: 17.0 months**
- **101 tentative approvals**
- **479 receipts**



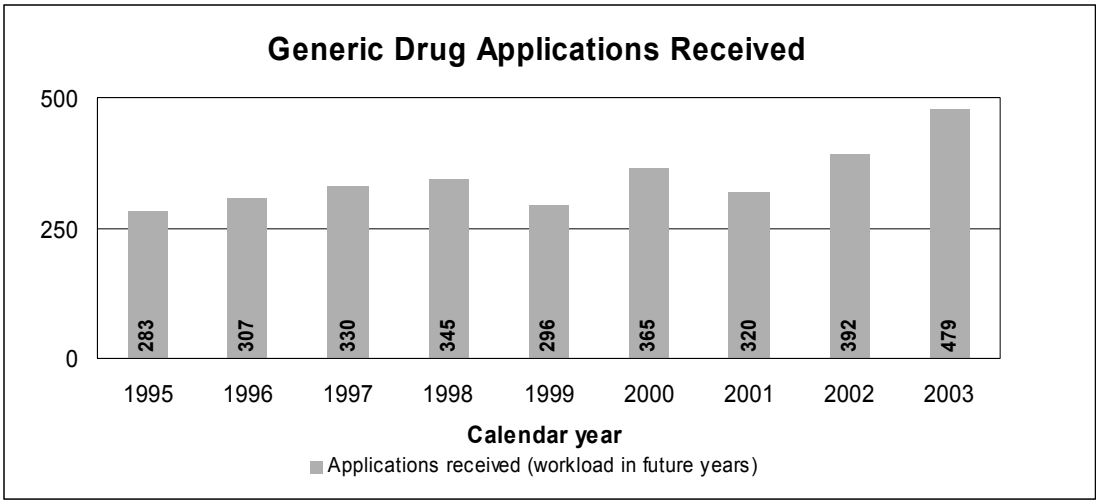




## New law aims to speed approval of generics

Provisions of the *Medicare Prescription Drug, Improvement and Modernization Act of 2003,* which became law on Dec. 3, 2003, are expected to decrease time-consuming legal delays in the approval and marketing of generic products.

The law incorporates much of the substance of our final regulation issued in 2002, particularly the limitation on 30-month stays that may delay availability of generic drugs. The law codifies several points regarding patent notification and forfeiture of 180-day exclusivity on the part of a generic applicant.

We are working on new regulations to implement the law.




### 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.**

### Scientific basis for generic drug review

**We have continued to articulate the scientific underpinnings of our review process and to work to define mechanisms to evaluate equivalence of certain unique products.**

## Generic drug review efficiencies

Receipts of generic drug application increased more than one-fifth in 2003 to 479 from 392 in 2002. This dramatic increase in applications makes it imperative that we have the ability to process generic drug applications more efficiently

We are continue to look for ways to improve our process and also to provide communication and guidance to industry, with the overall goal of getting generic drug products to the consumer as efficiently as possible.

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.
- A collaborative effort with the Generic Pharmaceutical Association to assist the industry. Over the past year, this project has already resulted in six important meetings between us and members of the generic drug industry.
- Two "ANDA Basics" workshops held to assist generic drug makers in understanding the review process and provide training on how to prepare a generic drug application, known formally as an abbreviated new drug application or ANDA.
- Efforts to encourage submission of applications in an electronic format for greater efficiency.

### 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 CVS and Kmart. We have partnered with Express Scripts to get the word out to their consumers about the quality and value of generic products.**

**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.**

# *Electronic Submissions*

The number of new drug applications submitted electronically, the number of participating companies and the number of applications with electronic components continues to grow.

The major change last year was the inclusion of two additional types of submissions that can be provided in electronic format: investigational new drug applications and drug master files.

Electronic submissions following the electronic Common Technical Document (page 45) specifications provide our reviewers significant advantages over paper submissions and electronic submissions following past specifications.

The eCTD allows our reviewers to build a cumulative table of contents for viewing the entire life cycle of the applications. The CTD and eCTD standardized table of contents puts the same information in the same place every time regardless of application type.

This reduces the amount of time reviewers spend trying to find where information is located. It not only improves the efficiency of finding documents but also provides a comprehensive picture of the changes to the application over time. This is particularly useful in the efficient reviewing continuous marketing applications under PDUFA.

Last year, we made further strides in establishing standards for the submission of clinical and animal toxicity study data and annotated electrocardiogram waveform data.

We cooperation with outside organizations working to publish standards for the submission of study data. These groups include the Clinical Data Interchange Standards Consortium and the Standard for Exchange of Non-clinical Data consortium working through Health Level Seven.

We continue to receive individual case safety reports and other post-marketing reports from manufacturers in electronic format, including adverse event reports (page 35).

### Internet resources

**□ The guidance and specifications for the eCTD may be found at http://www.fda.gov/cder/regulatory/guidance**

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

### All submissions can use eCTD

**As of August 2003, we are able to receive all applications and related submissions in electronic format following the electronic Common Technical Document specifications. This includes:**

**□ New drug applications**

**□ Generic drug applications**

**□ Biologics licensing applications**

**□ Investigational new drug applications**

**□ Drug master files**

# *Antimicrobial resistance*

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

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

### Antimicrobial resistance education campaign

**Last year, we joined with the Centers for Disease Control and Prevention to launch an education campaign on antibiotic resistance.**

**The campaign includes print, radio and TV public service announcements and brochures.**

**We are both now working on materials for the Spanish-speaking audience.**

# *Pregnancy labeling*

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

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

We are working with medical review divisions and pharmaceutical companies to update product labels with available data regarding human pregnancies exposed to drugs during pregnancy.

