

2007 Center for Drug Evaluation and Research UPDATE



Improving Public Health Through Human Drugs



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

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Director's Message

I am happy to present the *CDER 2007 Update*, which documents the Center for Drug Evaluation and Research's activities and performance across program areas. CDER's continued ability to carry out its mission of protecting and advancing America's health rests squarely on the commitment of our talented and dedicated staff.

CDER continues to work to assure that medicines are safe, effective and available to the public, and to provide clear and easily understandable drug information to health professionals, patients and consumers. Our ability to carry out this mission has been bolstered by recent legislation.

On September 27, President George W. Bush signed into law the Food and Drug Administration Amendments Act (FDAAA) of 2007. This new law is a significant addition to FDA authority.

FDAAA reauthorized and expanded the Prescription Drug User Fee Act (PDUFA) to ensure that CDER has the resources needed to conduct complex and comprehensive drug reviews and to provide more resources for drug safety activities. Two other important laws were reauthorized; the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Both laws encourage more research into developing treatments for children.

A number of our 2007 initiatives were in response to a comprehensive report on the nation's drug safety system that we asked the Institute of Medicine (IOM) to conduct. We have taken steps to put many of IOM's recommendations in place, including establishing a new advisory committee to address how we communicate information about the efficacy, safety and use of drugs and other FDA-regulated medical products.

On June 4, 2007, FDA established a Risk Communication Advisory Committee, as suggested by IOM and endorsed in the FDAAA. The committee is comprised of practitioners and experts in risk communications. These highly-qualified individuals will play a vital role in helping us improve our practices, procedures and programs. As a result of these efforts, consumers and health-care professionals can make better-informed decisions about the risks and benefits of all regulated products.

Safety First/Safe Use

When I assumed the role of Acting Director of CDER in October 2007, I announced an initiative called *Safety First/Safe Use*. This initiative builds on authorities and opportunities provided by the FDAAA. These authorities further establish our critical role in assuring the safe and appropriate use of drugs after they are marketed and gives us substantial resources and regulatory tools. Essentially, FDAAA supports our ability to manage safety throughout the entire life cycle of pharmaceutical products.

We have been tremendously successful in developing a world-class pre-market review process. This process enables us to approve safe and effective drugs effectively and efficiently without sacrificing the quality of our reviews. Over the past 15 years, additional resources and commitments resulting from PDUFA brought unprecedented accountability to the new drug review and institutionalized project management, prioritization and tracking for pre-market drug review. Now we are going to apply the same high standards to managing the post-marketing safety process.

Safety First refers to steps that strengthen and modernize our internal policies and processes to manage significant drug safety issues. *Safe Use* describes CDER's mission to expand partnerships with other components of the health care system to ensure that medicines are used safely and appropriately.

The specific objectives of *Safety First* are to:

- Create and maintain a collaborative, multidisciplinary, team-based approach to the review of drug safety.
- Apply our world class project management skills to make sure we have the same focus on and attention to post-market safety issues as we do to drug development.
- Align our policies and processes to ensure that the most appropriate and best-qualified experts lead or have an equal voice in regulatory decisions.
- Build the scientific, administrative and technological capacity to carry out the provisions of FDAAA and PDUFA IV.
- Ensure that significant post-market safety issues are our highest priority.

As we put these changes in place, we will also begin focusing on the longer-term goal of influencing the safe and appropriate use of drugs by the healthcare system. The preliminary objectives of the *Safe Use* initiative are to:

- Develop a cutting-edge pharmacovigilance system for evaluating drug performance using electronic health data.
- Collaborate with stakeholders in the healthcare system to devise effective, efficient steps to ensure drugs are used as appropriately as possible, in ways that minimize medical errors and manage risks aggressively.

Critical Path Initiative

Several years ago, we launched the Critical Path Initiative. This initiative was designed to bridge the gap between basic scientific research and the medical product development process. It called for a collaborative cross-sector effort to modernize the drug development process.

The Critical Path Initiative has rapidly matured and is now poised to yield benefits. Today, we are building on our unique position to work with outside stakeholders to identify areas ripe for improvement, and to coordinate, develop and/or disseminate solutions to scientific hurdles that are impairing the efficiency of developing and evaluating regulated products.

Many critical path tools, such as new biomarkers and more informative clinical trial designs produce enhanced information about the safety and efficacy of the product. This is information that health-care providers can use to tailor therapies to the individual needs of patients.

For example, better methods for selecting patients and assessing their responses during a clinical trial can translate directly to better methods of diagnosing and monitoring patients in the clinic, and better methods for targeting treatments to the patients who are most likely to benefit. Such tools will help bring individualized medicine into the physician's office and help to shape the medical practice of the future.

Posted descriptions of some of our Critical Path activities are on our Web site. We will be adding new activities as they begin to take shape.

CDER's initiatives hold the potential to usher in a new era of certainty and predictability in the development and performance of products that we regulate. We are extremely proud of the work outlined in this CDER 2007 Update. The ultimate beneficiaries of our efforts will be the public whom we serve.

Janet Woodcock, M.D.

Introduction

Who we are

The Center for Drug Evaluation and Research is America's consumer watchdog for medicine. Approximately half of us are physicians or other kinds of scientists. We are part of one of the nation's oldest consumer protection agencies—the U.S. Food and Drug Administration. The FDA is an agency of the federal government's Department of Health and Human Services.

Our mission

CDER promotes and protects public health by ensuring that safe and effective drugs are available to Americans. The Food and Drug Administration Act of 1997 affirmed our public health protection role, clarified the FDA's mission and called for the FDA to:

- 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.
- Protect the public health by ensuring that human drugs are safe and effective.
- Participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.
- 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.

Our mission was further enhanced on September 27, 2007 when H.R. 3580, the Food and Drug Administration Amendments Act (FDAAA) was signed into law. This new law represents a significant addition to FDA authority and reauthorized the:

- Prescription Drug User Fee Act, allowing FDA to fund reviews of new drugs and shorten review times.
- Medical Device User Fee and Modernization Act which allows FDA to make significant improvements in the medical device review program.
- Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act to encourage more studies to develop treatments for children.

What we do

We evaluate new drugs for safety and effectiveness before they can be sold. Our evaluation, called a review, ensures that the drugs we approve meet our tough standards for safety, effectiveness and quality. Once drugs are on the market, we monitor them for problems.

Reviewing drugs before marketing. FDA does not conduct the clinical studies that support marketing. A drug company seeking to sell a drug in the United States must conduct the studies intended to demonstrate effectiveness and defining the drug's risks. 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 known risks, we approve it for sale. By setting clear standards for the evidence we need to approve a drug, we help medical researchers bring safe and effective new drugs to American consumers more rapidly. We also review drugs that you can buy over the counter without a prescription and generic versions of over-the-counter and prescription drugs.

Watching for drug problems. Once a drug is approved for sale in the United States, our consumer protection mission continues. We monitor the use of marketed drugs for unexpected health risks. If new, unanticipated risks are detected after approval, we take steps to inform the public and change how a drug is used or even remove it from the market. We monitor changes in manufacturing to ensure they will not adversely affect safety or efficacy. We evaluate reports about suspected problems from manufacturers, health-care professionals and consumers. We try to make sure an adequate supply of needed drugs is always available to patients who depend on them.

Monitoring drug information and advertising. Accurate and complete information is vital to the safe use of drugs. In the past, drug companies promoted their products almost entirely to physicians. More frequently now, they are advertising directly to consumers. We oversee advertising of prescription drugs, whether to physicians or consumers. We pay particular attention to broadcast ads that can be seen by many consumers. The Federal Trade Commission regulates advertising of over-the-counter drugs. Advertisements for a drug must contain a truthful summary of information about its effectiveness, side effects and circumstances when its use should be avoided.

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; and regulatory standards and consistency.

Protecting drug quality. In addition to setting standards for safety and effectiveness testing, we also set standards for drug quality and manufacturing processes. We work closely with manufacturers to see where streamlining can cut red tape without compromising drug quality. To ensure a safe and effective drug supply, we enforce federal requirements for drug approval, manufacturing and labeling. When necessary, we take legal action to stop distribution of products in violation of these requirements. As the pharmaceutical industry has become increasingly global, we are involved in international negotiations with other nations to harmonize standards for drug quality and the data needed to approve a new drug. This harmonization will go a long way toward reducing the number of redundant tests manufacturers do and help ensure drug quality for consumers at home and abroad.

Why we do it

Our goal is to protect and promote the health of Americans. Protecting consumers includes listening to them. We hold public meetings 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 obtain enhanced public input into our planning and priority-setting practices.

Drug Review

New Drug and Biologic Review

Drug Review Definitions

- *Review and approval times.* Review time is time spent examining the application. Approval time represents review time plus industry's response time to our requests for additional information.
- *Priority reviews.* These products represent significant improvements compared with marketed products. We have a goal of reviewing 90 percent of these applications within six months.
- *Standard reviews.* These products have therapeutic qualities similar to those of already marketed products. We have a goal of reviewing 90 percent of these applications within 10 months.
- *Actions and filings.* An application is filed when we determine it is complete and accept it for review. We make a filing decision within 60 days of receiving an application. Approval is one of the actions that we can take once an application is filed. Another action is seeking more information from the sponsor. There is no direct connection between applications filed in one year and actions in the same year.
- *Orphan drugs.* We administer a program that provides incentives to develop drugs for use in patient populations of 200,000 or fewer. Sponsors of orphan drugs receive the following inducements: seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance from FDA and grants of up to \$200,000 a year.
- *Accelerated approval.* This program makes products for serious or life-threatening diseases available earlier in the development process by relying on an effect on a surrogate end point to predict clinical benefit. An effect of the drug on a surrogate end point can be observed significantly sooner than can a long-term clinical benefit. Sponsors must perform additional studies to demonstrate long-term clinical benefit.
- *Fast-track development.* This program facilitates the development and expedites our review of new medicines that demonstrate the potential to address unmet medical needs for serious or life-threatening conditions. Fast track emphasizes our close, early communication with sponsors.
- *Median times.* Our charts show review and approval times as medians. The value for the median time is the number that falls in the middle of the group after the approval times 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 times. Our

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

- *Tentative approval*. This program is issued to the drug company when the application is approvable prior to the expiration of any patents or exclusivities accorded to the reference listed drug product. A tentative approval does not allow the applicant to market the product and postpones the final approval until all patent or exclusivity issues have expired.
- *New Molecular Entities* (NMEs) contain an active substance that has never before been approved for marketing in any form in the United States. Because of high interest in truly new medicines, we report approvals of NMEs and new biologic license applications (BLAs). The charts for all new drug applications (NDAs) and all BLAs include NMEs and new BLAs.

New drug applications

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

Biologic license applications

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

New Drug and Biologic Review Statistics

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

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

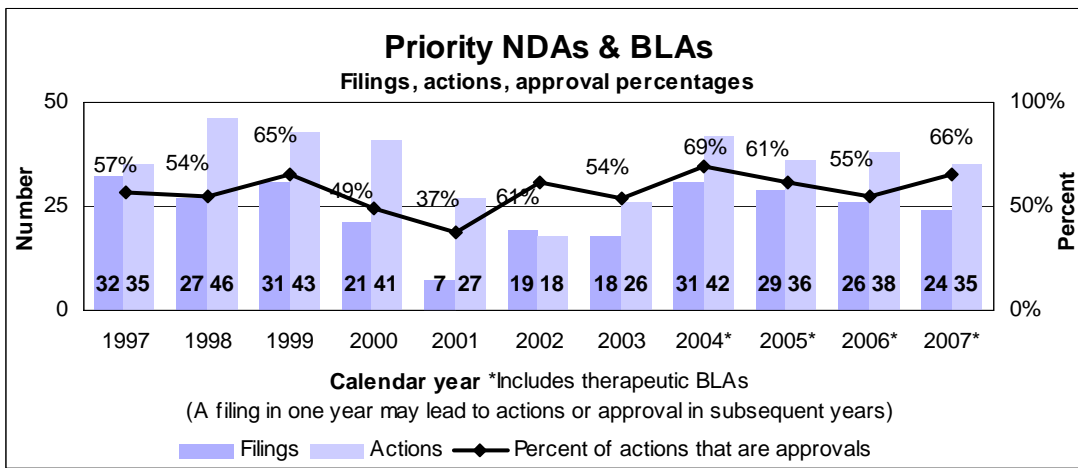
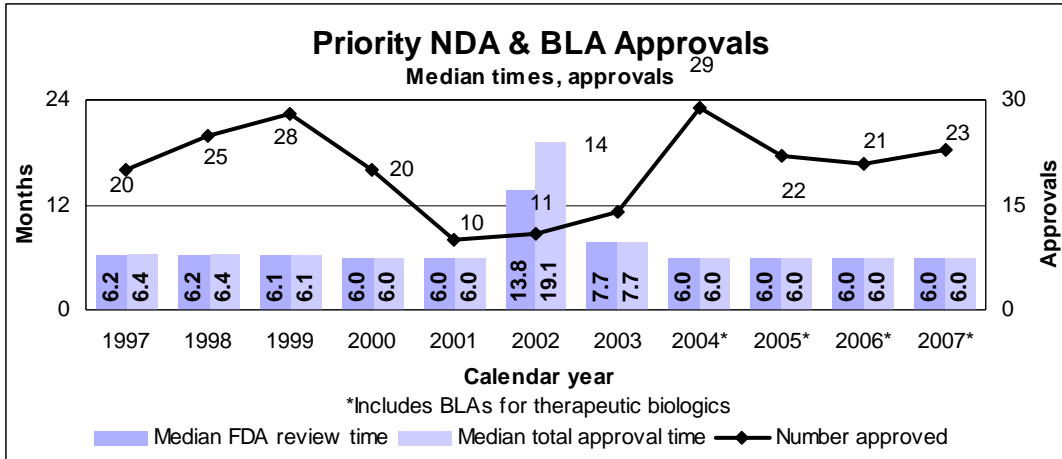
Additional review statistics are available at <http://www.fda.gov/cder/rdmt/default.htm>.

Approval totals in 2007

- **78 drugs and biologics**
 - 76 drugs
 - 2 biologics
- **18 truly new medicines**
 - 16 drug NMEs
 - 2 new biologic NMEs
- **13 tentative NDA approvals**
 - 10 priority PEPFAR new combinations
 - 3 standard tentative approvals
- **8 total orphan condition approvals**
 - 7 new drugs or biologics
 - 4 priority reviews of new drugs (including 3 NMEs)
 - 1 priority review of a new biologic
 - 3 standard reviews of new drugs
 - 4 new or expanded uses for orphan conditions
 - 2 priority reviews for drugs
 - 2 standard reviews for drugs

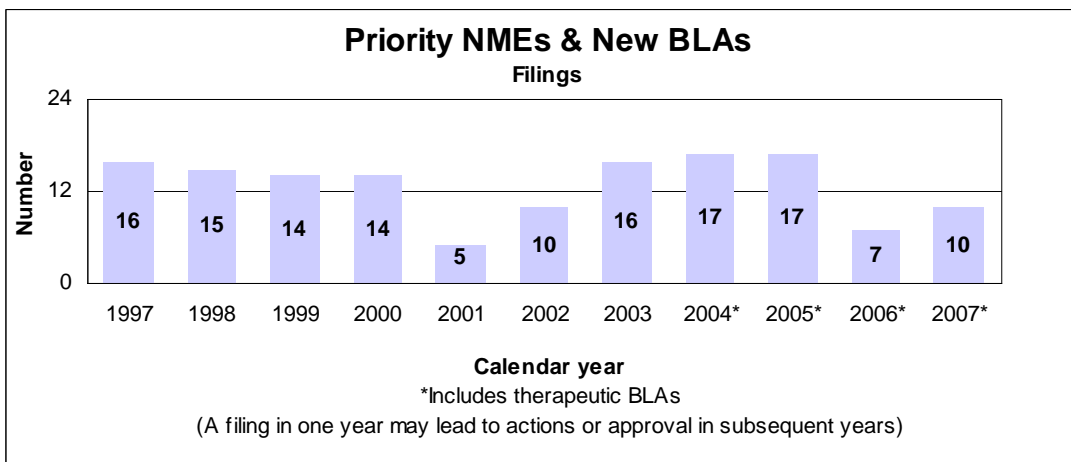
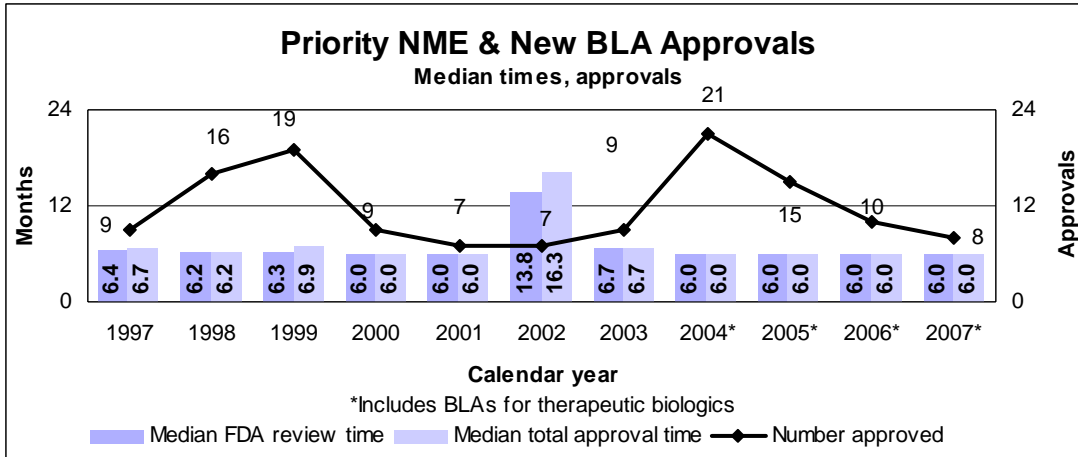
Priority new drugs and biologics

