Center for Drug Evaluation and Research

CDER 1997 Report to the Nation

Improving Public Health Through Human Drugs

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

Center for Drug Evaluation and Research
FDA

Contents

Index of Graphs iv
Letter from the Director v
Introduction 1
- What Americans Expect 1
- Application Review Program 1
- Post-Marketing Surveillance 1
- FDA Modernization Act 2

Application Approvals 3
- 1997 Performance and Workload 3
  - Total Original NDA Actions 3
  - Total Original NDA Approvals 4
  - New Molecular Entity Approvals 5
  - Efficacy Supplement Approvals 7
  - Manufacturing Supplement Approvals 8

PDUFA Application Review Performance 10
PDUFA Reauthorization Goals 13
Overdue Reduction 14
Refusal to File an Application 15
Clinical Holds 16
Post-Marketing Risk Assessment 17
- Adverse Event Reporting 17
- Drug Safety Issues 19

OTC Update and Significant Switches 20
Generic Drugs 22
Export Certificates 23
Drug Advertising and Promotion 24
International Harmonization 26
Applied Research 28
Communications 29
- Ombudsman's Activity 30

Improving Policy Consistency 31
- New and Proposed Rules 31
- Guidances to Industry 32
- MAPPs 33

Organizational Changes 34
Organizational Chart 35

Graphs

Calendar Year 1997 Actions and Approvals:
- Original NDA Actions 3
- Original NDA Approvals 4
- NME Approvals 5
- Efficacy Supplement Actions 7
- Efficacy Supplement Approvals 8
- Manufacturing Supplement Actions 9
- Manufacturing Supplement Approvals 9

PDUFA On-Time Review Performance:
- Original NDAs: 10
- Resubmissions of Original NDAs 11
- Efficacy Supplements 12
- Manufacturing Supplements 12

Refusal to File Actions 15

Clinical Holds 16

Post-Marketing Adverse Event Reports 17

PDUFA Submission Cohorts: Adverse Event Reports 18

Generic Drug Approvals 22

Export Certificates Issued 23

Regulatory Action and Launch Campaign Letters 24

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

May 1, 1998

Dear President/CEO:

I am pleased to send you the second annual report from the Center for Drug Evaluation and Research, U.S. Food and Drug Administration. The report highlights CDER's performance during 1997. This past calendar year has been both successful and eventful.

In our new drug review program, the Center approved 39 new molecular entities, the second highest total for these important new medicines. We continued to reduce review times. The median total time to approval for NMEs was 13.4 months—the most rapid ever. Moreover, American consumers were the first in the world to have access to more than half these drugs. We met all our six-month goals for priority drug reviews.

The many drug review achievements highlighted in this report validate the joint commitment made by CDER to accountability, predictability and quality. This commitment was embodied in the 1992 Prescription Drug User Fee Act and reaffirmed in last year's FDA Modernization Act and reauthorization of user fees. The United States now has one of the fastest, if not the fastest, drug review systems in the world. This has been accomplished without sacrificing the FDA's high standards of scientific rigor. Moreover, drugs approved in this country have the data needed for physicians and patients to make informed decisions.

The Center's management and user fee initiatives were the major component leading to the Innovations in American Government Award presented to the FDA by the Ford Foundation and Harvard University's John F. Kennedy School of Government. This prestigious award recognized the hard work that cut approval times for new drugs nearly in half while doubling the number approved. Americans now have access to new therapies faster, suffer less, recover more rapidly, live longer lives or enjoy an improved quality of life.

Our streamlining efforts have paid off in over-the-counter and generic drug reviews as well. Expanding the choices of modern, effective and safe drugs for self-medication directly benefits American consumers. Generic drug reviews represent a true success story. Despite a growing workload, a shrinking staff and the absence of user fees, the generics program approved a remarkable 431 products last year—a record for the 1990s— while reducing time to approval from 39.6 months to 19.3 months over the last five years.

We cannot, however, rest on our laurels. Our successes in streamlining drug reviews have unmasked other concerns Americans have with their medicines. As the number of drugs increase and development and review times shorten, safety issues grow increasingly complex and important in the public's mind.