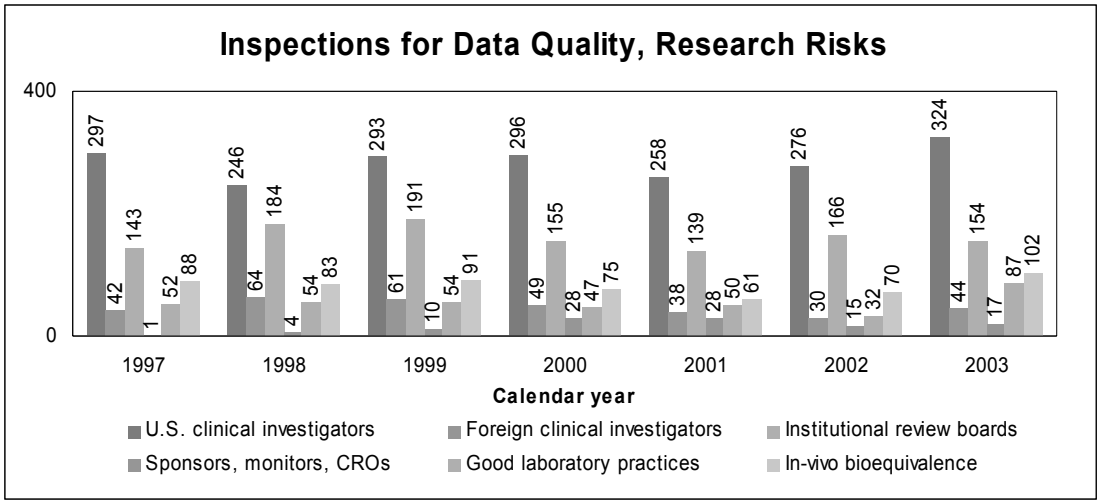
### *Improving knowledge about use of drugs in pregnancy*

In many cases, a disease or condition left untreated may be more harmful to a woman and her fetus or baby than a drug treatment. To improve our knowledge of how drugs work during pregnancy and when women are nursing, we have provided guidance to industry and our reviewers as well as sponsored research.

- In 2002, we published a final guidance that provides sponsors with advice on how to establish pregnancy exposure registries. Registries that prospectively monitor the outcomes of pregnancies in women exposed to a specific drug can provide clinically relevant human data for treating or counseling patients who are pregnant or anticipating pregnancy.
- We are working to finalize a guidance for our reviewers on how to evaluate the outcomes of human pregnancies exposed to drug products during pregnancy. This guidance was published in draft form in 1999.
- We are working on numerous guidances that address study design issues for determining the appropriate dose of a drug for pregnant women and nursing mothers. These pharmacokinetic studies evaluate the action of a drug over time during pregnancy and lactation, including the processes of absorption, distribution, localization in tissues, biotransformation and excretion.
- We have funded several studies to evaluate whether or not the dose a drug should be adjusted for pregnant women. Pharmacodynamic studies evaluate the biochemical and physiological effects of a drug and the mechanism of its actions, including the correlation of actions and effects of a drug with its chemical structure.
- We funded studies to look at specific anti-infective drug products that would be used to treat specific bioterrorism agents in special populations, such as children, women who are pregnant or nursing and the elderly.

**Research on high blood pressure in pregnancy**

**FDA's Office of Women's Health has funded studies to look at specific antihypertensive agents used to treat high blood pressure in pregnancy.**




### Inspections for data quality, research risks in 2003

**We conducted a total of 728 inspections in 2003 compared to 589 in 2002:**

- **324 U.S. clinical investigators**
- **44 foreign clinical investigators**
- **154 institutional review boards**
- **17 sponsors, monitors or contract research organizations**
- **87 good laboratory practices**
- **102 *in-vivo* bioequivalence**

### Top 5 deficiency categories for clinical investigator inspections

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

# *Assessing Data Quality, Research Risks*

When obtaining data about the safety and effectiveness of drugs, sponsors rely on human volunteers to take part in clinical studies and high quality laboratory 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 26) 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 or prisoners.

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

### International inspections of clinical research

**We have conducted 510 inspections of clinical research in 53 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.**

**These efforts include our work with the International Conference on Harmonization (page 46) and the Declaration of Helsinki.**

# *Drug Review Team*

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

- *Biologists, biochemists* and *immunologists* evaluate the manufacturing processes for biological products to ensure the continued purity, potency and safety of these products. They also provide insights to the review team regarding the mechanism of action and potential and observed adverse events associated with specific products.
- *Chemists* focus on how a drug is manufactured. They make sure the manufacturing controls, quality control testing and packaging are adequate to preserve the drug product's identity, strength, potency, purity and stability.
- *Clinical pharmacologists* and *biopharmaceutists* evaluate factors that influence the relationship between the body's response and the drug dose and evaluate the rate and extent to which a drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated. They also assess the clinical significance of changes in the body's response to drugs through the use of exposure-response relationships and check for interactions between drugs.
- *Microbiologists* evaluate the effects of anti-infective drugs on germs. These medicines—antibiotics, antivirals and antifungals—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.

### Scientific training for reviewers

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

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

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

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

**□ Last year, we brought in 40 visiting professors to talk directly to individual review divisions about critical, new drug-related research and techniques.**

### 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 special courses on the most critical needs and interest of our reviewers. Recent topics were:**

**□ 2004: Applying exposure-response concepts to drug development**

**□ 2003: Drug safety assessment tools**

**□ 2002: Pharmaco-genetics**

**□ 2001: Assessment of QT prolongation (cardiac arrhythmia) in drug development**

# 2

# DRUG SAFETY AND QUALITY

**Mission**

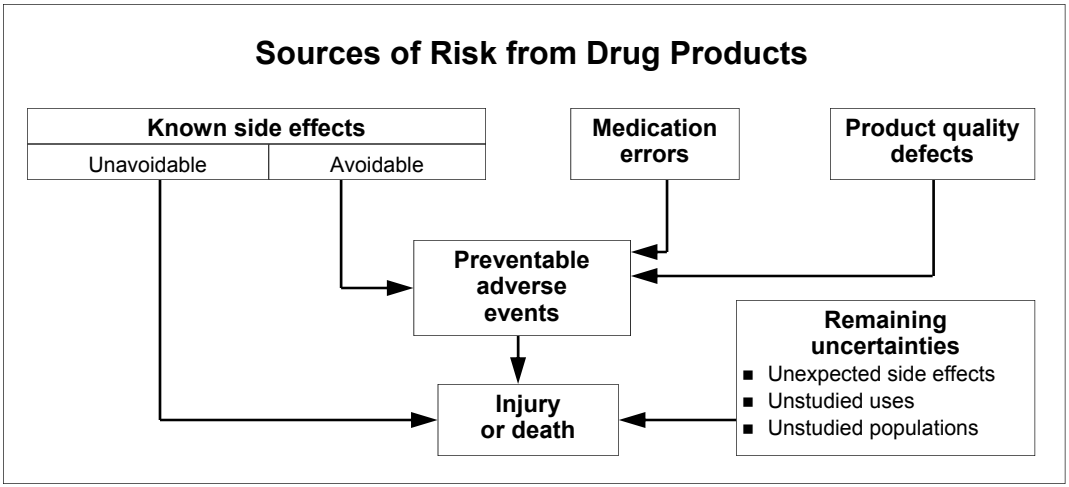
**We protect the public health by ensuring that human drugs are safe and effective.**