- **23 approvals**
 - 22 drugs
 - 1 biologic
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 24 filings
- 35 actions



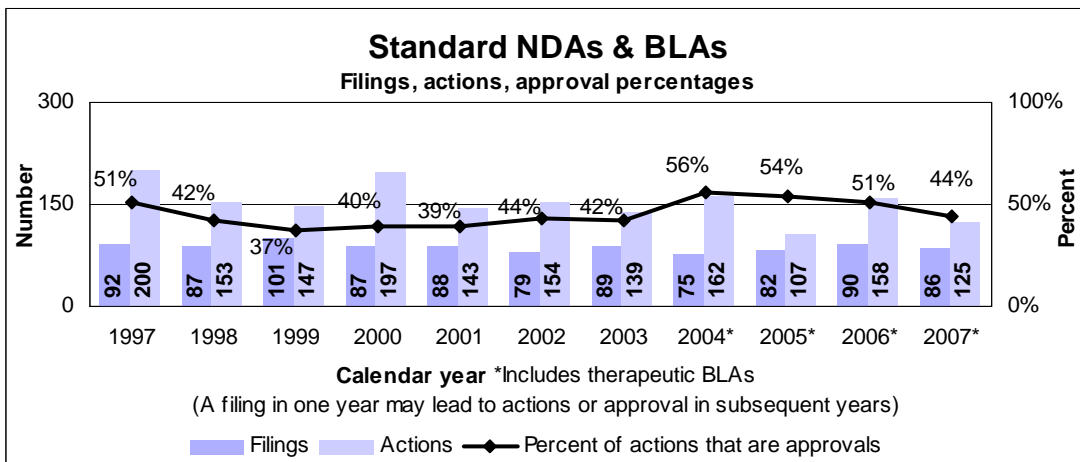
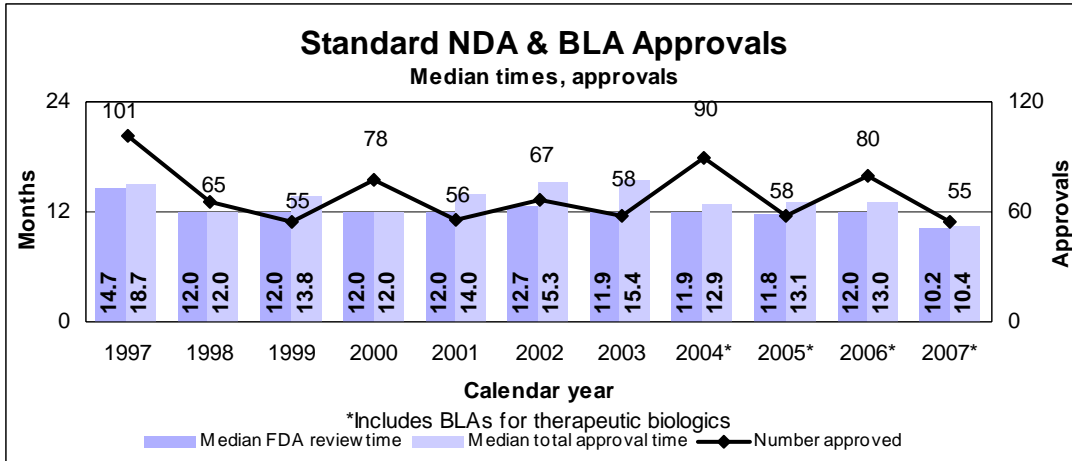
Priority new molecular entities and new biologics

- **8 approvals**
 - 7 Drug NMEs
 - 1 new BLA
- Median review time: 6.0 months
- Median approval time: 6.0 months
- 10 filings



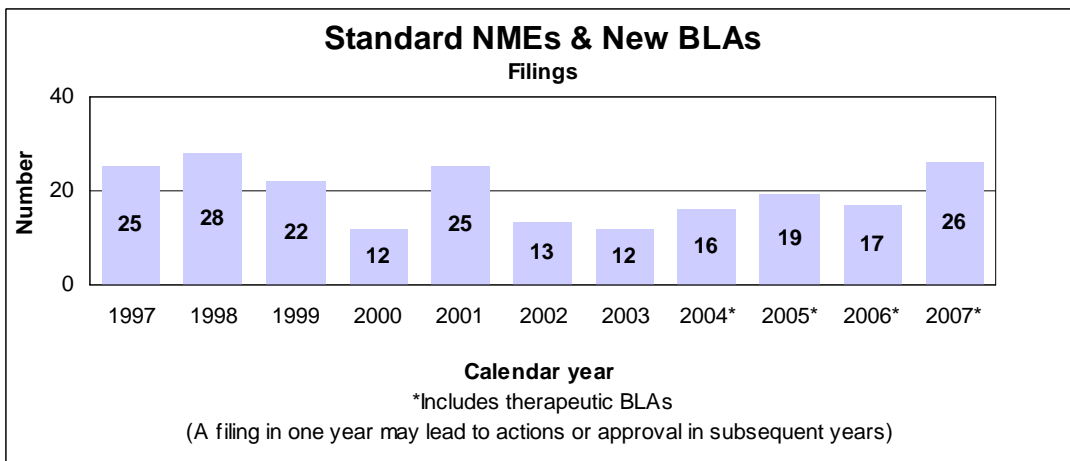
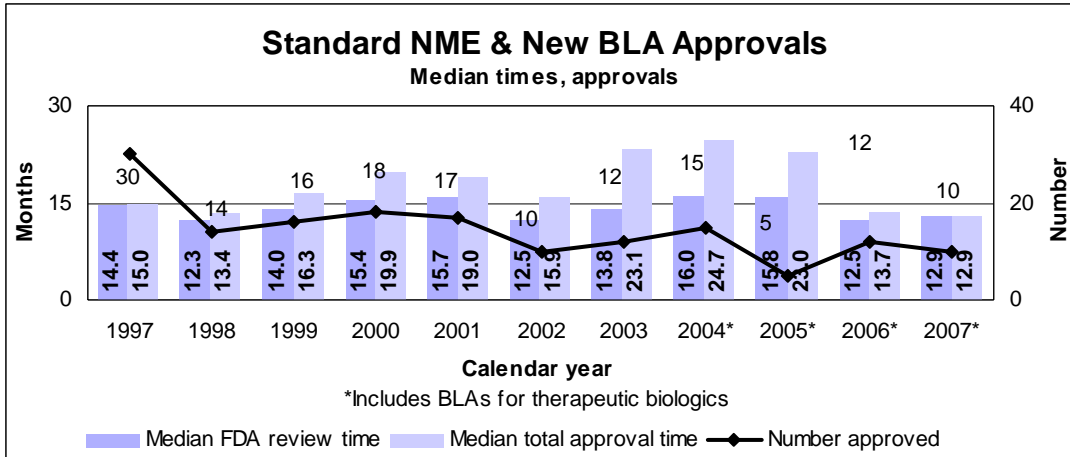
Standard drugs and biologics

- **55 approvals** (all NDAs)
 - Median review time: 10.2 months
 - Median approval time: 10.4 months
- 86 filings
- 125 actions



Standard new molecular entities and new biologics

- 10 approvals (all NMEs)
- Median review time: 12.9 months
- Median approval time: 12.9 months
- 26 filings



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.

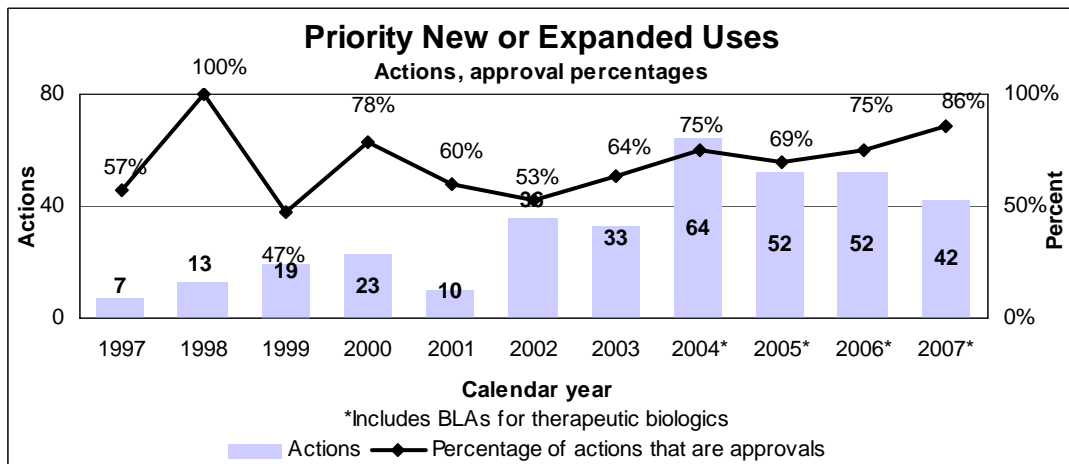
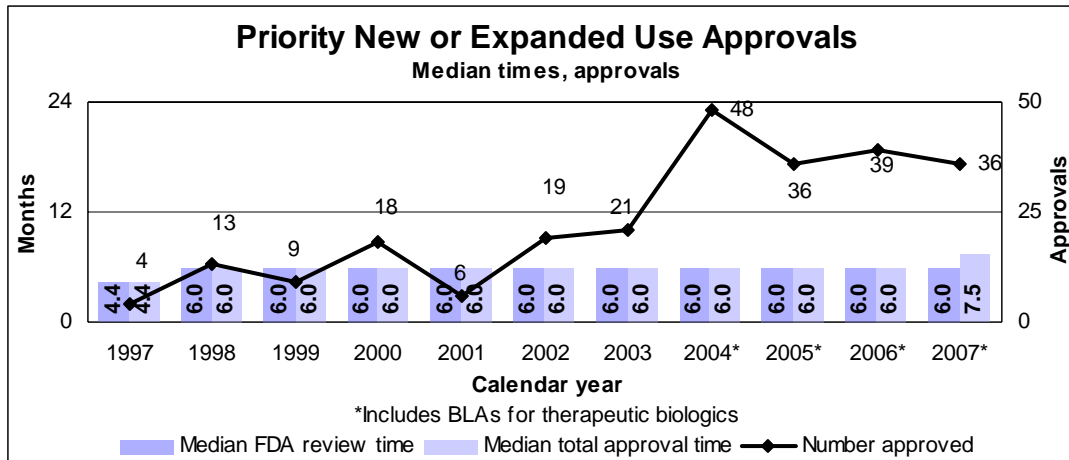
Approval totals

- 127 reviews of drugs and biologics
- 119 reviews of drugs
- 8 reviews of biologics

Priority new or expanded uses (efficacy supplements)

- **36 approvals**

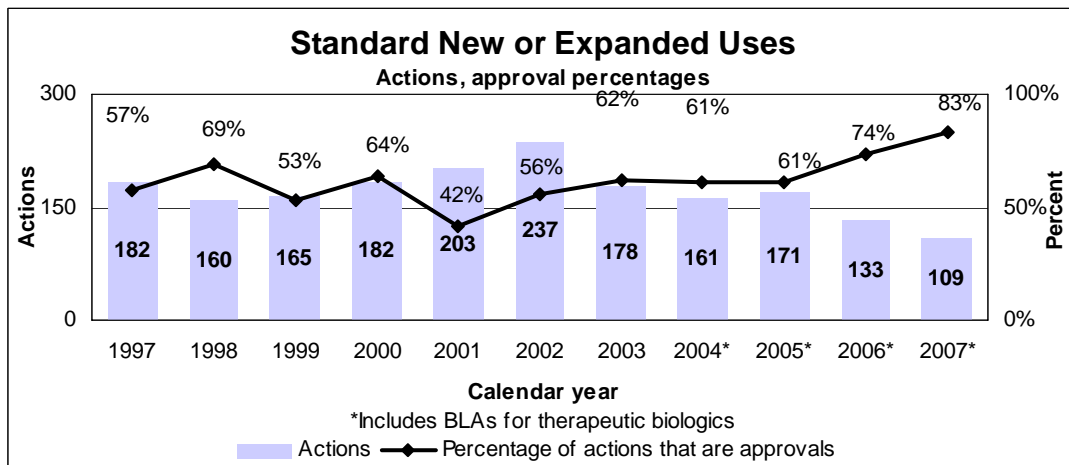
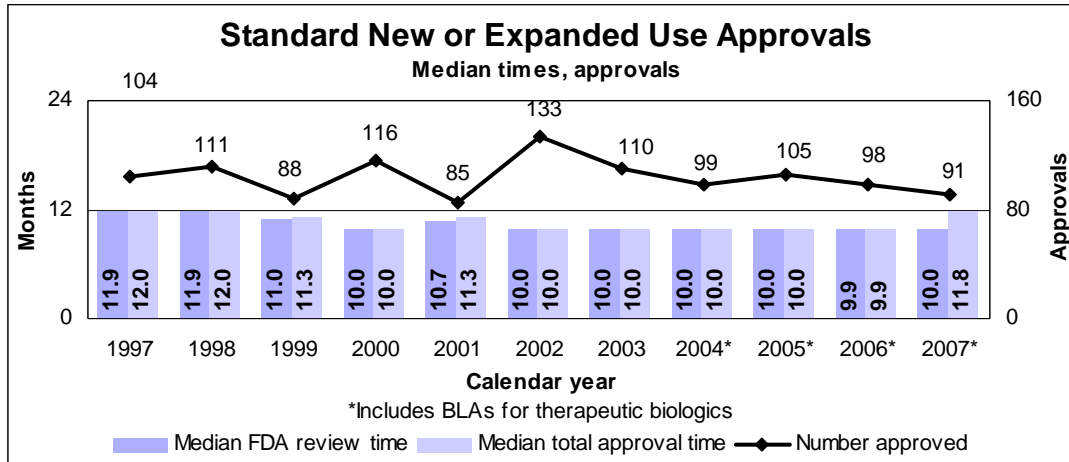
- 33 reviews of drugs
- 3 reviews of biologics
- Median review time: 7.6 months
- Median approval time: 6.0 months
- 42 actions



Standard new or expanded uses (efficacy supplements)

- **91 approvals**
 - 86 reviews of drugs
 - 5 reviews of biologics
- Median review time: 10.0 months
- Median approval time: 11.8 months

- 109 actions



Generic Drug Review

Generic drugs are not required to repeat the extensive clinical trials used in the development of the original, brand-name drugs. For many products such as tablets and capsules, generics must show *bioequivalence* to the brand-name reference listed drug. This means that the generic version must deliver the same amount of active ingredient into a patient's bloodstream over the same time period as the brand-name reference listed drug.

The rate and extent of absorption of a drug is called its *bioavailability*. The bioavailability of the generic drug is compared to that of the brand-name drug. If the bioavailability of the two is similar, the drugs are bioequivalent.