We are in the process of implementing a new Adverse Event Reporting System that will make use of terminology agreed to under the International Conference on Harmonization. This state-of-the-art system will provide enhanced signal detection and replace an overtaxed, manual system.

Manufacturer's reports entered into this new system will represent the first implementation of electronic submissions. We are moving to a completely electronic submission and review environment by the year 2002. Our international harmonization efforts laid the critical foundations for this transformation. Last year, we reached landmark agreement on common medical terminology and standards for secure transmission of information between the pharmaceutical industry and regulatory authorities of the United States, Japan and the European Union.

Harmonization efforts have been so successful that what once seemed only a dream is becoming a reality more rapidly than any of us could have imagined. By the turn of the century, it is highly likely that we will have reached agreement on having essentially the same new drug review document submitted to the regulatory authorities in all three regions.

We are expanding on the lessons learned through our cooperative experience with PDUFA. We are spearheading new collaborative efforts with academia, industry, professional societies and health organizations. These hold the promise of finding scientifically sound ways of expediting drug development and making it easier for manufacturers to take advantage of newer production technologies.

Finally, the FDA Modernization Act of 1997 and the reauthorization of PDUFA have presented the Center and the Agency with a huge portfolio of tasks. The time for implementing some of these changes is short. If you want input into the process, I urge you to contact the Agency leads identified on FDA Modernization Act of 1997 Implementation Chart available on the World Wide Web at **http://www.fda.gov/po/modact97.html.**

I look forward to reporting to you next year on what is promising to be a most challenging year. If you have any questions about this report, please contact Murray Lumpkin, M.D., Roger Williams, M.D., or me at (301) 594-5400.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Introduction

What Americans Expect

American consumers rely on the U.S. Food and Drug Administration's Center for Drug Evaluation and Research to:

- Facilitate the availability of safe and effective drugs.
- Keep unsafe or ineffective drugs off the market.
- Improve the health of Americans.
- Provide clear, easily understandable drug information for safe and effective use.

Application Review Program

Before new drugs can be marketed in the United States, they must undergo an independent review by scientists at the Center for Drug Evaluation and Research. If the review establishes that a drug's benefits outweigh its known risks, the Center approves it for marketing.

In addition to prescription drugs, CDER regulates over-the-counter drugs. The Center's continuing evaluation of products that have been on the market for a number of years and its review of new over-the-counter drugs and drugs reclassified from prescription status, ensure these drugs contain acceptable ingredients, doses, formulations and consumer labeling.

The Center regulates the generic counterparts of prescription and over-the-counter drugs. Companies seeking approval for generic drugs must demonstrate that their products are the same as the reference drugs in terms of strength, dosage form, route of administration, intended use, quality and performance.

Post-Marketing Surveillance

The practical size of pre-marketing clinical trials means that CDER and the industry cannot learn everything about the safety profile of a drug before it is approved. Americans have chosen to accept this risk in order to have drugs developed within a reasonable time. The trade-off for accepting this risk is the continued vigilance of the Center and industry to collect and assess data during the post-marketing life of a drug.

Introduction

The Center monitors the quality of marketed drugs and their advertising and promotion through product testing and surveillance. In addition it develops policies, guidance and standards for drug labeling, current good manufacturing practices, clinical and good laboratory practices, and industry practices to demonstrate the safety and effectiveness of drugs.

FDA Modernization Act

On Nov. 21, the FDA Modernization Act of 1997 became law. The act contains some of the most sweeping changes to the Food, Drug and Cosmetic Act in 35 years. The act codifies—and validates—many of CDER's Reinventing Government initiatives and other existing programs.

Of critical importance to CDER is the reauthorization of the Prescription Drug User Fee Act (PDUFA). The Modernization Act extends PDUFA for five more years, through fiscal year 2002. Under this program, the pharmaceutical industry pays "user fees" that enhance the Center's resources for certain drug review activities.