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

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

Highlights of drug safety and quality activities in 2003 include:

- Processing and evaluating 370,887 reports of adverse drug events, including 29,955 submitted directly from individuals.
- Reviewing about 3,000 reports of medication errors, half of which are due to error-prone labeling.
- We held a public workshop to gather consumer and scientific input on our proposals for risk management strategies during drug development and after a drug is marketed.
- Signing a cooperative research and development agreement to develop advanced software tools for quantitative analysis of drug safety data.
- Proposing a regulation that calls for over-the-counter medicines commonly used in hospitals and all prescription medicines to have a bar code. The rule became final in 2004.
- Issuing 737 letters to help ensure that the promotion of drug products presents a fair balance of risks and benefits and isn't false or misleading.
- Clarifying our policy on prescription drugs that are sold without a prescription and providing an incentive to have them incorporated into the U.S. drug regulatory system.
- Developing technology for the rapid identification of counterfeit drug products.
- Conducting shelf-life extensions for stockpiled drugs.




# *Types of Risks from Medicines*

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

*Known side effects.* Predictable adverse events are identified in the drug's labeling. These cause the majority of injuries and deaths from using medicines. Some are avoidable, and others are unavoidable.

- *Avoidable.* In many cases drug therapy requires an individualized treatment plan and careful monitoring. Other avoidable side effects are known drug-drug interactions.
- *Unavoidable.* Some known side effects occur with the best medical practice even when the drug is used appropriately. Examples include nausea from antibiotics or bone marrow suppression from chemotherapy.

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

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

# *Drug Safety*

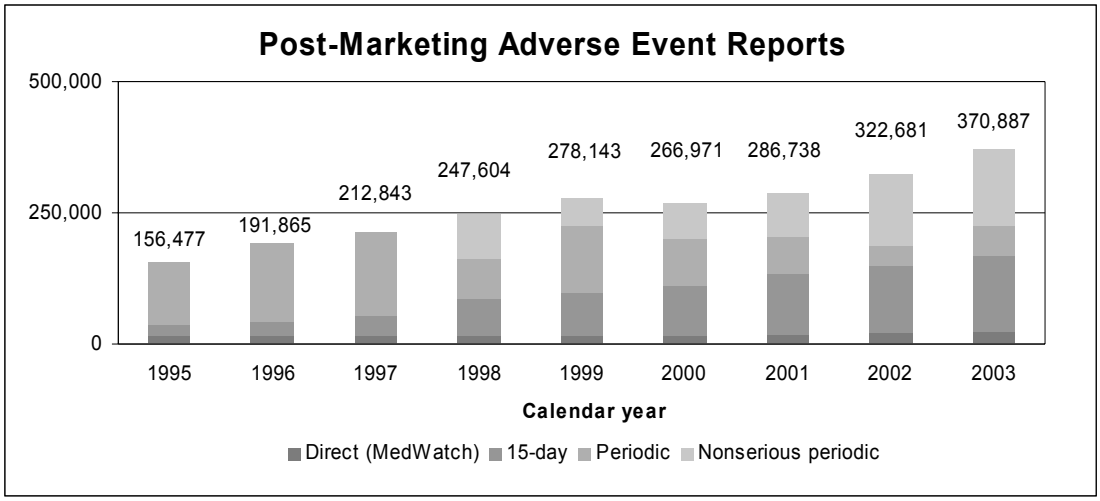
We evaluate the safety of drugs available to American consumers using a variety of tools and disciplines. We maintain a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process. We monitor adverse events such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

### Risk management public workshop, concept papers

**We held a three-day public workshop to discuss risk-management activities in April 2003. Before the workshop, we issued three concept papers for discussion:**

- **Premarketing Risk Assessment**
- **Risk Management Programs**
- **Risk Assessment of Observational Data: Good Pharmaco-vigilance Practices**

**The concept papers, presentations and transcripts of the workshops served as the basis for draft guidances issued in May 2004 at http://www.fda.gov/bbs/topics/news/2004/new01059.html.**




### Adverse event reporting

**In 2003, we received 370,887 reports of suspected drug-related adverse events:**

- **22,955 MedWatch reports directly from individuals**
- **144,310 manufacturer 15-day (expedited) reports**
- **58,998 serious manufacturer periodic reports**
- **144,624 nonserious manufacturer periodic reports**

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

As we discover new knowledge about a drug's safety profile, we make risk assessments and decisions about the most appropriate way to manage any new risk or new perspective on a previously known risk. Risk management methods may include new labeling, drug names, packaging, "Dear Health Care Practitioner" letters, education or special risk communications, restricted distribution programs or product marketing termination.

## Adverse Event Reporting System

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

### AERS on Internet

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

## Electronic submissions

AERS was designed and implemented so that the majority of the reports would be entered electronically. We are in the process of migrating the reporting format from paper to electronic. In a pilot program, we are accepting electronic individual case safety reports from six major drug firms. Electronic submissions into AERS represent 21 percent of the total expedited reports we received in 2003. We estimate the cost of receiving a report is reduced at least 30 percent per report for those submitted electronically.

### Report types

- ***Direct reports from MedWatch.*** **An individual, usually a health care practitioner, notifies us directly of a suspected serious adverse event.**
- ***15-day (expedited) reports.*** **Manufacturers report 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.**

### MedWatch drug safety Internet resources

**The latest medical product safety information can be found at http://www.fda.gov/medwatch/.**

**You can sign up for immediate e-mail notification of MedWatch safety information at http://www.fda.gov/medwatch/elist.htm.**

### Data mining

**We signed a 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.**

**Data mining for simple drug-event signal generation is one part of the 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 medication errors for all FDA-regulated medical products. Reports can be filed by mail, fax, telephone or the Internet. Direct reports, primarily from healthcare professionals, have increased by 51 percent from 1998 to 2003.
- 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 40,000. We also have 170 MedWatch Partner organizations. Last year, These individuals and groups received:

- 33 safety alerts for drugs.
- 25 to 45 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. Medication Guides must be distributed to patients with each prescription dispensed. We require Medication Guides when the information is necessary for patients to use the product safely and effectively or to decide whether to use or to continue to use the product. Last year, we approved Medication Guides for one innovator product and generic lindane and isotretinoin products:

- *Mefloquine hydrochloride (Lariam).*
- *Lindane Shampoo* (generic product).
- *Lindane Lotion* (generic product).
- *Isotretinoin (Claravis)* and *Isotretinoin (Sotret),* Medication Guide previously approved for Accutane and Amnesteem.