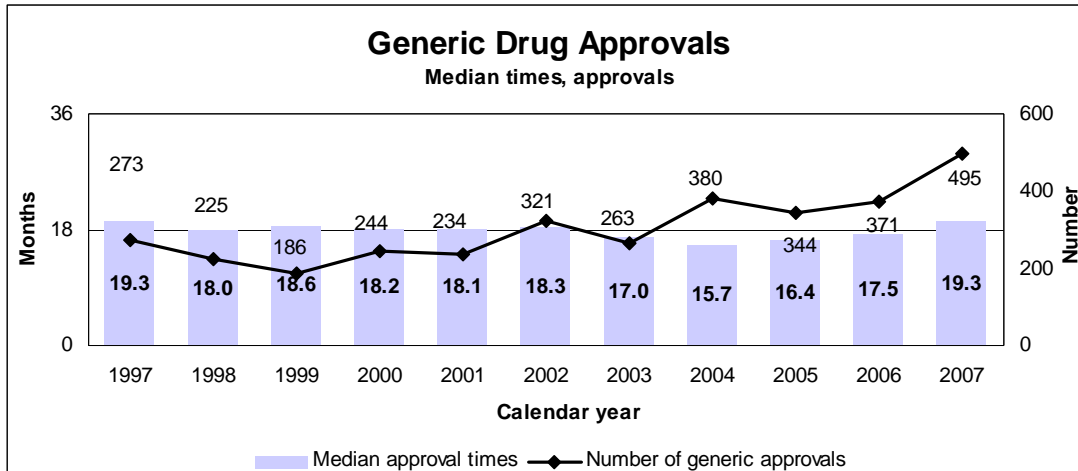
Brand-name drugs are subject to the same bioequivalency tests as generics when their manufacturers reformulate them.

Generic drug 2007 approvals

We had 683 approval actions with 495 fully approved and 188 tentatively approved generic drug products in calendar year 2007. This included a substantial number of products that represent the first time a generic drug was available for the brand-name product.

The median statistic for total approval time showed an increase this year due, in part, to the high numbers of new applications for the last two years. We have made several changes to improve the efficiency of our generic drug review process in order to try to keep up with the dramatic increase in applications. These efforts will continue.

- 495 generic drugs
- Median approval time 19.26 months
- 188 tentative approvals
- 882 receipts

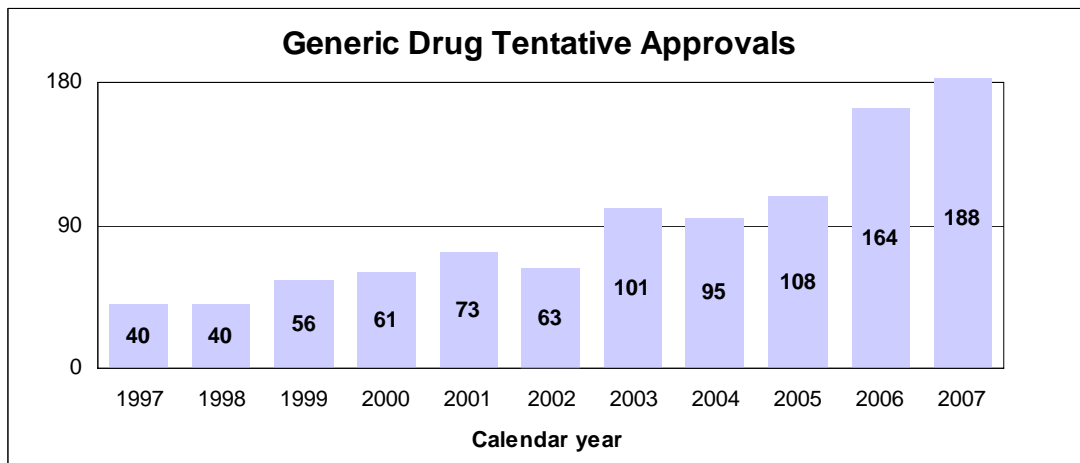


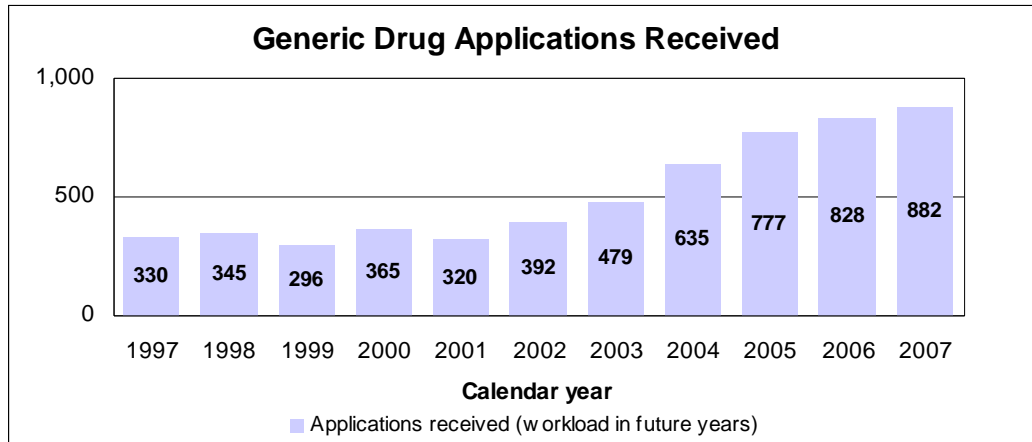
Tentative vs. full approval

The difference between a full approval and a tentative approval is that the final approval of these applications is delayed due to an existing patent or exclusivity on the innovator drug product. The FDA review of an application that is tentatively approved requires the same amount of work as a review that results in a full approval. Tentative approvals are displayed in our approvals chart only when they are converted to full approvals.

Tentative approvals key to affordable, worldwide AIDS relief

Tentative approval is a key regulatory mechanism to support the availability of drugs for the President’s Emergency Plan for AIDS Relief.





Notable 2007 generic drug approvals

- *Alendronate tablets*. Used to treat certain types of osteoporosis and Paget's disease.
- *Carvedilol tablets*. A beta blocking agent used to treat congestive heart failure and hypertension.
- *Cetirizine tablets*. An antihistamine for treatment of various allergic conditions.
- *Granisetron tablets*. For the prevention and treatment of nausea or vomiting related to cancer therapy and postoperative nausea and vomiting.
- *Irinotecan injection*. Used for treatment of colon and rectal cancer.
- *Zolpidem Tablets*. Used for the short-term treatment of insomnia.

Generic drug review efficiencies

The dramatic increase of generic drug applications makes it imperative that we process applications more efficiently. Our steps to improve our processes and to improve the content and completeness of generic drug applications include:

- The Generic Initiative for Value and Efficiency which focuses on using existing resources to help FDA modernize and streamline the generic approval process.
- *Question-based Review* to assist sponsors in providing information that demonstrates their understanding of the manufacture of the product.
- *Posting bioequivalence information*, including data tables, information about laboratory tests and necessary studies.
- *Focused hiring* which increase staff in critical review components.

- *Holding joint meetings and workshops* with academia and industry to improve knowledge of the submission process and quality of applications.
- Encouraging electronic submission of applications.

Reducing hurdles to generic drug availability

We expedite the review of applications that, at the time of submission, represent the first generic application for an innovator product that had no patent or exclusivity protection.

We are working to implement recently passed legislation aimed at reducing certain delays in acting on generic drug applications.

Over-the-Counter Drug Review

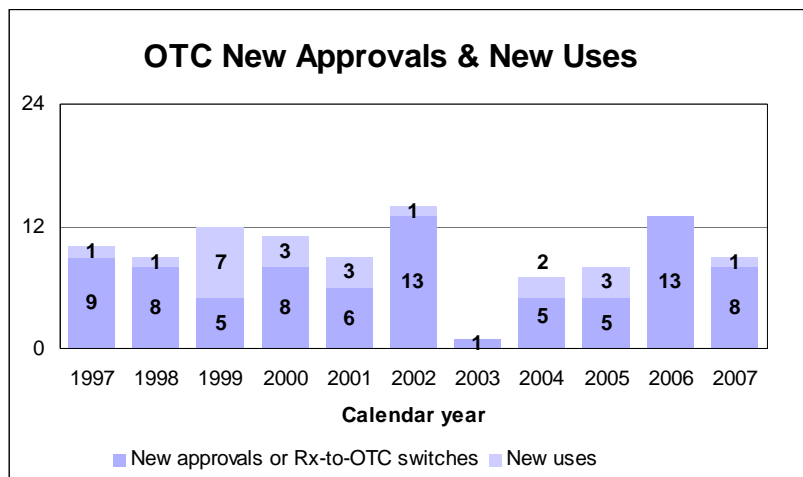
How we regulate OTC drugs

Although many drugs are approved for OTC use through the new drug review process, other OTC medicines are regulated under the OTC drug review process. This process relies on published monographs created by public rule making. 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. FDA maintains an online library of all OTC monographs which can be found at http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm.

In 2007, we approved one new drug application for first-time over-the-counter sale, eight prescription-to-OTC switches and one new strength.

OTC approval statistics

- 1 first-time OTC
- 8 Rx-to-OTC switches
- 1 new strength



First-time OTC:

- *Orlistat 60 mg (Alli) capsules* for weight loss in overweight adults, 18 years and older, when used along with a reduced-calorie, low-fat diet and exercise program.

Rx-to-OTC Switches:

- *Cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg (Zyrtec-D) tablets* for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat, and nasal congestion in adults and children 12 years of age and older.
- *Cetirizine HCl 1 mg/ml (Children's Zyrtec Allergy) syrup* for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat in adults and children 2 years of age and older.
- *Cetirizine HCl 1 mg/ml (Children's Zyrtec Hives Relief) syrup* for the relief of itching due to hives (urticaria) in adults and children 6 years of age and older.
- *Cetirizine HCl 5 mg and 10 mg (Children's Zyrtec Allergy) chewable tablets* for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat in adults and children 6 years of age and older.
- *Cetirizine HCl 5 mg and 10 mg (Children's Zyrtec Hives Relief) chewable tablets* for the relief of itching due to hives (urticaria) in adults and children 6 years of age and older.
- *Cetirizine HCl 5 mg and 10 mg (Zyrtec Allergy) tablets* for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat in adults and children 6 years of age and older.
- *Cetirizine HCl 5 mg and 10 mg (Hives Relief) tablets* for the relief of itching due to hives (urticaria) in adults and children 6 years of age and older.
- *Omeprazole 20 mg delayed-release tablets* for the treatment of frequent heartburn in adults 18 years of age and older.

New Strength:

- We approved a new *20 mg famotidine* strength formulation of *Pepcid AC chewable tablet* for the treatment or prevention of meal-induced heartburn, acid indigestion and sour stomach for adults and children 12 years of age and older replacing the old 10 mg strength chewable tablet.

Pediatric Drug Development

President Bush signed into law the FDA Amendments Act of 2007 in September. This law reauthorizes and amends the Best Pharmaceuticals for Children Act of 2002 (BPCA) and the Pediatric Research Equity Act of 2003 (PREA). Both laws encourage more research into developing treatments for children. Some highlighted changes to BPCA and PREA are:

- Authorization to establish an internal review committee. The Pediatric Review Committee will review requests for waivers and deferrals, review pediatric assessments and pediatric plans prior to approval and pediatric written requests prior to issuance.
- The clinical, clinical pharmacology and statistical reviews are to be made public for applications submitted in response to both PREA and BPCA.
- Adverse event reporting now affects both PREA and BPCA. The review of reports has been modified to occur one year after labeling is approved.

Pediatric Research Equity Act. In 2007, CDER granted 86 waivers and 32 deferrals. There were 32 applications with PREA requirements fulfilled. As of June 2007, there have been nine PREA-related labels identified and posted. Since FDAAA, there were seven pediatric assessments approved, six deferrals and 23 waivers granted.

Pediatric Review Committee. In 2007, there were 23 CDER products reviewed by the committee.

Pediatric exclusivity. We issued 20 on-patent written requests and one off-patent. During 2007, there were 14 exclusivity determinations, 13 of which were granted exclusivity and 17 labels with new pediatric information approved.

Improved safety, dosing information. The failure to produce drugs in dosage forms that can be taken by young children—such as liquids or chewable tablets—can deny children access to important medications. As a result of pediatric testing under BPCA, we now have 15 drugs with new pediatric formulations and seven drugs with recipes in their labels to provide directions for the pharmacist to compound an age-appropriate formulation.

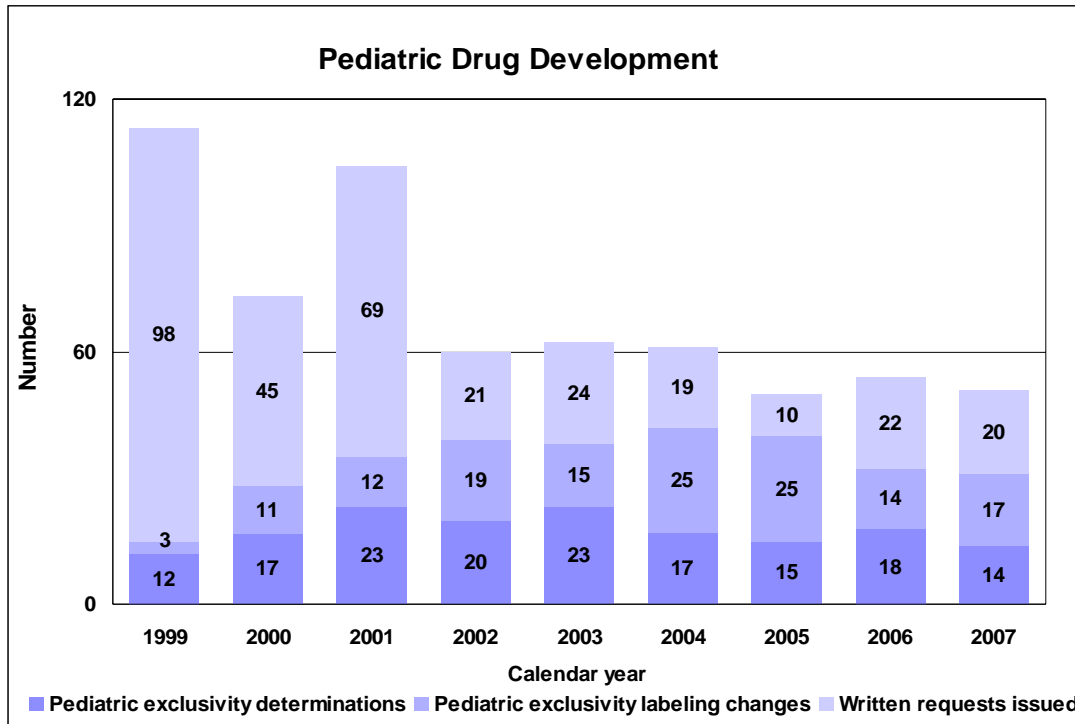
Public disclosure. We have posted 83 summaries of the medical and clinical pharmacology reviews responsive to BPCA 2002. These summaries are located at <http://www.fda.gov/cder/pediatric/Summaryreview.htm>.

Adverse events reporting. Seventy-seven drugs have been presented to the Pediatric Advisory Committee. The law mandates review of all adverse event reports for a one-year period after pediatric exclusivity is granted.

2007 pediatric exclusivity statistics

- 20 written requests issued

- 17 pediatric exclusivity labeling changes granted
- 14 exclusivity determinations made



Maternal Health Team

The Maternal Health Team mission is to increase knowledge about the safe and effective use of medicines during pregnancy and breast-feeding. We encourage research in this area and provide scientific guidance to industry and FDA reviewers. When more information about medicine use during pregnancy and breastfeeding becomes available, we work with FDA reviewers and drug manufacturers to update medicine labels.

Women who are pregnant or breast-feeding often need to use prescription and/or over-the-counter medicines. During pregnancy, treating a disease or condition with a medicine may be safer for the woman and her baby than not treating the condition. It is important that health-care providers and pregnant women have the information they need to make the best medicine choices. Breastfeeding offers many health benefits to mother and baby, and these benefits should be considered along with the possible risks of infant exposure to medicine through breast milk.

In 1997, FDA started reviewing the pregnancy and breast-feeding sections of prescription medicine labels and the regulations that describe how the label is written and the information it must include. Based on feedback from government agencies, medical experts, clinicians and the public, FDA developed a new format for pregnancy and breast-feeding sections of medicine labels that will be presented to the public for comment as a proposed rule in the Federal Register.

Scientific guidance

- *Determining the appropriate dose of a drug for pregnant women.* In 2004, we published draft guidance for industry that provides a basic framework for designing, conducting and analyzing pharmacokinetic and pharmacodynamic studies in pregnant women.
- *Evaluating study results on approved drugs when used during pregnancy.* In 2005, we issued our final guidance for FDA reviewers about evaluating the effects of medicines on the growing fetus.
- *Lactation studies in women.* In 2005, we published draft guidance for industry describing a basic framework for designing, conducting and analyzing clinical lactation studies. We reviewed public comments received in response to this publication and held an Advisory Committee Meeting on November 29, 2007 to obtain expert advice.
- *Pregnancy exposure registries.* In 2002, we published a final guidance for industry that provides advice on how to establish a registry that prospectively monitors outcomes of pregnancies in women exposed to a specific drug. The Maternal Health Team is updating this guidance to clarify recommendations on reporting of major and minor congenital malformations, nonteratogenic endpoints, patient recruitment procedures and control group considerations.