### Drugs with special safety restrictions

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

**Consumers should not buy these drugs over the Internet.**

**As of April 30, 2003, these drugs are:**

- **Alosetron**
- **Bosentan**
- **Clozapine**
- **Dofetilide**
- **Fentanyl citrate**
- **Isotretinoin**
- **Mifepristone**
- **Sodium oxybate**
- **Thalidomide**
- **Trovafloxacin mesylate or alatrofloxacin mesylate injection**

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

### DailyMed update

**We are collaborating on a multi-agency effort to improve patient safety through accessible medication information. Called DailyMed and still in development, 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.**

### Drug shortages on the Internet

**We have a Web site that lists current drug shortages, describes efforts to resolve them and explains how to report them.**

- **The site is at http://www.fda.gov/cder/drug/shortages.**
- **We have an e-mail address to provide the public a communication tool for drug shortage information at DrugShortages@cder.fda.gov.**

# *Medication Error Prevention*

### *Avoiding name, label, 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 and packaging that might contribute to problems or confusion in prescribing, dispensing or administering.

We review about 250 reports of medication errors each month. About half are due to error-prone labeling such as look-alike labels, poor package design and confusing names. We provide a root cause analysis of these reports that may result in 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 to be required on medicines in hospitals*

In March 2003, we proposed a regulation that called for over-the-counter medicines commonly used in hospitals and all prescription medicines to have a bar code. The rule became final in February 2004.

The bar-code rule aims to protect patients from preventable medication errors by helping ensure that health professionals give patients the right drugs at the appropriate dosages and 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*

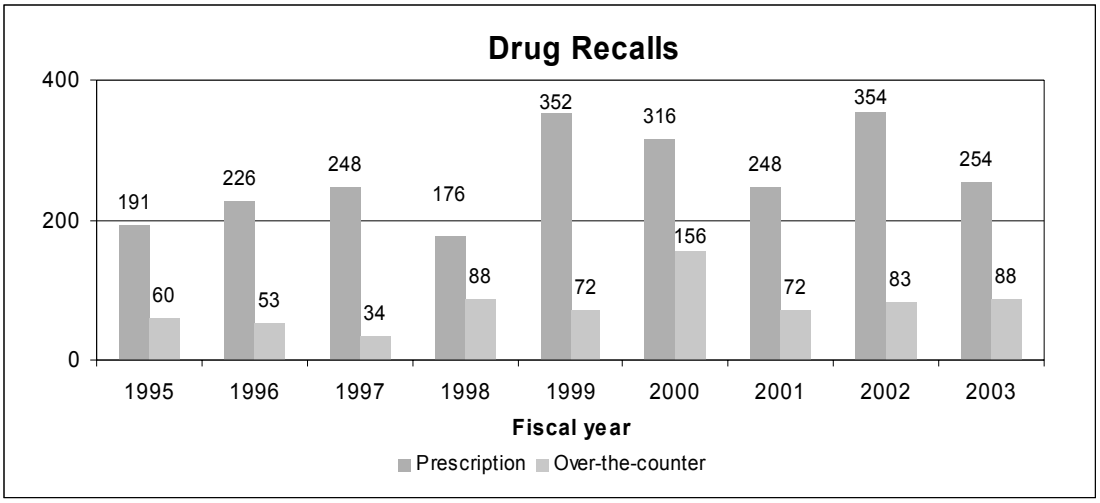
Utilizing data obtained from manufacturers and distributors, our drug shortage program provides supply and production information in response to federal government requests in relation to counterterrorism efforts.

### Estrogen labeling safety changes

**We made safety changes to the labeling of all estrogen and estrogen with progestin products for use by postmenopausal women to incorporate new risk information and to emphasize individualized decisions that appropriately balance the benefits and the potential risks of these products.**

**These changes, including a boxed warning, reflect our analysis of the landmark Women's Health Initiative study, sponsored by the National Institutes of Health. The study showed that postmenopausal women taking estrogen plus progestin have an increased risk of heart attack, stroke, breast cancer and blood clots.**

**Complete information is at http://www.fda.gov/cder/drug/infopage/estrogens_progestins/default.htm.**




**Drug recalls in fiscal year 2003**

- **254 prescription drugs**
- **88 over-the-counter drugs**

# *Drug Recalls*

**Top 10 reasons for drug recalls in fiscal year 2003:**

- **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.

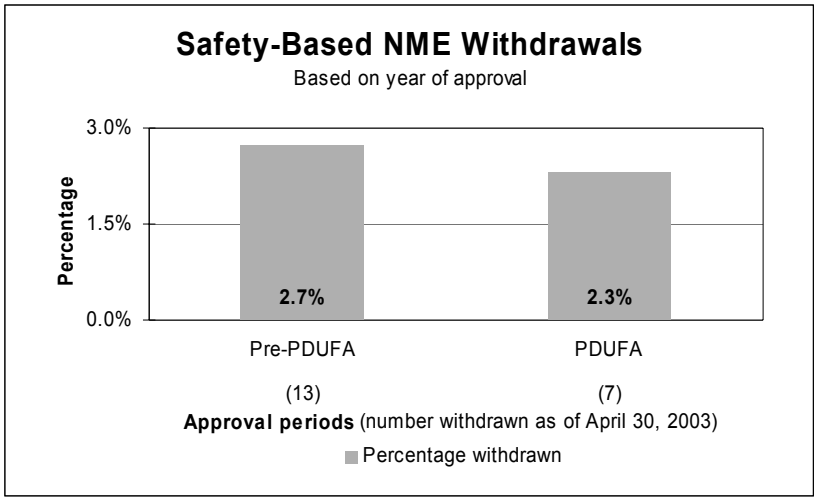
Manufacturers or distributors usually implement voluntary recalls in order to carry out their responsibilities to protect the public health when they need to remove a marketed drug product that presents a risk of injury to consumers or to correct a defective drug product. A voluntary recall of a drug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




# *Safety-based Drug Withdrawals*

## No safety-based withdrawals in 2003

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

### *Record of safety-based market withdrawals*

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

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

*PDUFA period.* Between Jan. 1, 1994, and April 30, 2004, we approved 303 NMEs, and 7 (2.3 percent) have been withdrawn. Nearly all drugs we approved in this period were reviewed under PDUFA goals.