Critical Path Initiative

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

Despite recent innovations, many serious and life-threatening diseases still lack effective treatments. In our view, the scientific tools needed to develop medical products have not kept pace with the rapid advances in product discovery. As a result, fewer of the sound ideas spawned in medical laboratories are producing safe and effective treatments.

Because of our unique vantage point, we can work with companies, patient groups, academic researchers and other stakeholders to coordinate, develop and help disseminate solutions to scientific hurdles that are impairing the efficiency of medical product development.

Critical Path Progress in 2007

Developing Critical Path Opportunities Document for Generic Drugs

In May of 2007, we released *Critical Path Opportunities for Generic Drugs*. This document identifies key opportunities to improve standards and methods to evaluate bioequivalence for locally acting drugs. It also helps increase understanding of the manufacturing controls needed to produce complex pharmaceutical formulations with consistently high quality.

Improving warfarin dosing

Because there is wide variation in patient response to this blood thinning drug that may lead to severe consequences of under- or over-dosing, we are involved in two projects.

- We relabeled warfarin in August 2007 to recommend that prescribers consider testing for genetic variants of enzymes that alter the body's ability to metabolize or respond to warfarin. In parallel, we approved the first warfarin sensitivity test, which detects these genetic variants.
- We are developing dosing models that may lead to safer initial dosing for warfarin.

Examining the genetic basis of adverse events

In 2007, the Serious Adverse Events Consortium, a nonprofit partnership among several leading pharmaceutical companies, the FDA and academic institutions, launched initial research programs designed to identify genetic markers that may help predict which individuals are at risk for serious drug-related adverse events. Two areas of initial focus will address drug-related liver toxicity and a rare but serious drug-related skin condition called Stevens-Johnson Syndrome.

Advancing biomarker qualification

The Predictive Safety Testing Consortium is a collaboration of the CPath Institute, 17 pharmaceutical industry partners and FDA. One goal of this consortium is to validate the predictive value of new preclinical biomarkers of toxicity and qualify their use in specific regulatory contexts. In 2007, a set of biomarkers of nephrotoxicity were submitted to FDA for qualification through a pilot process. They were evaluated at the agency to understand evidentiary standards and metrics associated with the qualification of novel biomarkers.

In addition, we are collaborating with a public-private research partnership tasked with discovering, developing and qualifying new biological markers to support new drug development, preventive medicine and medical diagnostics. The Biomarker Consortium includes representation from the Foundation for the National Institutes of Health, FDA, Centers for Medicaid and Medicare Services, NIH and the pharmaceutical, biotechnology, diagnostics and medical device industries.

Identifying indicators of cardiac toxicity

FDA and Mortara Instruments, a manufacturer of electrocardiographic equipment, are working to create a repository for digital ECGs and a suite of tools to enable their efficient review. FDA invited sponsors to upload digital ECGs directly to the repository, where they are made immediately available to the reviewers. Currently, the warehouse contains more than one million ECGs. In addition to supporting our mission to evaluate the effects of drugs on the heart, the repository is an important research resource for future studies to identify improved predictors of cardiovascular risks related to use of medications.

In a second phase of this effort, FDA and an academic research center founded the Cardiovascular Safety and Research Consortium to coordinate and support research projects involving the warehouse.

Developing guidances on advanced clinical trial design

We began developing guidance to facilitate innovations in study design and analysis related to end of Phase 2a meetings, adaptive trial designs and non-inferiority trial designs.

Developing tools for product characterization and manufacturing understanding

The industrialization challenges posed by the demands of physical product design, characterization, scale-up and manufacturing are often little understood outside of FDA and the pharmaceutical manufacturing communities. Many product failures during development are ultimately attributable to problems relating to the transition from laboratory prototype to industrial product. To improve predictability in this area, it is crucial that FDA has both improved technical standards—tests, procedures and reference materials—and improved methods for design, characterization and product manufacture.

A number of studies in these areas were initiated to respond to critical manufacturing science questions.

Pharmacogenomics, personalized medicine

The Critical Path recognizes the importance of pharmacogenomics and encourages its use in drug development. Pharmacogenomics allows health-care providers to identify differences in people's drug-risk-response profiles and predict the best possible treatment options for them.

In 2007, FDA continued laying the groundwork for incorporating pharmacogenomics in our regulatory reviews and into clinical practice. Our activities included:

- Issuing a Draft Companion Guidance to the Pharmacogenomics Guidance on Recommendation for the Generation and Submission of Genomic Data.
- Publishing *Guiding Principles for Joint FDA EMEA Voluntary Genomic Data Submission Briefing Meetings*.
- Posting on our genomics Web site Valid Genomic Biomarkers in Drug Labels.
- Co-authoring *Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice*.
- Initiation of Part 2 of the Microarray Quality Control initiative to identify sources of variability in genomic classifiers derived from microarray gene expression and genome-wide association study data.
- Receiving 12 additional voluntary genomic data submissions from industry.

More information is at <http://www.fda.gov/cder/genomics>.

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 non-clinical and clinical studies

- *Biomarkers for organ damage.* We are identifying, evaluating and establishing relevant protein biomarkers in blood in both animal models and in humans. These will help detect the very earliest damage that can be caused by certain drugs to the heart, kidney, immune system and liver.
- *Biomarkers for inflammation.* To enhance safety within broad segments of patient populations and enable safe development of new drug classes, we are working on the identification and elucidation of associated serum biomarkers and mechanisms responsible for the development of vascular inflammation in specific organ systems.
- *Medicinal plants, herbs.* We established scientific research capabilities in the analyses of medicinal plant and herbal products.
- *Imaging drug targets.* We continue to explore noninvasive imaging technology to extend our long-standing interest in the application of accurate dose-concentration-response principles by viewing drugs and their actions directly at the level of the drug target, rather than indirectly via plasma concentrations.
- *Better use of exposure-response data.* We are developing a standardized approach for using exposure-response information to help evaluate the risks and benefits of drug therapies and recommending dose adjustments in special populations.
- *Pediatric pharmacokinetics.* We are developing a pediatric population pharmacokinetics study design template to facilitate implementation of sparse sample strategies in pediatric drug development.

Biotechnology research

We evaluate therapeutic biotechnology product submissions as well as carry out scientific research related to biologics regulatory issues.

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

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

Informatics and computational safety analysis

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

How our scientific research helps us

Scientists at our own labs in Bethesda and White Oak, Maryland, and St. Louis, Missouri, perform research that helps us:

- Understand how pharmaceutical products are developed and manufactured to ensure quality and safety.
- Study specific characterizations and properties of pharmacological products in order to make sound scientific and regulatory decisions.

- Set standards for specific products based on scientific evaluation.
- Develop appropriate methodology for complex and novel products.
- Determine how best to label products.
- Address various public health issues.
- Study new technology to determine regulatory requirements.

Evaluation of new technologies

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

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

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.

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

Research to support regulatory decision making

Numerous issues arise in the routine review of drug products which require us to conduct some research in order to make scientifically informed decisions regarding the marketing of a product, including its labeling.

The research often serves to provide scientific justification for policy development and enforcement actions. The research conducted in our labs covers the broad spectrum of our responsibilities, including:

- *Application review.* Reviewers will work with researchers to resolve specific questions having to do with a specific product before finalizing decision to approve. For example, we performed basic laboratory tests that encouraged manufacture of Prussian blue as a treatment of people exposed to harmful levels of radioactive materials and poisons and for counter-terrorism agents.
- *Regulatory policy.* Reviewers, research staff and researcher-reviewers will also generate research activities to determine appropriate regulatory policy. Examples include altered stability and performance of split tablets and filtration of biologics to remove viral contamination.

- *Product testing.* Our scientists test marketed products when there is a question of safety or quality, such as the delivery characteristics of a metered dose inhaler to make sure they meet standards.
- *New technology.* Our researchers help us understand new technologies and determine how they will fit into the regulatory scheme. Examples include drug delivery systems using nanoparticles, the toxicity of nanomaterial and the validation of new test methods.
- *Manufacturing.* We conduct research on various aspects of manufacturing to better understand a product's critical attributes and how they affect product quality and product lifecycle. Examples include the ability of critical product attributes to stimulate an immune response and the impact of adhesion variability on transdermal patches.
- *Formulation changes.* We determine how certain changes in formulation, such as different inactive ingredients, affect the safety, efficacy and quality of products.
- *Process analytical technologies.* We research various techniques for process analytical technology, including new spectroscopy methods for characterizing tablets and future follow-on biologics.
- *Mechanism of action.* We research the mechanisms of action of a given product. This knowledge is critical for designing the bioactivity and potency test that is required for all biologics as well as in biomarker development.
- *Biomarkers.* We are developing potential safety and efficacy biomarkers to help understand how products can be better employed.

Counterterrorism biotechnology research

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

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

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

Scientific collaborations

We collaborate on scientific projects in an effort to leverage our knowledge and experience with others because a single institution or firm lacks the resources to conduct some types of research. We have a number of collaborative projects that are being done under:

- Cooperative research and development agreements.
- Material transfer agreements.
- Involvement with various non-profit collaboration groups such as the National Institute for Pharmaceutical Technology and Education and the Product Quality Research Institute.
- Work with academic organizations such as the University of Delaware and Purdue University.

Collaborations bring together experts representing industry, academia and government and cover a wide array of scientific and regulatory issues related to pharmaceutical products. These collaborations help us maintain the high level of science necessary to ensure that all products are safe and effective and of high quality. A number of the Critical Path Initiatives, such as the Biomarker Consortium, are also being done through these collaborations.

Pharmaceutical analysis

We collaborate with other organizations to ensure the availability of high quality standards and calibration materials. We collaborated with state pharmacy boards to evaluate Internet pharmaceuticals. We evaluated the quality of a select group of the most-often-ordered pharmaceutical products from foreign Internet suppliers.

Laboratory support

- We assessed several technologies for rapid identification of drug products and raw materials to guard against counterfeit products. 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.
- We developed methods to evaluate quality attributes of drug products and raw materials by chemical imaging. These properties include polymorphic form, hydration state, stability and purity.

User Fee Program

Americans deserve timely access to potentially lifesaving new drugs as soon as possible once they are proven safe and effective. The Prescription Drug User Fee Act of 1992 received its second five-year extension in 2002, known as PDUFA III. This reauthorization helps us ensure that we have the staff and resources to review applications promptly, and get safe, effective new drugs into the hands of the people who need them. The reauthorization also allows user fees to support some safety activities, both during development and for newly approved medicines. The current user fee law maintains our high review performance goals, includes increased consultations with drug sponsors and provides for earlier feedback on their submissions.

User fee performance

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

- We met or exceeded almost all our performance goals for the fiscal year 2006 receipts.
- We are on track to meet or exceed most user-fee performance goals for the fiscal year 2007.

Continuous marketing application pilot programs

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

- *Pilot 1* allows applicants to submit predefined portions of their marketing applications called reviewable units before submitting the completed application. Each reviewable unit has a six-month goal for issuing a discipline review letter. In 2007, we did not meet our performance goal for reviewable unit submissions.
- *Pilot 2* allows us to enter into agreements with sponsors for frequent scientific feedback and interactions during the clinical trial phase of product development. As of Sept. 30, 2007, there were nine development projects entered in the Pilot 2 program.

More information is available at www.fda.gov/cder/pdufa/CMA.htm.

Drug Safety and Quality

Monitoring Drug Safety

We monitor the use of marketed drugs for new or emerging information about the health risks of these products. As risks are detected, we inform the public and health-care providers so they will have the latest information when making prescribing and use decisions. In addition, we develop policies, guidance and standards for drug labeling, current manufacturing practices, clinical and laboratory practices and industry practices. Our goal is to ensure the greatest benefits of drug therapies while minimizing their risks.

Advertising and Drug Information

It is critical to receive accurate information to ensure the appropriate use of drugs. We regulate the information that comes with an over-the-counter drug. Previously, drug companies promoted their products almost exclusively to physicians. Now companies advertise directly to consumers. We oversee advertising of prescription drugs, whether to physicians or consumers, by ensuring that drug advertisements and other promotional materials are truthful and balanced. Drug advertisements must contain an accurate summary of information about a drug's effectiveness, side effects and circumstances when its use should be avoided.

Protecting drug quality and safety

We also set standards for drug quality and manufacturing processes. We enforce federal requirements for drug approval, labeling, and manufacturing to ensure a safe and effective drug supply. As the pharmaceutical industry has become increasingly global, we cooperate with other nations to harmonize standards for drug quality and approval. We base decisions to approve a drug—or to keep it on the market if new safety findings surface—on a careful balancing of risk and benefit. We also consider the tools we have to help minimize the risks to patients from a drug's use. As all drugs have risks, we tolerate higher risks for drugs that treat serious and life-threatening conditions that have no or few treatment options. We consider many issues both in approving a drug as well as monitoring it after approval including:

- Who will be using the drug and how it will be used?
- Will the drug be used by older people or children?
- Will it be used with other medications leading to side effects from interactions?
- Will it be administered by a physician, or will consumers be able to buy it over the counter?
- How serious and common are the drug's side effects compared to the seriousness of the disease being treated?

Comprehensive oversight of drug safety

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

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

Types of Risks from Medicines

The practical size of premarketing clinical trials means that we cannot learn everything about the safety of a drug before we approve it. 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. Categories of medicine risks include:

- *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.* The drug is administered incorrectly or the wrong drug or dose is administered.
- *Remaining uncertainties.* In addition to rare events occurring in about 1 in 10,000 persons, these include long-term effects and unstudied uses and populations.

Modernizing Drug Safety

We take very seriously our response to safety-related issues raised by consumers, health professionals and academic researchers. We use emerging science and technology to develop better tools for our drug safety program. We are strengthening the drug safety system with three key efforts in science, communications and operations.

Strengthening the science of drug safety

- We are developing scientific approaches to detecting, understanding, predicting and preventing adverse events.
- We are developing and incorporating quantitative tools in the assessment of benefit and risk.
- We are conducting a pilot program to review the safety profiles of selected new molecular entities on a regular basis.

Improving communications

- We are conducting a comprehensive review of current public communication tools and developing a comprehensive risk communication strategic plan.
- We conducted focus group testing with consumers and pharmacists of our risk communication tools.
- We issued a guidance document, “Drug Safety Information-FDA’s Communication to the Public,” in March 2007 which describes our current approach to communicating drug safety information to the public.
- We plan to conduct assessments of the effectiveness of specific risk minimization action plans.
- We established a new advisory committee to help improve communication of drug risks to the public.

Improving operations and management

- We have engaged external management consultants to help us develop a comprehensive strategy for improving organizational culture.
- We made specific organizational and management changes to increase communications among review and safety staff. We have pilot programs to involve safety experts in the application review process.
- We have a central tracking system that enables staff to track the progress and outcome of safety evaluations.

- We created an associate center director position for safety policy and communication, and elevated the Office of Surveillance and Epidemiology to report directly to the center director.
- We are improving the use of advisory committees, including making the selection process of committee members more transparent.

Our response to Institute of Medicine (IOM) report

We requested in 2005 that the Institute of Medicine convene an expert panel to assess the U.S. drug safety system and to make recommendations to improve risk assessment, surveillance and the safe use of drugs. The IOM report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, recognizes specific progress and reform already underway and makes substantive recommendations about additional steps to improve our drug safety program.

In January 2007, we completed our review of the IOM recommendations and issued a response to each of the recommendations. One example of the more than 40 improvements underway is our Risk Communication Advisory Committee (RCAC) comprised of highly qualified individuals who are mostly academicians, several of whom are familiar with the perspectives of patients, consumers and health-care professionals. Recommendations from RCAC will play a vital role in helping people understand and appropriately respond to our health messages. This understanding will significantly bolster our capacity to protect and promote public health.

Drug Safety Communication Channels

We use a broad range of methods to communicate drug safety information to the public. Some of our most common forms of communications are:

- *Professional labeling for prescription drugs.* Summary of essential information needed for the safe and effective use of a drug by health-care providers.
- *Patient-directed labeling for prescription drugs (patient package inserts and Medication Guides).* Summary of essential information needed for safe and effective use of the drug by patients.
- *Over-the-counter “Drug Facts” labeling.* Summary of essential information needed for the safe and effective use of a drug by consumers.
- *Public health advisory.* Information and advice regarding an emerging drug safety issue or other important public health information targeted to the general public.
- *Patient information sheet.* Concise summary in plain language of the most important information about a particular drug. Includes an alert when appropriate to communicate an important and often an emerging drug-safety issue to patients, consumers, lay caregivers and interested members of the general public.

- *Health-care professional sheet.* Concise summary of an important, and often emerging, drug safety issue, with background information about the detection of the issue and points to consider for clinical decision-making by health-care professionals.
- *Alerts on patient information and health-care professional sheets.* Summary of an important and, often, emerging drug-safety issue. Alerts are tailored to the needs of the primary target audience for each type of information sheet. Health-care professionals, patient, consumers, lay caregivers and interested members of the general public require this information.

Prescription drug information

We strive to make prescription drug information more useful and available by using:

- *Revised format for prescription drug labeling.* Our January 2006 final regulation amends the content and format of information in professional labeling for prescription drugs, commonly called the package insert. The new label provides the most important information about new and recently approved prescription drugs and new uses in a format that is better understood, easily accessible and easier for physicians to remember.
- *DailyMed public database of drug information.* The National Library of Medicine will provide an up-to-date electronic repository of all medication labeling so that physicians will have easy access to the latest labeling.
- *Electronic submission of drug labeling.* This allows physicians to quickly search and access specific information they need before prescribing a treatment.

Medication guides

Medication guides are printed information sheets dispensed with some prescription medicines to help patients avoid serious adverse events.

We require medication guides when we determine that any or all of these apply:

- The information is necessary to prevent serious adverse effects.
- Patient decision-making should be informed by information about a known serious side effect.
- Patient adherence to directions for using a product is essential to its effectiveness.

Public health advisories and early communications in 2007

We issued 16 public health advisories and early communications to alert health-care providers and consumers about:

- The dangers, including death, of using *topical anesthetics* for cosmetic procedures.
- A study that was stopped early because *interferon gamma 1b* did not help idiopathic pulmonary fibrosis patients.
- Patients who receive *erythropoiesis-stimulating agents* may have a higher chance of serious and life-threatening side effects including death.
- *Pergolide* being withdrawn from the market due to the potential for heart valve damage.
- *Zelnorm* being withdrawn from the market due to the chance of heart attack and stroke.
- Caution using *cough and cold products* in children under 2 years of age, and the need to properly measure liquids and follow label directions.
- The possibility of heart problems in patients taking *proton-pump inhibitors, omeprazole and esomeprazole*. Later data showed that the risk of heart problems was not confirmed.
- The increased risk of morphine overdose in infants of nursing mothers taking *codeine* who are rapid metabolizers.
- The report of a death of a patient with cystic fibrosis who inhaled *colistimethate*, an antibiotic made for intravenous use, that was compounded by a pharmacy.
- Reports of deaths and life-threatening side effects in patients who incorrectly used *buccal fentanyl tablets*.
- The possibility of an association between the use of *bisphosphonates*, drugs used to treat osteoporosis and atrial fibrillation.
- Results of a study that showed patients who receive the antibiotic *cefepime* may be at increased risk for death compared to patients who receive similar antibiotics.
- Reports of suicidal thoughts, aggressive and erratic behavior, and drowsiness in patients who have taken *varenicline*.
- Important information on the safe use of the *fentanyl transdermal system* to minimize the possibility of life-threatening side effects and death.

Podcasts of public health advisories

We are now broadcasting audio versions of our public health advisories. Our advisories are short, to the point, fact-based and provide emerging safety information about drugs.

In 2007, we produced 12 podcasts. These audio advisories serve as an alternative to finding this information on our Web site, reading about it in the newspapers or hearing about it from patients.

Patient Safety News Broadcasts of public health advisories and early communications

FDA Patient Safety News is a televised series for health-care personnel, carried on satellite broadcast networks aimed at hospitals and other medical facilities across the country. It is also available on FDA's website. The subjects of some stories are the emerging safety information about drugs described in our public health advisories and early communications.

Drug Promotion Review

Information about a drug available to physicians and consumers is critically important for its safe use. We ensure that drug advertisements and other promotional materials are truthful and balanced. We operate a comprehensive program of education, voluntary compliance, surveillance and enforcement for drug advertising and promotion.

Surveillance of drug promotion activities

Drug advertising and promotion must be truthful, fairly balanced and not misleading. When we find advertising and promotion that is not, we issue two types of letters to ensure compliance with our regulations. These are advisory comments when a company requests review of draft promotional materials and regulatory letters resulting from our surveillance.

Regulatory letters citing violations

We issued 20 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 unapproved uses. These were either untitled letters for general violations or warning letters for more serious or repeat violations. Examples of promotional violations include promotion at a Pharmacy & Therapeutics Committee, Internet sites, e-mails, plus traditional materials such as journal advertisements, sales brochures and TV ads.

Launch campaign advisory letters

When requested, we review advertisements and other promotional materials before drug companies launch marketing campaigns that introduce new drugs or new indications or dosages for approved drugs. In 2007, we issued 129 advisory letters to companies regarding their promotional materials for launch campaigns.

Other advisory letters

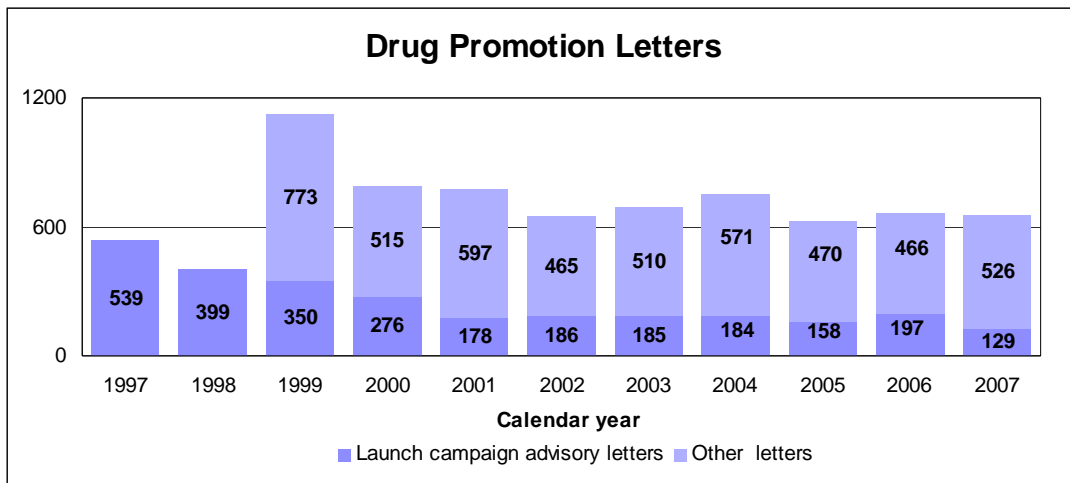
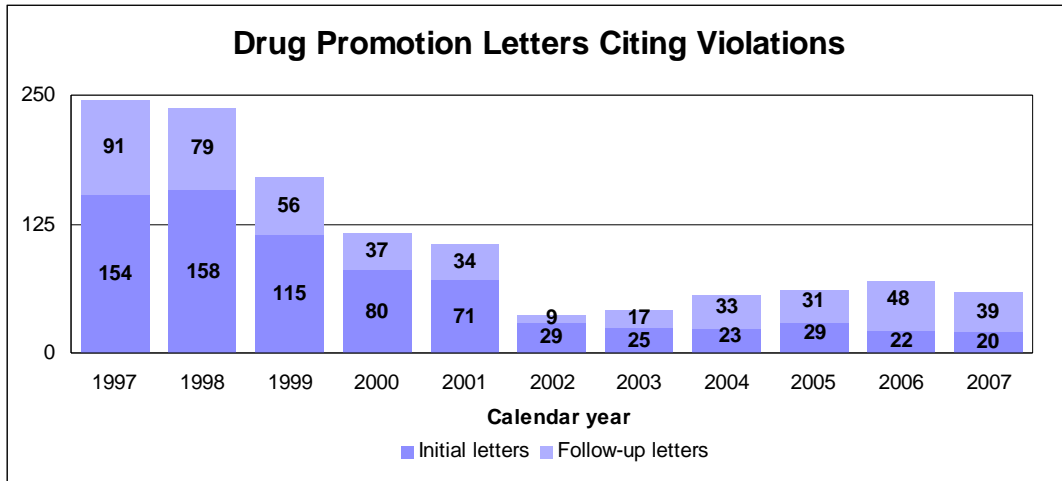
We issued 391 other advisory letters to the industry regarding proposed promotional pieces, both professional and consumer directed. We also issued 135 other types of correspondence to the pharmaceutical industry, such as letters of inquiry, closure letters or acknowledgement letters.

Drug promotion letters in 2007

In 2007, we issued 714 letters concerning drug promotion. These were:

- **59 letters citing violations**
 - **20 initial**
 - **39 follow-up**
- **655 other drug promotion letters**
 - **129 launch campaigns**

- 526 others



Direct-to-consumer promotion

We are conducting research to help develop policy for our oversight of direct-to-consumer advertising. Data from our studies as well as those conducted by consumer groups and other entities shows that direct-to-consumer ads may encourage some patients to seek care for under treated conditions. This often results in patients obtaining treatment for serious medical conditions of which they were unaware. However, physicians and consumers have expressed concerns that direct-to-consumer ads may not always provide a balanced view of the benefits and risks of a product.

FDA Amendments Act of 2007

On September 27, 2007 the FDA Amendments Act of 2007 became law. The act modifies the Food, Drug and Cosmetic Act to specifically address direct-to-consumer prescription drug advertising for the first time. It contains provisions that will change existing requirements for direct-to-consumer prescription drug advertisements and the authority FDA has to oversee this area.

For example, the act gives FDA new authority to require submission of direct-to-consumer television drug advertisements for review before the ads are aired publicly. It also gives FDA authority to seek civil monetary penalties against companies who run false or misleading direct-to-consumer prescription drug advertisements. The act further requires that the statement of risks in broadcast direct-to-consumer advertisements for prescription drugs be presented in a clear, conspicuous and neutral manner, and that print direct-to-consumer drug advertisements include information on how to report adverse drug events to FDA. CDER is working actively to meet its mandate under the various direct-to-consumer drug advertising provisions of the law in the time frames expected.

This act also reauthorized the Prescription Drug User Fee Act (PDUFA) for five more years, through fiscal year 2012. It created a new voluntary user fee program for review of direct-to-consumer prescription drug television advertisements. Under this new program, the pharmaceutical industry would have paid user fees when they voluntarily submitted draft prescription drug television advertisements to CDER or CBER for advisory review. These fees would have enhanced CDER and CBER resources for certain prescription drug promotional review activities. However, the Consolidated Appropriations Act of 2007 failed to provide FDA with the authority to collect user fees for this new program, and as a result it was not able to commence.

Ongoing Direct-to-consumer promotion research

We continue work on three studies to help find the best way or ways to present information in the “brief summary,” the page of risk information in a print ad:

- *Purpose.* The first study will concern the purpose of the brief summary—how do people use it and what topics do they find most useful. This study is underway and we expect to have data collected for this study by September 2008.
- *Content.* The second study will address content issues in the brief summary, including the amount of common side effect information and the inclusion of numerical context.
- *Format.* The third study will examine format issues, such as graphics, layout and font. We expect to have data collected for these two studies by the fall 2008.

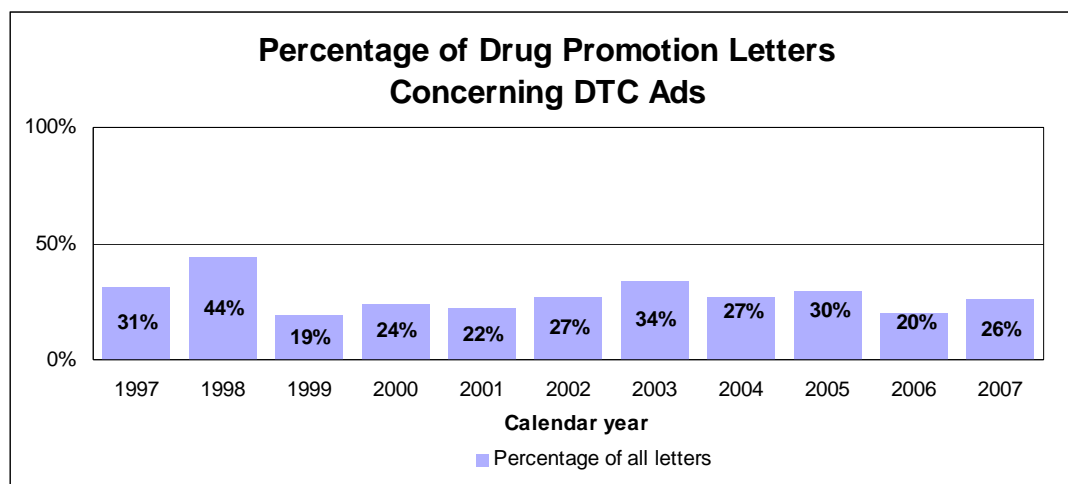
We have designed research to investigate the role of distraction in broadcast television ads. CDER will explore the collective role of the audio, textual and visual portions of the ad in the understanding of the risk and benefit information in ads. This study was

published in the *Federal Register* for comment in August 2007. After extensive revision and external peer review, the second comment period is expected to commence by summer 2008.

New Direct-to-consumer research

We are developing a new study that will investigate the communication of effectiveness information on the main advertising page of print advertisements. By varying the presentation of this information, we will determine which manipulations bring consumers closer or farther away from an independent physician assessment of the effectiveness of the drug product in actual practice. This multi-phase study is in early development.

Direct-to-consumer promotion letters



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

- 2007: 188 (26%)
- 2006: 150 (20%)
- 2005: 203 (30%)
- 2004: 217 (27%)
- 2003: 254 (34%)
- 2002: 188 (27%)
- 2001: 190 (22%)
- 2000: 215 (24%)
- 1999: 247 (19%)
- 1998: 282 (44%)
- 1997: 240 (31%)

Drug Safety Surveillance

We evaluate the safety of drugs available to American consumers using a variety of tools and disciplines. We maintain a system of post-marketing 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 drug reactions, drug-drug interactions and medication errors.

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

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.

Population-based drug safety evaluation

We have established several contracts that give us access to population-based data resources. This enables us to evaluate the use and safety of newly marketed drugs in real world settings. The databases we work with provide healthcare data on more than 20 million persons in the United States in different geographic areas and include special populations, such as children and pregnant women. We also work with a database from the United Kingdom that provides electronic medical record data on nearly 10 million persons receiving their health care from a general practitioner.

We use these databases to:

- Evaluate the extent of drug exposure in the population and the levels of potential risk that may be associated with that exposure.
- Provide a mechanism for collaborative investigations to test hypotheses, particularly those arising from suspected adverse reactions reported to us.
- Enable our rapid access to U.S. population-based data sources to examine patterns of care and their impact on the safe use of drugs.

CDER is developing a guidance on best practices for pharmacoepidemiologic studies of drug safety issues using electronic healthcare data. FDA entered into collaborations with the Veterans Health Administration, the Centers for Medicaid & Medicare, and the Agency for Health Care Research Quality to enable access to their large databases to look at drug effects and evaluate drug safety signals.

Data mining

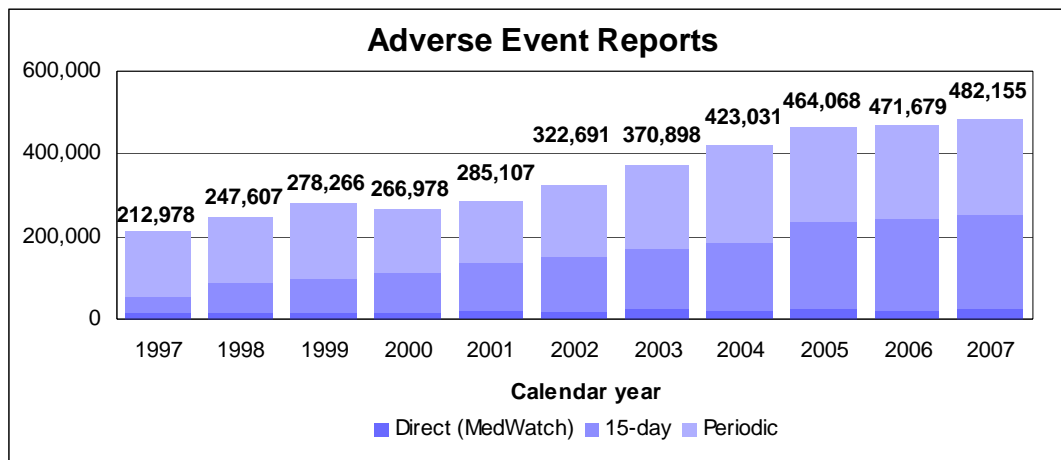
Our safety evaluators and epidemiologists routinely use data mining software for quantitative analysis of drug safety data. Using data mining for drug-event signal generation increases our awareness and understanding of trends and patterns in adverse drug reactions. In 2007, CDER began a pilot project between Office of Surveillance and Epidemiology and Office of New Drug's Division of Cardiovascular and Renal Products to increase post-marketing data mining surveillance of all products within this division.