**Recent safety-based drug withdrawals**

**Drug name (year approved/ year withdrawn)**

- **Phenylpropanolamine (—/2000)** (never approved by FDA)
- **Fenfluramine (1973/1997)**
- **Azaribine (1975/1976)**
- **Ticrynafen (1979/1980)**
- **Zomepirac (1980/1983)**
- **Benoxaprofen (1982/1982)**
- **Nomifensine (1984/1986)**
- **Suprofen (1985/1987)**
- **Terfenadine (1985/1998)**
- **Encainide (1986/1991)**
- **Astemizole (1988/1999)**
- **Flosequinan (1992/1993)**
- **Temafloxacin (1992/1992)**
- **Cisapride (1993/2000)**

**Recent safety-based drug withdrawals** (cont.)

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

*Returned to market in 2002 with restricted distribution.

# *Drug Promotion Review*

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

### *Launches and advisories*

When requested, we review advertisements and other promotional materials before drug companies launch marketing campaigns that introduce new drugs or campaigns that introduce new indications or dosages for approved drugs. In calendar year 2003, we issued 185 advisory letters to companies regarding their promotional materials for launch campaigns.

We issued 346 other advisory letters to the industry regarding proposed promotional pieces, both professional and consumer directed. In addition, we issued 159 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

### *Regulatory actions*

We issued 42 regulatory action letters to companies for prescription drug promotions determined to be false, misleading, lacking in fair balance of risks and benefits or that promoted a product or indication before approval. These were either "untitled" letters for violations or "warning" letters for more serious or repeat violations. Examples of specific types of violative promotions include promotional exhibit hall displays, oral representations, Internet sites, plus traditional materials such as journal advertisements and sales brochures.

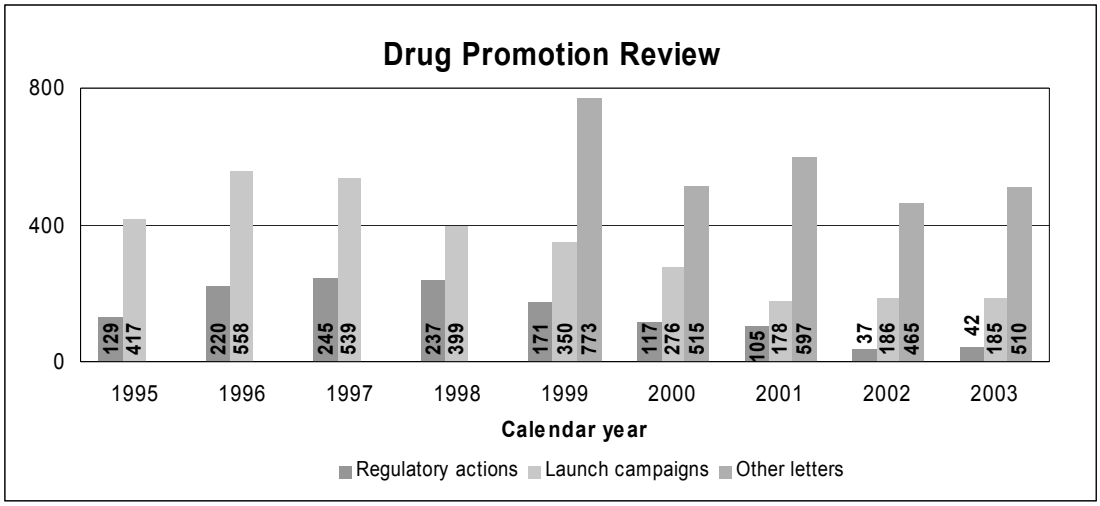
### *Direct-to-consumer promotion*

Included in our letters were 254 regarding direct-to-consumer promotion. This compares with 188 letters in 2002. Included in last year's letters were 47 for launch campaigns and 163 for non-launch advisories. Ten were regulatory letters.

We are working on improving our oversight of DTC advertising. Evidence from our own studies as well as those conducted by consumer groups and other entities consistently shows that DTC 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.

**DTC letters**

- **2003: 254**
- **2002: 188**
- **2001: 190**
- **2000: 215**
- **1999: 247**
- **1998: 282**
- **1997: 240**




**Drug promotion review statistics**

**We issued a total of 737 drug promotion letters last year.**

- **42 regulatory action letters**
- **185 launch campaigns**
- **510 advisory acknowledgement or closure letters**

### *DTC advertising surveys*

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

Preliminary findings of the two surveys indicate that:

- About 40 percent of patients and about 45 percent of physicians feel DTC advertising encourages information seeking about potentially serious medical conditions.
- About 80 percent of patients and 70 percent of physicians feel DTC advertising creates awareness of new treatments.
- About 42 percent of patients and 75 percent of physicians feel DTC advertising make it seem that the drug will work for everyone or make the patients think the drug works better than it does.
- About 40 percent of physicians believe that patients understand the possible risk and negative effects of drugs, compared to 80 percent who believe patients understand the benefits and positive effects.
- Slightly less than half (47%) of physicians report feeling at least a little pressure to prescribe when asked for a prescription.

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

**Proposed rule to revise prescription drug labeling**

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

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

### *DTC public meeting*

To explore DTC advertising issues, we held a two-day public meeting where we presented information from our two patient and one physician surveys. We heard from researchers who have investigated the promotion of prescription drugs directed to consumers through print, broadcast and other types of media.

### Prescription drugs sold without approved applications

**We identify drugs that are marketed without an approved new or generic drug application.**

**We estimate that there are several thousand illegally marketed drug products in the United States, comprising several hundred unique molecules.**

**We issued a draft guidance in October that describes how we intend to:**

**□ Exercise our enforcement discretion regarding these products.**

**□ Provide an incentive to be the first manufacturer to obtain approval for one of these drugs. After a grace period, we will consider taking enforcement action against unapproved competitors, which may result in *de facto* exclusivity.**

**□ Avoid unnecessarily restricting patient access to useful medicines.**

**□ Reiterate our risk-based criteria for enforcement action.**

# *Drug Product Quality*

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

- Evaluating the findings of inspections that examine the conditions and practices in plants where drugs are manufactured, packed, tested and stored.
- Monitoring the quality of finished drug products in distribution, through sampling and analysis.