Adverse Event Reporting System

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

In 2007, we received 482,155 reports of suspected drug-related adverse events from the MedWatch program and from the postmarketing 15-day and periodic safety reports submitted by manufacturers:

- 23,033 MedWatch reports directly from health-care providers and consumers.
- 230,922 manufacturer 15-day reports for adverse events that are both serious and unexpected (not in the approved labeling).
- 228,200 manufacturer periodic reports for adverse events that are both serious and expected or non-serious.



Report types

- *Direct reports to MedWatch.* An individual, usually a health-care practitioner, notifies us directly of a suspected serious adverse event.
- *15-day (expedited) reports.* Manufacturers report adverse events that are both serious and unexpected as soon as possible but within 15 days of discovering the problem.
- *Manufacturer periodic reports.* These report all other adverse events, such as those that are not serious and that are already described in the product's labeling. These reports are submitted quarterly for the first three years of marketing and annually thereafter.

Adverse event electronic submissions

Electronic submission of adverse event reports permits more timely receipt and evaluation at a considerable cost savings for both the FDA and industry. In late 2007, 40 sponsors submitted their 15-day reports electronically, and 11 submitted periodic adverse event reports electronically.

Since electronic submissions began in 2000 for 15-day reports and in 2001 for periodic reports, the number of electronic submissions has grown tremendously each year. Our initiative to encourage electronic reporting continues to make progress and remains a high priority.

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

MedWatch

Safety Information and Voluntary Adverse Event Reporting

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

- Rapidly disseminating new safety information on the internet and providing e-mail listserve and RSS feed notification to health professionals, institutions, the public and our MedWatch partner organizations, 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, medication use errors and therapeutic failure and inequivalence for CDER-regulated drugs and therapeutic biologics. Reports can be filed by mail, fax, telephone or online at www.fda.gov/medwatch/report.htm.
- Educating health professionals— both practitioners and students— 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. We also offer a video self-learning module, "FDA MedWatch and Patient Safety", at:

www.connectlive.com/events/fdamedwatch/

Individual health-care professionals and consumers can sign up for our GovDelivery e-mail notification service, which now has over 92,000 subscribers. We also have 160 MedWatch partner organizations who work with MedWatch to promote FDA's drug safety program. In 2007, these individuals and groups received:

- 102 safety alerts for drugs and therapeutic biologics.
- 25 to 70 safety-related labeling changes for drugs each month, these include important changes to boxed warnings, warnings, contraindications, precautions and adverse reaction sections, and new or updated patient labeling information, medication guides and patient package inserts.

Medication Error Prevention

We review proposed brand names, labels, labeling and packaging to help prevent medication errors in prescribing, dispensing or administering drug products. To ensure the safe use of drugs we avoid brand names that look or sound like the name of existing products.

We review about 2,000 post-marketing reports of medication errors each month. About half are due to error-prone labeling such as similar looking labels and labeling, poor package design, confusing instructions for use and confusing names. We investigate the causes and contributing factors of these errors and recommend revisions to the label, labeling and/or packaging of these products to avert further error.

In January 2007, we conducted a public workshop to explore how labels on intravenous drug products could be designed to minimize medication errors and to define the limitations faced by the different stakeholders. The workshop was an opportunity to hear from all stakeholders in order to gain a better understanding of the medication error issues they face and the challenges they have in making changes to improve patient safety.

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.

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

Drug Recalls and Safety-Based Withdrawals

Recalls

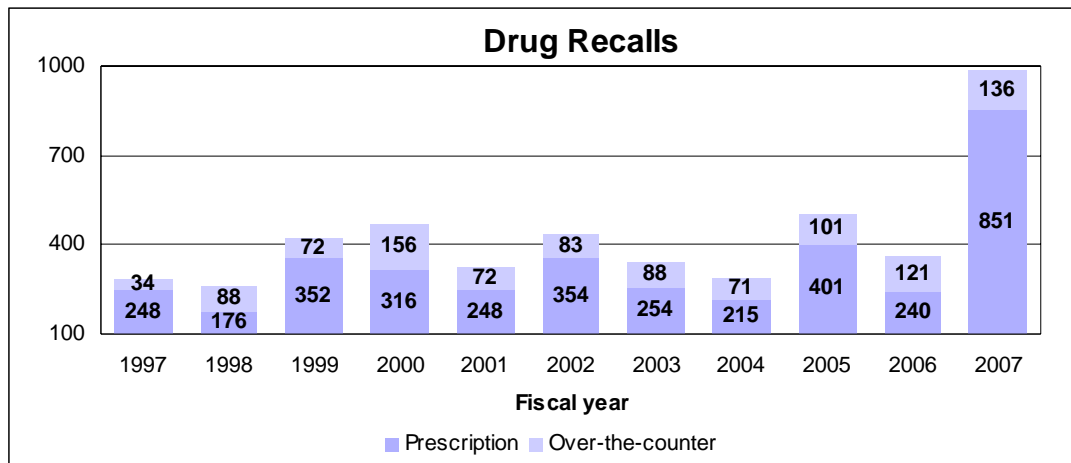
In some cases, a drug product must be recalled due to a problem occurring in the manufacture or distribution of the product that may present a significant risk to public health. These problems usually, but not always, occur in one or a small number of batches of the drug. In other cases, a drug is determined 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.

It should be noted that FDA has statutory authority to recall biologics and devices but not drugs. There are occasions where FDA has requested a recall and the company has refused. In those instances, FDA may decide to pursue an appropriate regulatory action.

Drug recalls in fiscal year 2007

- 136 over-the-counter drugs
- 851 prescription drugs



How we coordinate drug recalls

We coordinate drug recall information, assist manufacturers or distributors in developing recall plans, and coordinate the preparation of health hazard evaluations with medical officers in the review divisions to determine the risk posed to the public by products being recalled. Recall actions are classified in accordance with 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. We also work with our field offices to conduct follow-up inspections where needed to investigate the reasons for the recall in order to mitigate the opportunity for reoccurrence.

Number of recalls by fiscal year

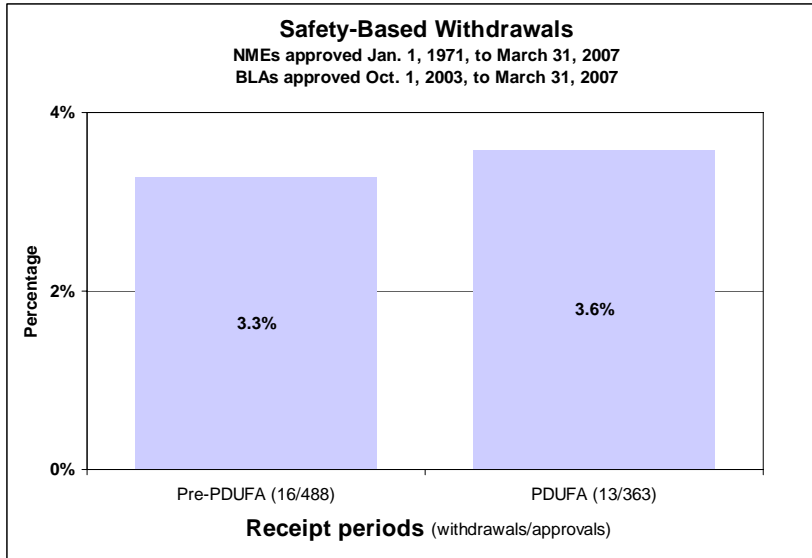
Different factors can affect the number of recalls in any one year. For example, one firm had more than 100 recalls in 2005, which caused a significant increase for that fiscal year. In 2007, one repacker caused over 670 recalled products. This event caused 2007 to be the highest year for recalls that CDER has recorded.

Top reasons for drug recalls in fiscal year 2007

- Correctly labeled product in incorrect package
- Temperature abuse
- Subpotent (single-ingredient drugs)
- Chemical contamination
- Impurities/degradation products
- Failed USP dissolution test requirements
- Labeling illegible
- Marketed without an approved New Drug Application/abbreviated New Drug Application
- Lack of assurance of sterility
- Label mix-up
- Stability data does not support expiration date
- Microbial contamination of non-sterile products

Safety-Based Drug Withdrawals

In some cases, there is an intrinsic property of a drug that makes it necessary to withdraw the drug from the market for safety reasons. Because there has been concern expressed that sponsor user fees might have affected FDA decisions, the rates of withdrawal before and after user fees have been compared. The rates of safety-based withdrawals of new molecular entities are similar for the period before we collected user fees and for the period, beginning Oct. 1, 1992, after we began to collect user fees. The time periods are based on when we received an application rather than when we approved it. Beginning Oct. 1, 2003, approvals include new therapeutic biologics. Applications exempt from user fees are also counted.



No safety-based drug withdrawals in 2006

There were no market withdrawals of drugs or biologics for safety reasons in calendar year 2006.

Safety-based drug withdrawals in 2007

As of Aug. 1, 2007, there were two market withdrawals of NMEs for safety reasons:

- *Pergolide*, approved in 1988, a drug used to treat Parkinson's disease, was voluntarily removed from the market because of the risk of serious damage to patients' heart valves.
- *Tegaserod maleate*, approved in 2002, a treatment for irritable bowel syndrome, was voluntarily discontinued from marketing on March 30, 2007, due to cardiovascular risk findings. While the manufacturer continued to study the drug, we announced a program to allow access to the drug by adult women under age 55 who are identified by their physicians as appropriate candidates for the drug.

Compliance Oversight

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

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

We identify, evaluate and analyze inspection findings for trends in deficiencies. We publish guidances to assist drug manufacturers and distributors 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 manufacturers are acceptable to supply active pharmaceutical ingredients or finished drug products to the U.S. market.

Risk-based surveillance sampling of drugs

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

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

Criteria for risk-based sampling

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

Misbranded drugs, unapproved drugs, and unsubstantiated claims

We often encounter misbranded, unapproved, and fraudulent products that make unsubstantiated claims. Consumers may use these products inappropriately. They may use a fraudulent product for treating a serious disease in place of an approved treatment, or they may delay the use of a proper treatment in favor of a fraudulent remedy. Fraudulent products may also contain toxic compounds or other hazardous substances that have the potential to cause serious illness, injury or even death. For these reasons,

products that are unapproved, mislabeled, fraudulent, or make unproven claims may pose a significant health risk.

Protecting consumers from unapproved, misbranded or fraudulent drugs

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

We may also take steps to warn the public about unapproved, misbranded and fraudulent products. These steps include issuing press releases and MedWatch alerts to warn consumers about the potential health risks associated with these products. For example, in 2007:

- We issued a warning letter to a firm that marketed several transdermal vitamin therapy products for the prevention and treatment of diseases such as cancer, heart disease, osteoporosis and diabetes.
- We also continued to take enforcement actions against firms that marketed products promoted as dietary supplements for treating erectile dysfunction and enhancing sexual performance, and containing potentially harmful undeclared prescription drug ingredients. Additionally, we continued our efforts to warn consumers about these illegal products by issuing press releases, consumer alerts, articles in consumer oriented publications, and posting information on the FDA website.

Compounded drugs

We generally defer to state authorities regarding the regulation of traditional pharmacy compounding. Traditional pharmacy compounding involves a pharmacist's customizing of reasonable quantities of drugs in response to a practitioner's prescription for an individual patient with medical needs that cannot be met by FDA-approved drugs.

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

Furthermore, some pharmacies compound drugs that are contaminated, dangerously weak or strong. Of special concern are the compounding of sterile and more complex dosage forms, such as extended-release drugs, as mistakes in their preparation often lead to serious defects and patient injury. Our steps to protect the public from these products

include issuing enforcement letters, referring complaints to state authorities and providing support when states ask. We also pursue enforcement actions, such as seizure of violative products and injunctions against firms and responsible individuals.

Compounding enforcement in 2007

- We warned a firm to stop manufacturing and distributing thousands of doses of unapproved inhalation drugs under the guise of compounding. In a letter to the firm, we identified a range of serious concerns including inadequate quality control, concerns about potency and compounding copies of FDA-approved drugs.
- We sent a warning letter to a repacker of active pharmaceutical ingredients (APIs) that was distributing the API domperidone for use in pharmacy compounding. FDA is concerned with the public health risks associated with domperidone. Domperidone is not an ingredient in any FDA-approved drug. FDA does not sanction its use in pharmacy compounding and will not exercise its enforcement discretion with respect to compounded drugs containing domperidone.
- We warned a firm to stop manufacturing and distributing thousands of doses of injectable drugs under the guise of compounding. FDA inspection revealed that the firm received over 70 adverse event reports associated with the use of its betamethasone injectable drug. In a letter to the firm, we identified a range of serious concerns including inadequate quality control, concerns about potency, and compounding copies of FDA-approved drugs.

Drug Imports

We take steps to assure that drugs imported or offered for import into the United States are approved, when required, and do not pose a safety hazard to consumers.

These steps include:

- Preventing entry of products that have been removed from the U.S. market for safety reasons.
- Implementing controls over the importation of drugs, such as human growth hormone, which may pose unique risks to consumers who obtain them outside the legitimate drug distribution system.

Drugs sold without required applications

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

We estimate that there are several thousand illegally marketed drug products in the United States, comprised of several hundred unique molecules. In June 2006, we issued a guidance document, *Marketed Unapproved Drugs—Compliance Policy Guide*, that

clearly articulates our expectation that manufacturers of products requiring FDA approval submit applications to show that their products are safe and effective.

The guidance outlines our enforcement policies aimed at efficiently and rationally bringing all such drugs into the approval process and protecting the public health without imposing undue burdens on consumers or unnecessarily disrupting the market. It also creates incentives for manufacturers of marketed, unapproved drugs to seek approval of their products, a process essential to ensuring that physicians prescribe and patients take drug products that are safe, effective, properly manufactured and accurately labeled.

Unapproved drug actions

In 2007 we took action against the following classes of unapproved drugs:

- Trimethobenzamide suppository drug products, used to treat nausea and vomiting in adults and children but lacking evidence of effectiveness.
- Products containing ergotamine, which are used to treat vascular headaches, including migraines. Most of the companies, in addition to marketing these products without FDA approval, omitted from the drugs' labeling critical warnings regarding the potential for serious, possibly fatal, interactions with certain other drugs.
- Timed-release drug products containing guaifenesin, which are commonly used to relieve cough symptoms. These products lack assurance, through the FDA approval process, that the product releases its active ingredients safely and effectively over the entire time in which the product is intended to work.
- Prescription drug products containing hydrocodone, a narcotic widely used to treat pain and suppress coughs. The action did not affect other hydrocodone formulations, which have FDA approval.

By comparing agency data with a number of private drug data files, we have improved our ability to accurately identify unapproved drug products in the U.S. market. This enhances our ability to develop a rational strategy for bringing all such drugs into the approval process and protecting the public health.

Regulation of OTC drugs

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

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

We monitor the statements that accompany these products along with their formulations to make sure that they comply with the appropriate application or final monograph. We also monitor the formulations, labeling and promotional materials associated with over-the-counter drugs marketed without an approved application or final monograph,

including fraudulent drugs, and take enforcement actions against these products where necessary.

- We issued warning letters to two prominent firms marketing OTC topical antimicrobials with unsubstantiated claims not covered by FDA's OTC drug review and without an approved application. Given the extensive advertising and promotion of one such product for use by school children, we issued a press release to alert consumers to the violative nature of that product.
- Following reports of consumer confusion and/or overdose involving several leading brand name and private-label OTC cough-cold drug products packaged with dosage delivery cups, we found that the markings on the cups were inconsistent with the labeled dosage directions. We engaged in discussions with the three manufacturers of these products and all initiated nationwide recalls to consumers.

Assessing Data Quality, Research Risks

When obtaining data about the safety and effectiveness of drugs, sponsors rely on high-quality laboratory studies and human volunteers to take part in clinical studies. Protecting volunteers from research risks is a critical responsibility for us and all involved in clinical trials.

We perform on-site inspections to protect the rights, safety 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 contract research organizations; laboratories that obtain data; and sites performing bioequivalence studies in humans and preclinical studies in animals.

Our programs to protect volunteers are challenged by increases in the number of clinical trials; the number of sites participating in each clinical study; the types and complexity of products undergoing testing; and the increased number of trials performed in countries with less experience and limited or no standards for conducting clinical research.

Sponsors and clinical investigators protect volunteers by ensuring that:

- Clinical trials are appropriately designed and conducted according to good clinical practices.
- Research is reviewed and approved by an institutional review board.
- Informed consent is obtained from participants.
- Ongoing clinical trials are actively monitored.
- Special attention is given to protecting at-risk populations, such as children and the mentally impaired.