We identify, evaluate and analyze inspection findings for trends in deficiencies. We develop guidances to assist drug manufacturers in gaining a better understanding of our regulations. We communicate the expectations of compliance through outreach programs. We review 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.

## Reporting systems for drug quality problems

Two important post-marketing tools help us rapidly identify significant health hazards and quality problems associated with the manufacturing and packaging of drugs:

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

### Risk-based surveillance sampling of drugs

**We monitor the quality of the nation's drug supply through surveillance and sampling of foreign and domestic finished dosage forms and bulk shipments of active ingredients.**

**The drug products surveyed are selected according to a risk-based strategy that targets products with the greatest potential to harm the public health. FDA district offices conduct follow-up inspections to determine the cause of sample failures and to assure corrective action by the firms.**

### Sampling criteria

**□ Microbial/endotoxin concerns**

**□ Stability concerns**

**□ Sterility issues**

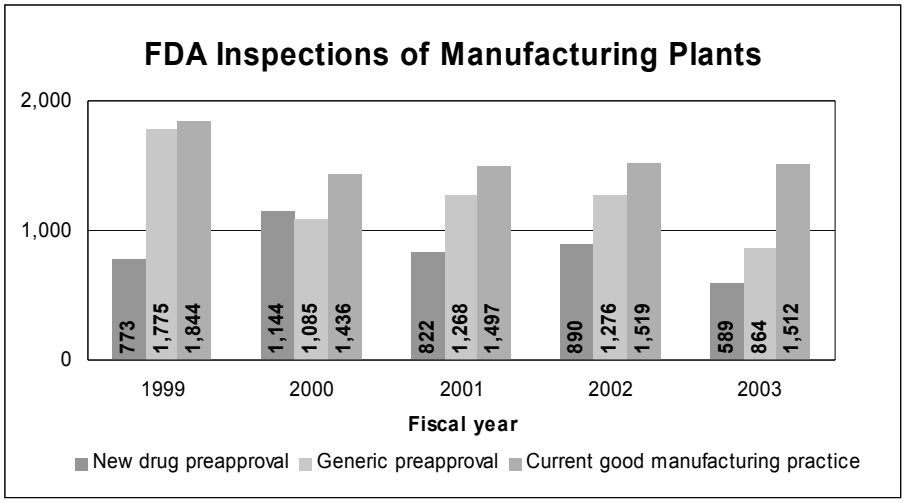
**□ Dissolution issues**

**□ Impurities/ contaminants**

**□ Product quality history**

**□ Counterfeit drugs**

**□ History of violations**




### Protecting consumers from misbranded or fraudulent drugs

**We protect consumers from mislabeled, fraudulent or hazardous products. We locate and identify these products for sale on the Internet as well as from traditional retail outlets, and we take steps 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 or individuals.**

**International commerce in pharmaceuticals continues to be an important regulatory topic. We work with the FDA field force to implement legal requirements establishing which drugs may be imported by manufacturers, distributors and consumers.**

**We protect the public health by ensuring that imported drugs are not counterfeit and meet applicable legal requirements relating to safety and effectiveness.**

## 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.

## Misbranded drugs, unsubstantiated claims

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

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

### Preapproval inspections

**During fiscal year 2003, FDA evaluated:**

- **589 plants in support of new drug applications**
- **864 domestic firms in support of generic drug applications**

### Good manufacturing practice inspections

**There were 1,512 good manufacturing practice inspections in fiscal year 2003.**

- **We reviewed 51 field recommendations for regulatory action and approved 34. These included 27 warning letters, four injunctions and three seizures.**
- **We reviewed 184 foreign establishment inspection reports, resulting in one warning letter and one import alert.**

# *Drug Product Quality Science*

## Process analytical technologies initiative

Our goal for this initiative is to facilitate the introduction of new and emerging technologies that will improve the capability and efficiency of the pharmaceutical manufacturing process while maintaining or improving product quality. Known as process analytical technologies (PAT), these are systems for continuous analysis and control of manufacturing processes based on real-time or rapid measurements during processing. They can also be non-destructive. These systems involve in-line, on-line or at-line monitoring, measuring and controlling in manufacture of drug substance and drug products.

We are using a collaborative process to develop this initiative. We are bringing together experts in the areas of analytical and physical chemistry, pharmaceutical technology, regulatory compliance, chemical engineering and international pharmaceutical manufacturing. These include experts from industry and academia along with our own and those from other FDA components.

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

A steering committee comprised of senior FDA managers is involved in the development of a general guidance on the use of these new technologies. A special review team is now in place to evaluate process analytical technologies as the pharmaceutical industry begins implementation in existing and new manufacturing processes. On the team, our own chemistry reviewers and compliance officers will join FDA's field investigators on inspections.

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

We entered into a a cooperative research and development contract with a major pharmaceutical company to develop and implement chemical imaging as a process analytical technology tool.

### *Process analytical technologies Web site launched*

FDA's effort to facilitate the introduction of new technologies to the manufacturing sector of the pharmaceutical industry now 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 46).**

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

# 3

# INTERNATIONAL ACTIVITIES

### Mission

**We participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.**

## International Conference on Harmonization

Harmonization—making the drug regulatory processes more efficient and uniform—is an issue that is important not only to Americans, but to drug regulatory agencies and pharmaceutical companies throughout the world. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use has worked to bring together government regulators and drug industry experts from innovator trade associations in the European Union, Japan and the United States.

We are leading the FDA's collaboration with the ICH. This work is making new drugs available with minimum delays not only to American consumers but also to patients in other parts of the world.

### ICH guidance documents

**As of April 30, 2004, we had published:**

- **47 final ICH documents**
- **8 draft documents.**

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

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.

### *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.

### *eCTD improves review efficiency*

Electronic submissions using the eCTD specifications can be used to submit all applications and related submissions (page 30) 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's computer is disconnected from the network.