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

Inspections for data quality, research risks in 2007

We conducted 767 inspections in 2007:

- 369 U.S. clinical investigators
- 104 foreign clinical investigators
- 103 institutional review boards
- 23 sponsors, monitors, or contract research organizations
- 46 non-clinical laboratories
- 122 in-vivo bioequivalence studies

The top five deficiencies found during inspections of clinical investigators in 2007 were:

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

International inspections of clinical research

We conducted 104 inspections of clinical research in 28 countries in 2007.

We participate in international efforts to strengthen protections for human volunteers worldwide and encourage clinical investigators to conduct studies according to the highest ethical principles. This includes our work with the International Conference on Harmonization.

Compliance actions in 2007

The Bioresearch Monitoring Program issued 15 warning letters in 2007: ten to clinical investigators, three to institutional review boards, one to a GLP facility, and one to a bioequivalence testing facility. We also initiated the disqualification process for five clinical investigators due to repeated or deliberate violations of the regulations or the submission of false information to the sponsor or FDA.

Bioresearch Monitoring Council

The Bioresearch Monitoring Council was established to coordinate activities and update the program across the five centers in FDA. The Council is composed of representatives of the five centers, Office of Regulatory Affairs (ORA) and the Office of Chief Council, and is conducted under the auspices of the Critical Path Program. The Division of Scientific Investigations is an active member of the Council. We participate on working groups that are charged with updating the compliance policy guides, guidances for clinical investigators, rewriting regulations for the bioequivalence program and the clinical testing of investigational products not conducted under an investigational new drug application. We also participated in the development of guidance for institutional review boards and a guidance regarding questions about the need and application of required information.

We participate as instructors in training courses for ORA investigators for bioresearch monitoring inspections, both at the introductory level and in advanced courses. The courses provide a review of the relevant regulations for each of the five bioresearch monitoring programs, case study review and evaluation and updates on program policies.

Internet resources

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

Drug Registration and Listing System

We maintain a database of human drug products in commercial distribution in the United States and all the domestic and foreign establishments involved in their manufacture, repackaging or re-labeling. The Drug Registration and Listing System provides a searchable database for:

- Manufacturers of a specific product.
- Products manufactured by a specific firm.
- Products with a specific ingredient or dosage form.
- Foreign manufacturers in a specific country.

This information helps us administer many key programs, including:

- Postmarketing surveillance.
- User fee assessments.
- Counterterrorism and emergency response.
- Monitoring of drug shortages and availability.
- Identification of products marketed without an approved application.

- Identification of sites for use in our risk-based inspections for good manufacturing practices and adverse drug events.
- Identification of drugs marketed in violation of the law for use in public alerts and enforcement actions.
- In conjunction with commercial databases, identification of marketed unapproved drugs.

Under the FDAAA, an electronic system will replace the current system of submitting paper forms for registration and listing.

Drug Registration and Listing System statistics for 2007

- 14,500 establishment registration forms processed.
- 43,200 drug product listing forms processed.
- approximately 19,500 inquiries answered.

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. We provide guidance to explain our current thinking on certain scientific and technical issues.

Prioritizing sites for inspection

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

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

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

Good manufacturing practice enforcement

We have acted under our regulatory enforcement program to address products not manufactured under current good manufacturing practice regulations. We provide expert technical support that employs science and risk-based principles in applying these regulations. As a result, many corrections are achieved voluntarily or through administrative means. Some corrections, though, require the involvement of the judiciary system. Notable 2007 actions include:

- An inspection of a large repackaging firm uncovered violations whereby some products were mislabeled and some products could have been contaminated by residues from other products packaged using the same equipment. Although the firm recalled many products, FDA officially warned the firm about the importance of implementing promised corrections due to the large scope of their operations—distributing to 47 states and over a 1.4 million patients—and to provide notice should future regulatory action be necessary.
- A manufacturer of highly-potent drugs was warned to improve their equipment cleaning procedures to prevent cross-contamination, and of the importance of organizing operations and drug storage areas to reduce the chance for mix-ups. The firm was also cautioned about the need to properly design and monitor their sterile product filling room.
- A large manufacturer of transdermal drugs was warned about the need to establish a scientifically-sound product specification and of the importance of monitoring all product specifications from batch-to-batch. The firm recalled batches that were not performing well and that were associated with complaints by consumers and health-care practitioners.
- Despite promised corrections, FDA warned a manufacturer of generic prescription drugs about the importance of properly documenting and investigating laboratory deviations and unusual test results.

Domestic drug plant inspections

In fiscal year 2007, FDA field office inspections included:

- **289 preapproval inspections in support of:**
 - 145 new drug applications
 - 177 generic drug applications
- **1,119 current good manufacturing practice inspections**
For these, we approved 15 actions:
 - 1 seizure
 - 14 warning letters
- **67 medical gas inspections**
We reviewed 67 medical gas inspections and approved two warning letters.

Biologics license inspections

Our experts conduct preapproval inspections in support of biologics license applications and supplements to them. In fiscal year 2007, there were:

- 10 domestic inspections
- 2 foreign inspections

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

- 90 supplements for facilities that did not require an inspection
- 23 annual reports

We held 43 meetings with industry.

Foreign drug inspections

There were a total of 333 inspections. Of these, 208 were PAI/GMP; 89 were PAI only; 24 were GMP; 6 were therapeutic drug product (GMP); and 6 were for cause inspections in 2007.

Council for Pharmaceutical Quality

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

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

Outreach on Drug Manufacturing

We published one final and two draft guidance documents that explain our current thinking on certain scientific and technical areas. Guidance documents that were issued to communicate proactively FDA's cGMP (current Good Manufacturing Process) expectations to the pharmaceutical industry include:

- “Testing of Glycerin for Diethylene Glycol.” This final guidance alerts pharmaceutical manufacturers, pharmacy compounders, repackers and suppliers to the potential public health hazard of glycerin contaminated with diethylene glycol (DEG), a poison. FDA has received and continues to receive (most recently in October 2006) reports about fatal DEG poisoning of consumers who ingested medicinal syrups, such as cough syrup or acetaminophen syrup, that were manufactured with DEG-contaminated glycerin. This guidance provides

recommendations that will help pharmaceutical manufacturers, repackers, and other suppliers of glycerin, and pharmacists who engage in drug compounding, avoid the use of glycerin that is contaminated with DEG and prevent incidents of DEG poisoning.

- “The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 - Good Manufacturing Practice (CGMP).” This draft guidance is intended to aid drug manufacturers (including ancillary testing laboratories) in the use of mechanical calibration as an alternate approach to the use of calibrator tablets in calibrating an apparatus used for dissolution testing. This guidance provides references to information on critical tolerances that should be achieved with mechanical calibration.
- “Q10 Pharmaceutical Quality System.” This draft ICH (International Conference on Harmonization) document establishes a new ICH tripartite guideline describing a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System. ICH Q10 describes one comprehensive approach to an effective pharmaceutical quality system that is based on International Organization for Standards concepts, includes applicable GMP regulations, and complements ICH Q8 “Pharmaceutical Development” and ICH Q9 “Quality Risk Management.” ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. The content of ICH Q10 that is additional to current GMP requirements is optional.

External Inquiries Program

We communicate our policies and guidance through our External Inquiries Program. Through this program, we coordinate receipt, assignment and response to a large number of foreign and domestic inquiries. Topics ranging from policy issues to current good manufacturing practice questions are covered. In fiscal year 2007, we provided responses to 667 external inquiries.

Drug Quality Surveillance Systems

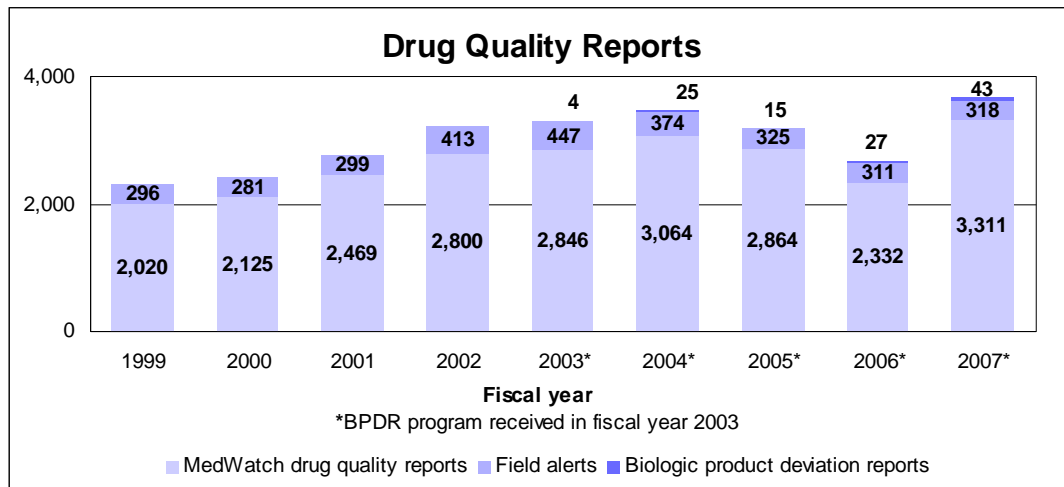
Our reporting tools help us rapidly identify significant health hazards and quality problems associated with the manufacturing and packaging of medicines. Problems that may affect a medicine’s safety, purity or potency may occur during manufacturing, processing, packing, labeling, storage or distribution.

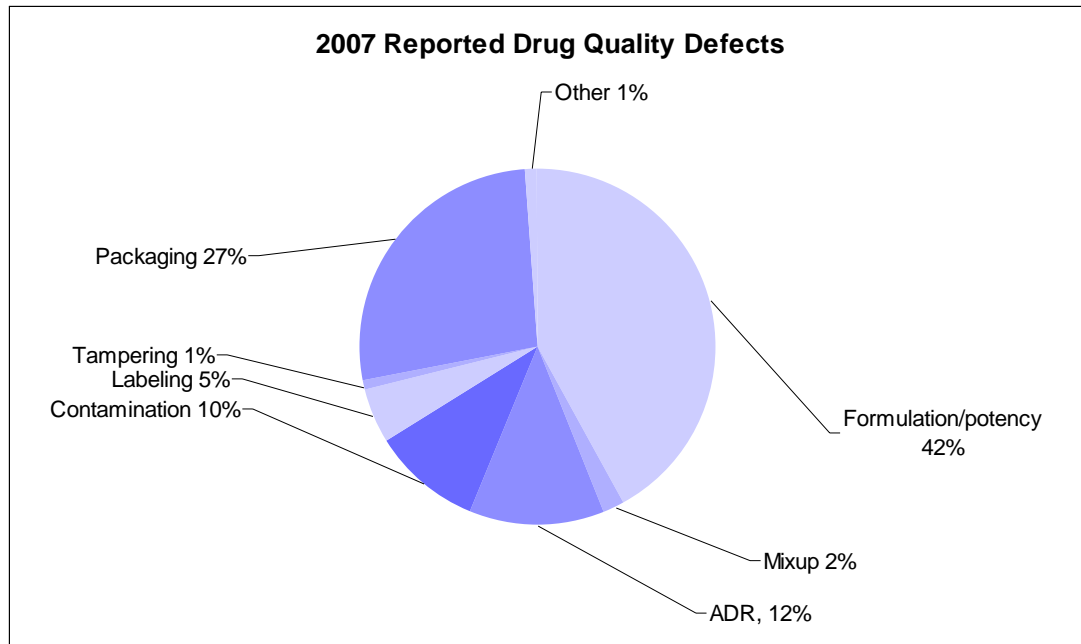
We evaluate reports and FDA field inspections to identify specific firms with manufacturing quality problems with the most potential impact on public health. We target these candidates for inspection and further product sampling and laboratory analysis. We recommend appropriate corrective actions based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

Drug Quality Reports

Types of reports

- *Drug Quality Reporting System.* Through MedWatch, we receive reports from consumers and health-care professionals of observed and suspected product quality defects. Our central reporting system assists us in evaluating and prioritizing these data to identify potential manufacturing quality problems and industry trends.
- *Field Alert Reports.* Applicant holders are required to promptly notify FDA district offices about possible quality and labeling problems that may represent a safety hazard. Experts in FDA district offices evaluate the reports and conduct further investigations when needed.
- *Biological Product Deviation Reports.* Licensed manufacturers are required to report any event associated with the manufacturing of a therapeutic biological that may affect its safety, purity or potency.





Postmarketing Adverse Event Reporting Compliance

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

Risk-based inspections

We inspect drug firms’ adverse event reporting based upon risk criteria associated with specific drug products and corporate performance. These include newly marketed drugs, emerging safety signals, previous violations and corporate transitions.

In fiscal year 2007, our field investigators inspected 77 domestic and seven foreign firms to assess compliance with our regulations for adverse event reporting. We sent two firms official notification that they had significant uncorrected deficiencies. We were able to work with 34 firms to obtain voluntary correction of deficiencies identified by our monitoring.

Outreach and education

In addition to our inspectional program for adverse event compliance, we improve safety reporting through educational presentations to industry. Our educational activities include formal presentations at global industry meetings and training for FDA field investigators.

These activities provide industry with a direct opportunity to expand its understanding of reporting requirements and best practices in drug safety, and alert industry to pending regulatory changes. These meetings also serve to expand our own knowledge of industry’s worldwide pharmacovigilance activities.

Drug Quality System

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

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

Our vision for “desired state” in manufacturing

The desired goals of regulating manufacturing for both the industry and FDA for all products are:

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

New drug quality assessment

Our chemists have transformed drug quality assessment from a checklist review to a scientifically sound, risk-based process. Their mission is to:

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

Biotechnology product quality assessment

We are also in the process of implementing the concepts of quality by design for biological products. The new process will closely follow the tenets already established for new drugs. We are in the process of designing a similar pilot program that will help us in developing a process for future submission and review of quality-by-design information in biologic license applications.

Generic drug quality assessment

We have developed a question-based review for quality evaluation of generic drug applications that is focused on product and process design and understanding. In January 2007, we fully implemented the initiative.

- We piloted and discussed the questions to determine how best to ensure that the quality-by-design applications would be beneficial both to the sponsors and to us in addressing quality-by-design concerns.
- We posted on the internet two models of the quality overall summary portion of an application and a frequently asked questions document to help generic drug sponsors implement quality by design and prepare high quality applications.
- We offered industry three workshops on how to prepare an effective quality overall summary and a generic drug basics course. We and the generic drug industry have held numerous teleconferences and Webcast meetings to discuss the progress of question-based review and to explain our expectations.

Focus on key product attributes for safety, efficacy

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

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

Quality-by-design pilot program

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

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

- Perform a risk-based assessment of product quality and process performance.
- Consider an applicant's proposal for regulatory flexibility in setting product specifications and post-approval changes.
- Better understand information that is available for better assessing quality of products.

Workshop explores drug quality system

We have held several scientific workshops for industry to explore how we can achieve the new drug quality system. We worked with industry scientists to:

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

Process analytical technology

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

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

We received a number of applications and manufacturing supplements in 2007 that incorporated process analytical technology into their manufacturing processes. More information on process analytical technologies can be found at <http://www.fda.gov/cder/OPS/PAT.htm>.

Counterterrorism, Emergency Response

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

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

Emergency Preparedness and Response

- CDER assisted in the development of the content for the "Radiation Event Medical Management" website available through the National Library of Medicine, at <http://remm.nlm.gov>. This is an internet-based diagnostic and treatment toolkit designed for health care providers, primarily physicians, who may have to provide medical care during a radiation incident.
- We played an extensive role in the October 2007 Top Officials 4 (TOPOFF 4) counterterrorism exercise, facilitating the issuance of notional emergency use authorizations for radiation countermeasures. More than 50 CDER participants played a role in the exercise.
- CDER's Office of Counterterrorism and Emergency Coordination established emergency coordinator positions and an emergency operations center to give the Center around-the-clock emergency management capability.

Facilitating medical countermeasure development

- We finalized our work with the Centers for Disease Control and Prevention on the ongoing human trials of gentamicin in plague in Africa. We continue to work with the National Institute of Allergy and Infectious Diseases and the U.S. Army Medical Research Institute of Infectious Disease on monkey studies of gentamicin, ciprofloxacin, levofloxacin, ceftriaxone and doxycycline in pneumonic plague.

- FDA announced the SNS labeling rule in the Federal Register on Friday, December 28, 2007. The interim final rule provides flexibility in labeling requirements for FDA-regulated medical products in the SNS. CDER's Office of Counterterrorism and Emergency Coordination participated in drafting this rule and is CDER's point of contact for SNS issues.
- CDER is fully engaged with HHS's Public Health Emergency Medical Countermeasure Enterprise (PHEMCME) (<http://www.hhs.gov/aspr/barda/phecme/index.html>). The Enterprise's mission is to define and prioritize requirements for public health emergency medical countermeasures; integrate and coordinate research, early- and late-stage product development and procurement activities addressing the requirements; and set deployment and use strategies for medical countermeasures held in the SNS. CDER subject matter experts served on the PHEMCE Biological, Chemical, and Radiological/Nuclear Working Groups and helped draft requirements papers for medical countermeasures.

Pandemic influenza preparedness

- We participated in several departmental and agency working groups and task forces to develop strategic plans for response to an influenza pandemic. The FDA Pandemic Influenza Preparedness Strategic Plan was posted in March 2007 and is available at http://www.fda.gov/oc/op/pandemic/strategicplanupdate03_08.html.
- CDER approved a supplemental new drug application for Tamiflu[®] (oseltamivir phosphate) Capsules that provides for an extension of the expiration dating from five years to seven years for 30 mg, 45 mg, and 75 mg dosage forms.

Counterterrorism guidances published in 2007

- The draft *Guidance for Industry Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention*, <http://www.fda.gov/cder/guidance/7423dft.pdf>, was issued November 2007.
- *Emergency Use Authorization of Medical Products*, <http://www.fda.gov/oc/guidance/emergencyuse.html>, was issued July 2007. This FDA guidance explains policies for authorizing the use of an unapproved medical product or unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces, or a significant potential to affect national security.

International Activities

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

President's Emergency Plan for AIDS Relief

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

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

We are encouraging manufacturers to submit applications for fixed-dose combination and co-packaged versions of previously approved antiretroviral therapies. Tentative approval, whether for a new drug application or a generic drug application, will be the regulatory mechanism by which low-cost versions of innovator drugs sold in the developed world will become eligible for purchase under the emergency plan. Our tentative approval means that a drug meets our standards for safety, efficacy and quality, but that existing patents or exclusivity prevent them from being sold in the United States.

We have an expedited review process to ensure that the United States could provide safe, effective and affordable quality drugs to developing countries. We encouraged U.S. and foreign firms who were developing generic drugs to treat HIV disease to apply under the president's plan. To meet the plan's approval timelines, our generic drug reviewers implemented many process changes, including a rolling review approach. Our average review time for these applications has been six months. We lack information about most clinical laboratories and manufacturing sites associated with the products seeking approval under the emergency plan. Therefore, we are engaged in outreach activities, manufacturer assistance, inspections and postmarketing monitoring.

15 countries in the President's plan

- Botswana
- Cote d'Ivoire
- Ethiopia
- Guyana
- Haiti
- Kenya
- Mozambique
- Namibia
- Nigeria
- Rwanda

- South Africa
- Tanzania
- Uganda
- Vietnam
- Zambia

As of December 20, 2007, 58 generic drugs were eligible for purchase under the president's plan. We had fully approved four generic drug products and tentatively approved another 54. More information is available at www.fda.gov/oia/pepfar.htm.

Information-Sharing Agreements

With enhanced cooperation among regulators around the world, FDA has entered into international agreements in which we play a critical implementation role. Below is 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.

Countries:

- Australia
- Belgium
- Canada
- Denmark
- European Union
- France
- Germany
- Ireland
- Israel
- Japan
- Mexico
- Netherlands
- Singapore
- Sweden
- Switzerland
- South Africa
- United Kingdom

Organizations:

- European Medicines Agency (EMA)
- World Health Organization (WHO)

Examples of our agreements

Japan and Australia

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

European Medicines Agency

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

Mexico and Canada

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

Switzerland

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

International regulators forums

Over the years, CDER has been privileged to host many of our international colleagues interested in learning about our drug review process. In September 2005, the CDER Forum for International Drug Regulatory Authorities was established for the exchange of drug regulatory information between CDER and its counterpart agencies in other countries. Offered every spring and fall, it provides information about the U.S. drug regulatory processes in an organized and integrated manner. It explains the role of CDER as well as the science, technology, regulations and processes used to do our work.

The fifth forum was offered in October 2007. As of that date, we had provided information about the U.S. drug regulatory processes to 171 regulators from 50 countries. Our materials are posted on the Internet so participants can share what they have learned with their colleagues; www.fda.gov/cder/audiences/iact/forum/default.htm .

Assuring International Trade Quality

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

Drug exports

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

Drug imports

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

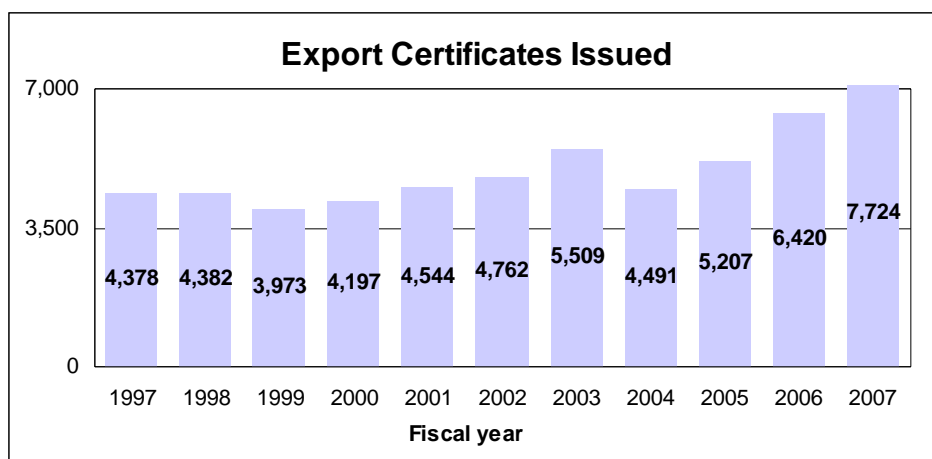
- *Enforce the law.* With FDA's field force, we enforce legal requirements determining which drug products may be imported by manufacturers, distributors and consumers.
- *Identify and interdict illegal drugs.* We take steps to ensure that imported drugs are not counterfeit, unapproved, adulterated or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

Foreign inspections

- **289 preapproval inspections in support of:**
 - 145 new drug applications
 - 177 generic drug applications
- **238 current good manufacturing practice inspections**

For most foreign inspections, both a cGMP and a preapproval inspection take place and are counted twice, once under each inspection program. We reviewed 208 inspection reports for foreign establishments to ensure compliance with good manufacturing requirements and to determine capability of producing drugs named in applications. Regulatory actions included five warning letters, two untitled letters, four import alerts and several regulatory meetings.

Export certificates



We issue export certificates that verify drug products being exported:

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

Harmonization

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

The drug regulatory systems in all three regions share the same fundamental concerns for the safety, efficacy and quality of drug products. Before ICH, many time-consuming and expensive technical tests had to be repeated in all three regions.

The ICH goal is to minimize unnecessary duplicate testing during the research and development of new drugs. The ICH process results in guidance documents that create consistency in the requirements for product registration in the three regions.

Harmonized guidances

We publish International Conference on Harmonization documents as guidances to industry at on the topics of drug safety, efficacy and quality. These guidances may be found at: www.fda.gov/cder/guidance/index.htm.

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

Electronic Common Technical Document

Electronic submissions using the eCTD can be used to submit all applications and related submissions such as promotional materials and adverse events. Among other things, the eCTD allows reviewers to:

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

Communications

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.

Public participation

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

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

- 23 advisory committee meetings.
- Three public workshops.
- Six public meetings.

Stakeholders in drug review, drug quality and safety

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

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

Consumer, industry outreach

- *Trade press.* We responded to over 1,700 telephone and e-mail requests from the specialized press for the pharmaceutical industry.
- *General information requests.* We answered nearly 40,000 telephone inquiries, about 67,017 e-mails and 789 letters from consumers, health professionals and industry. We responded to all phone calls and e-mails within 48 hours and letters within 30 days.
- *Support to FDA field offices.* We had over 800 requests from FDA field offices for information.
- *Videoconferencing.* We held 229 domestic and foreign videoconferences for academia, industry and associations.
- *Compliance information requests.* We responded to nearly 6,400 compliance inquiries and concerns from drug sponsors, clinical investigators, institutional review boards, industry, consumers, advocacy organizations and other government agencies.

Outreach for revised Rx drug labeling format

Our 2007 requirement provides that labels for new and recently approved prescription drugs and new uses be presented in a format that is better understood, more easily accessible and more memorable for physicians. Our communications efforts included:

- Produced and launched a web-based continuing educational module for health-care professionals.
- Published an article in *Pharmacy Today*, a publication of the American Pharmacists Association (APhA). APhA is the largest association of pharmacists in the United States. The *Pharmacy Today* publication is circulated to over 144,000 pharmacists.

Transparency of policies, decisions

- *Regulations.* We published one final regulation and we sought public comment on two proposed rules.
- *Guidances.* We published eight guidances for industry that explain our position on best practices in scientific and technical areas. We published another 21 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 32 new and revised documents in 2007.
- *Freedom of Information requests.* We responded to 3,498 requests under the Freedom of Information Act.

Public education programs

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

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

These are available at

<http://www.fda.gov/cder/drug/DrugSafety/drugSafetyConsumer.htm>.

Internet updates

We have more than 25,000 subscribers to our service that provides daily e-mail updates of new content on our Web site and more than 24,000 subscribers to our weekly e-mail updates. In 2007, there were 24,913,978 sessions: 273,552,280 page views and 670,008,349 hits on the CDER Web site. To subscribe, visit

<http://www.fda.gov/cder/cdernew/listserv.html>.

Ombudsman Activities

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

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

Consumers, law firms, and the pharmaceutical industry can contact our ombudsman's office by fax, phone, postal mail and electronic mail. Beginning in March, the ombudsman instituted a different tracking system for phone calls and electronic mail. Therefore, the phone and email data presented below reflect contacts and activities from

March through December 2007 and the numbers for fax and regular mail encompass the full calendar year.

In total, the ombudsman received 660 communications, the vast majority (94%) of which came via electronic mail and phone. In many instances, several emails or phone calls were exchanged per case. Follow up correspondences were not counted for this report.

Examples of cases and allegations from the Pharmaceutical Industry, Law Firms, Consultants, and Public or Private Research Institutions our ombudsman handled included:

- Regulatory jurisdiction.
- Generic drug decisions.
- Review delays.
- Whistle blower's informing about unethical clinical research conduct.
- Lengthy response times to Citizen Petitions and Suitability Petitions.
- Import/Export issues.
- Enforcement actions taken on marketed drugs that do not have FDA approval.
- Freedom of Information Act requests.
- New drug approval or nonapproval.
- Unlawful promotional activities by competitors.

Examples of cases and allegations from consumers and health care professionals our ombudsman handled included:

- Reporting of drug adverse events and medication errors.
- Drug costs and insurance problems.
- Drug shortages.
- Complaints from consumers about their doctors.
- Personal importation of drugs not lawfully marketed in the United States.
- Study protocol violations as reported by study participants.
- Generic drug does not seem to work the same as the brand drug.
- Oxycontin abuse and pleas to remove it from the market.
- Misleading product websites.
- Albuterol inhalers.

Jurisdictional Issues

Many times it is not readily apparent where in FDA a proposed product will be reviewed and regulated. Our ombudsman is our jurisdiction officer and a member of the steering committee that advises FDA's Office of Combination Products that coordinates intracenter jurisdictional issues.

This calendar year, our ombudsman responded to hundreds of informal jurisdiction questions from within and outside FDA and put forth CDER's position on 44 requests for designation. Most of the designations were drug/device combinations. More information about jurisdictional issues can be found at www.fda.gov/oc/combination/.

Outreach Efforts

The CDER ombudsman's office conducted outreach to explain its functions including product jurisdiction and dispute resolution at several internal and external venues. The office also created an informative website for use by CDER employees.

Appendix

Glossary of Terms

Drug Definitions

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 over-the-counter drugs without a doctor’s prescription. You can successfully diagnose many common ailments and treat them yourself with readily available OTC products. These range from acne products to cold medications. As with prescription drugs, we closely regulate OTC drugs to ensure that they are safe, effective and properly labeled.

Generic drugs

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

Drug Review Definitions

- *Review and approval times.* Review time is time spent examining the application. Approval time represents review time plus industry's response time to our requests for additional information.
- *Priority reviews.* These products represent significant improvements compared with marketed products. We have a goal of reviewing 90 percent of these applications within six months.
- *Standard reviews.* These products have therapeutic qualities similar to those of already marketed products. We have a goal of reviewing 90 percent of these applications within 10 months.
- *Actions and filings.* An application is filed when we determine it is complete and accept it for review. We make a filing decision within 60 days of receiving an application. Approval is one of the actions that we can take once an application is filed. Another action is seeking more information from the sponsor. There is no direct connection between applications filed in one year and actions in the same year.
- *Orphan drugs.* We administer a program that provides incentives to develop drugs for use in patient populations of 200,000 or fewer. Sponsors of orphan drugs receive the following inducements: seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance from FDA and grants of up to \$200,000 a year.
- *Accelerated approval.* This program makes products for serious or life-threatening diseases available earlier in the development process by relying on an effect on a surrogate end point to predict clinical benefit. An effect of the drug on a surrogate end point can be observed significantly sooner than can a long-term clinical benefit. Sponsors must perform additional studies to demonstrate long-term clinical benefit.
- *Fast-track development.* This program facilitates the development and expedites our review of new medicines that demonstrate the potential to address unmet medical needs for serious or life-threatening conditions. Fast track emphasizes our close, early communication with sponsors.
- *Median times.* Our charts show review and approval times as medians. The value for the median time is the number that falls in the middle of the group after the approval times 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 times. Our guide to understanding median approval time statistics is available at <http://www.fda.gov/cder/present/MedianAPtime/index.htm>.
- *Tentative approval.* This program is issued to the drug company when the application is approvable prior to the expiration of any patents or exclusivities

accorded to the reference listed drug product. A tentative approval does not allow the applicant to market the product and postpones the final approval until all patent or exclusivity issues have expired.

- New Molecular Entities (NMEs) contain an active substance that has never before been approved for marketing in any form in the United States. Because of high interest in truly new medicines, we report approvals of NMEs and new biologic license applications (BLAs). The charts for all new drug applications (NDAs) and all BLAs include NMEs and new BLAs.

New drug applications

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

Biologic license applications

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

Internet Resources

CDER Drug and Biologic Approval Reports

You can find reports on drug and biologic approvals at <http://www.fda.gov/cder/rdmt/default.htm>

Generic drug Web site

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

OTC drug Web site

Information for consumers, manufacturers and health-care professionals about OTC drugs can be found at <http://www.fda.gov/cder/offices/otc/default.htm>. The Web site includes details about how we regulate OTC drugs. We also include information to help ensure safe use of OTC drugs, including information about pain relievers, reporting adverse drug events, and the use of nonprescription cough and cold medicines in children.

Critical Path

The FDA's comprehensive Web site on the Critical Path is at <http://www.fda.gov/oc/initiatives/criticalpath/>. Reports available on the site include those on:

- Generic drugs
- Opportunities initiated during 2006
- The opportunities report
- The list of 76 opportunities
- The original 2004 report and analysis

The site also includes information on meetings and workshops.

Counterterrorism and Emergency Response

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

Public Health Advisories

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

Medication Guides

A list of products with Medication Guides is available at http://www.fda.gov/cder/Offices/ODS/medication_guides.Htm.

Podcasts

Our audio advisories can serve as an alternative to finding this information on our Web site, reading about it in the newspapers or hearing about it from patients. More information is at <http://www.fda.gov/cder/drug/podcast/default.htm>.

Patient Safety News

Patient Safety News segments are available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/index.cfm>. The subjects of some stories are the emerging safety information about drugs described in our public health advisories and early communications.

Medication Errors

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

Adverse Event Reporting

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

MedWatch

- You can find the latest medical product safety information at <http://www.fda.gov/medwatch/>.
- You can sign up for immediate e-mail or RSS feed notification of MedWatch safety information at <http://www.fda.gov/medwatch/elist.htm>.
- You can access a video self-learning tutorial *FDA MedWatch and Patient Safety* at <http://www.connectlive/events/fdamedwatch>. You will learn more about why your voluntary reporting to MedWatch is critical to our safety surveillance efforts, how we use your reports to make drugs safer and how you can receive new, timely safety information from us that results from your reports.

Drugs@FDA

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

- Approved and tentatively approved drug products.

- The regulatory history of an approved drug.
- Labels for approved drug products.
- All drugs with a specific active ingredient.
- Generic drug products for a brand-name drug product.
- Therapeutically equivalent drug products for a brand-name or generic drug product.
- Consumer information for drugs approved during the last 10 years.

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

User Fees

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

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