### Sixth International Conference on Harmonization

**At this biannual meeting in Osaka, Japan, the ICH members focused on areas such as:**

- **New technologies in the discovery of innovative drugs.**
- **Opportunities and new challenges for regulatory harmonization.**
- **Pharmacovigilance and global cooperation with regulatory harmonization initiatives outside the ICH regions.**
- **Practical implementation of the Common Technical Document.**

## International information-sharing agreements

In an era of enhanced cooperation among regulators around the world, FDA entered new international agreements in which we play a critical role in implementing. 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. New information-sharing agreements with Canada, Switzerland and the European Union add to those already in effect with Japan and Australia.

### *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 met several times with our counterparts regarding the exchange of 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*

**Swedish reviewer exchange program in development**

**We are developing a reviewer exchange program with the Swedish Medical Products Agency to provide continued improvement of quality reviews.**

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

### *Canada*

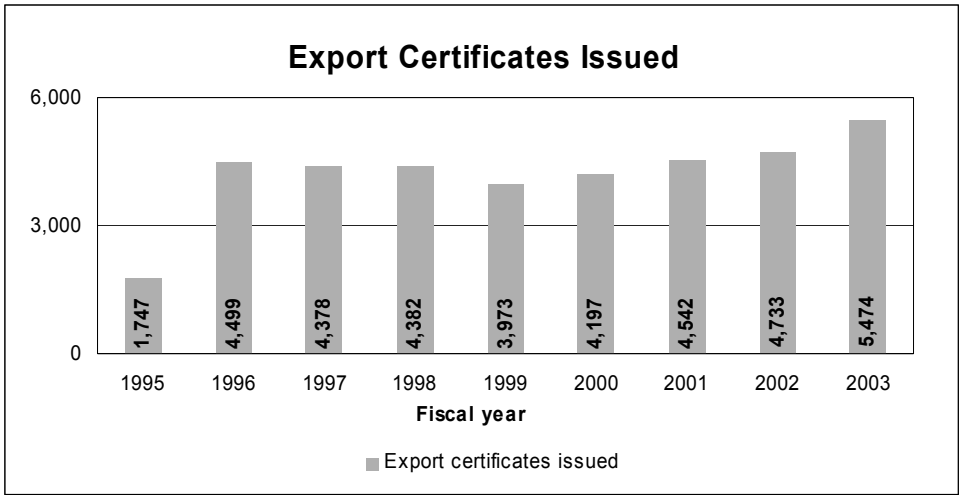
This agreement provides for the exchange of information about pending approvals, post-marketing surveillance and enforcement actions. It expands on information-sharing activities that began years ago as well as those developed more recently with Mexico and Canada. Exchanges of emerging compliance issues and site-specific information have already begun.

### *Switzerland*

The working arrangement with Switzerland began several years ago. 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 is being made in implementing this arrangement, including the exchange of technical staff and training opportunities.

**Export certificates issued in fiscal year 2003:**

- **5,474**




# *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.

**Internet resources**

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

# 4

# COMMUNICATIONS

### Mission

**We carry out our mission in consultation with experts in science, medicine and public health and in cooperation with consumers, users, manufacturers, importers, packers, distributors and retailers of human drugs.**

### Internet updates

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

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

Highlights from 2003 include:

- Meeting almost weekly with outside experts on difficult scientific and public health issues.
- Receiving more than 12 million visits and more than 205 million hits on our Internet information site, which has 50,000 pages and documents, five databases and 250,000 hyperlinks.

## Public participation

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

We held large public meetings and workshops to gather a wide variety of viewpoints on major scientific and regulatory issues, including:

- Risk management (page 34).
- Direct-to-consumer advertising (page 41).
- Evaluating drug names for similarities (page 37).
- Pharmaceutical good manufacturing practices initiative (page 6).
- Process analytical technologies (page 44).

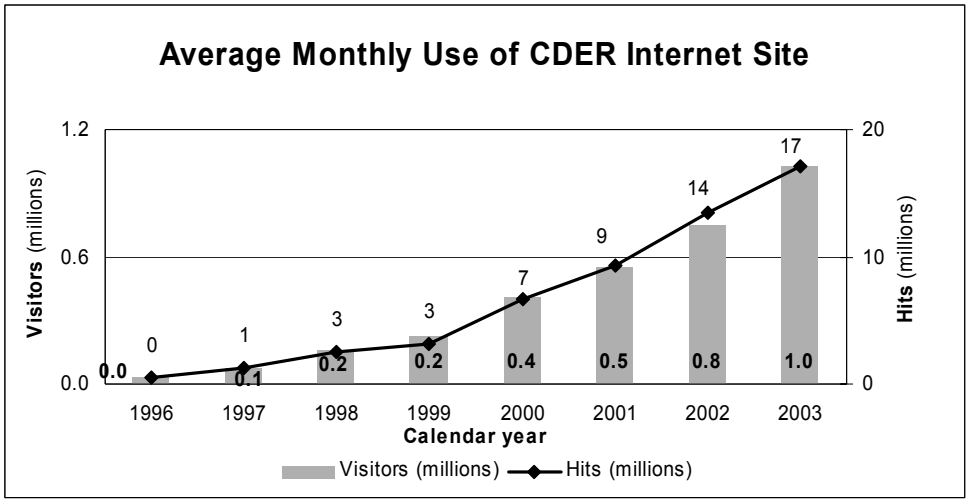
## Consumer and industry outreach

- *Regulations.* We published four final regulations, and we sought public comment on another three proposed regulations.
- *Guidances.* We published 32 guidances for industry that explain our position on best practices in scientific and technical areas. We published another 24 in draft form seeking public comment.
- *Manual of Policies and Procedures.* To foster transparency of our operations, we publish our internal operating policies and procedures on the Internet. We added 23 documents last year.
- *Drug reviews on Internet.* Our Internet site now contains our reviews of more than 1,500 approved drugs or new uses for approved drugs.

### 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 many 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**
- **Counterfeit drugs**
- **Drug interactions**
- **Generic drug quality**
- **Misuse of prescription pain relievers**
- **Over-the-counter medicine labels**
- **Safe use of aspirin**

**These are available on the Internet at http://www.fda.gov/cder/consumerinfo/DPAdefaultv.htm.**

- *Trade press.* We responded to about 2,200 telephone and e-mail requests from the specialized press covering the pharmaceutical industry.
- *Exhibits*. We exhibited at 31 conferences, reaching an estimated audience of more than 108,000 consumers, educators and health care professionals.
- *Videoconferencing.* We held 144 domestic and foreign videoconferences for academia, industry and associations.
- *CDER Live!* We produced one satellite television broadcasts 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.
- *Freedom of Information requests.* We responded to nearly 4,000 requests under the Freedom of Information Act.
- *General information requests.* We answered more than 36,000 telephone inquiries, 26,000 e-mails and 1,800 letters from consumers, health professionals and industry.

### Ombudsman activities

Our ombudsman's office changed management; however, the overall tenor of the office did not change. Our ombudsman serves as a portal for consumers, regulated industry and small business for, among other things, comment on programs, drug development and FDA center jurisdictional advice, general information on drug regulation, and adverse drug experience reporting.

Several people contacted the office to report irregularities and possible fraud in conducting and reporting clinical trials, promotional activities and violations in pharmaceutical manufacturing. Several hundred people contacted the office to express their opinions on advisory committee members, on whether we should approve specific therapies and unwanted e-mail promotion by on-line pharmacies.

The ombudsman's topic of the year was FDA's enforcement against importing drugs from Canada.

The e-mail account ombudsman@cder.fda.gov has become a preferred method of contacting us with more than 1,500 contacts. Approximately 570 of these were forwarded to our druginfo@cder.fda.gov account. We received approximately 400 specific issue contacts by telephone. Examples of our cases were:

- Review/drug development delay.
- Freedom of Information Act access.
- Docket posting dispute.
- User fees dispute.
- Intellectual property dispute.
- Management/employee disagreement.
- NDA priority designation dispute.
- Perceived retaliation complaint.
- Repackaging/expiration dating dispute.
- Import/export issues.

# *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 Drug Information
HFD-240, Room 12B-05
5600 Fishers Lane
Rockville, MD 20857

### Jurisdictional issues

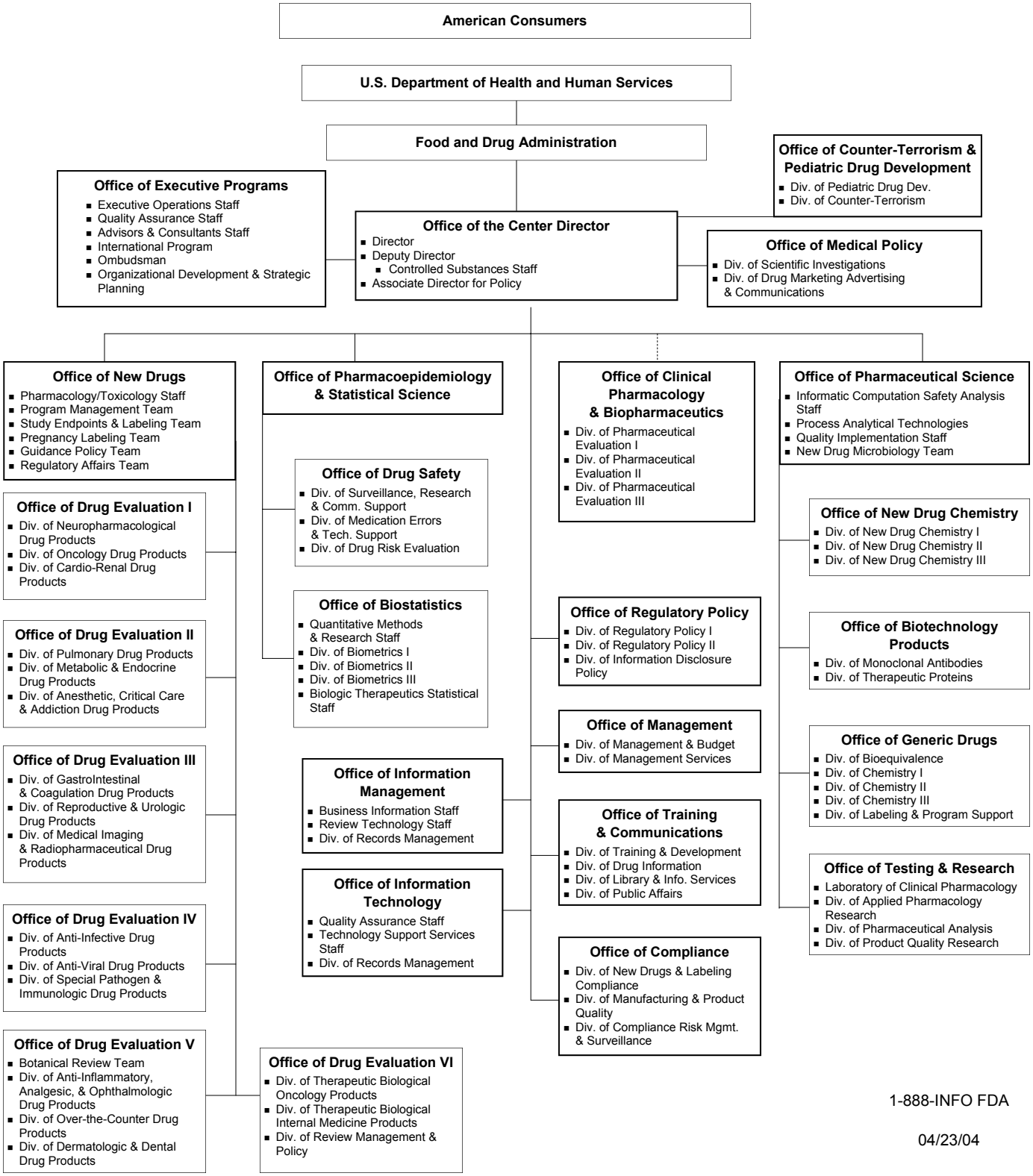
**Our ombudsman serves as our jurisdiction officer. Many times it is not readily apparent where proposed products will be reviewed and regulated either within the center or between FDA centers.**

**Our ombudsman is a member of a steering committee that advises the congressionally created the FDA Office of Combination Products. The office, created in December 2002, has a mandate to define or clarify regulations in the area of combination products such as:**

- **Primary mode of action**
- **Single-separate applications**
- **User fees**
- **cGMPs**

**Our ombudsman is also a member of the working group for the FDA's initiative in the area of novel drug delivery systems and in the agency's dispute resolution processes.**

# Organizational Structure of the Center for Drug Evaluation and Research




1-888-INFO FDA

04/23/04


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