Getting beneficial drugs on the market quickly is just as much a part of the Center's mission as is keeping unproven or dangerous drugs off the market. The Modernization Act creates heightened expectations for CDER's responsiveness in some new areas in the investigational new drug (IND) development phase as well as in the review phase of CDER's drug oversight activities.

In addition to renewing PDUFA, the Modernization Act contains a number of provisions that will change the way the Agency works and the way the Center performs drug reviews. Some provisions will make the process easier. But others will increase the Center's workload, especially over the short term, as the Center meets its mandate to develop new regulations and guidance documents for the industry.

The Center is working actively to implement these and many other provisions of the law in the time frames expected.

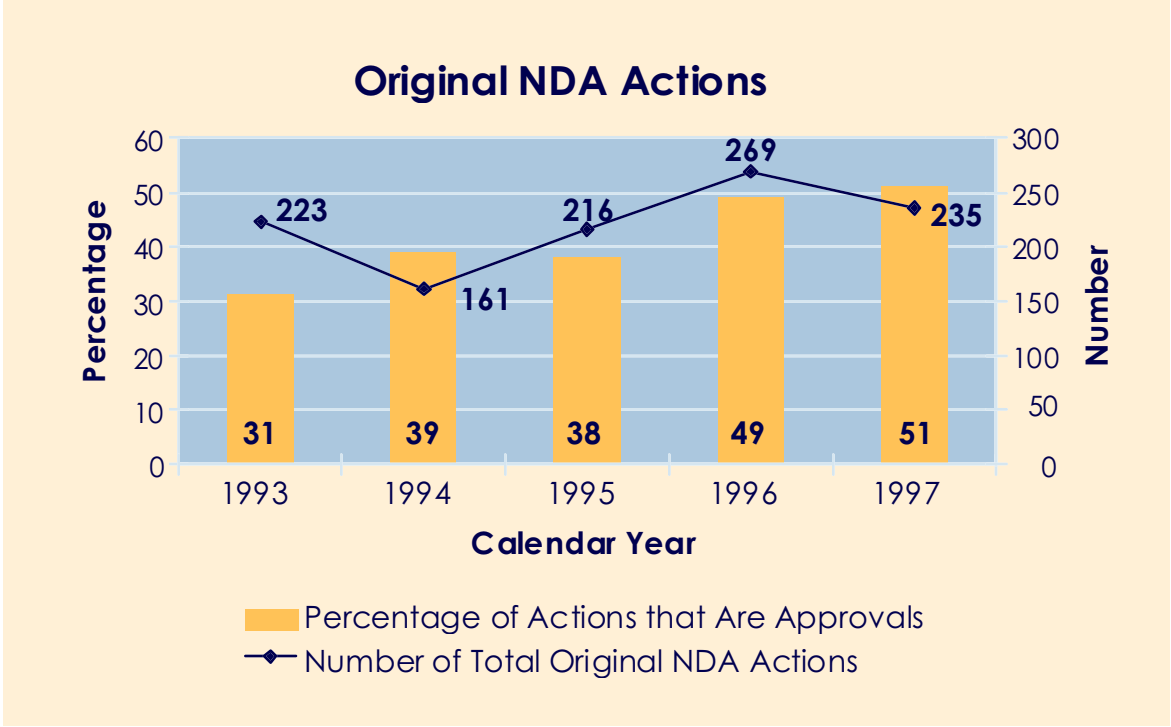
Application Approvals

1997 Performance and Workload

CDER achieved the fastest median approval times for new drug applications (NDAs) and approved the second highest total of new molecular entities (NMEs) in the calendar year 1997. NMEs represent products that contain an active substance that has not been previously marketed as a drug in the United States. Often these products represent new therapies or improved therapies for various diseases. Most importantly, the Center accomplished this without creating a backlog of applications.

Total Original NDA Actions

The Center took 235 actions on original new drug applications. PDUFA has resulted in more applications that can be filed immediately, and reviewed and approved more quickly. As a result, new products with the needed scientific data get on the market faster. The proportion of total actions that are approvals during the initial review cycle has risen steadily from under one-third in 1993 to just over half in 1997. Both CDER's and industry's



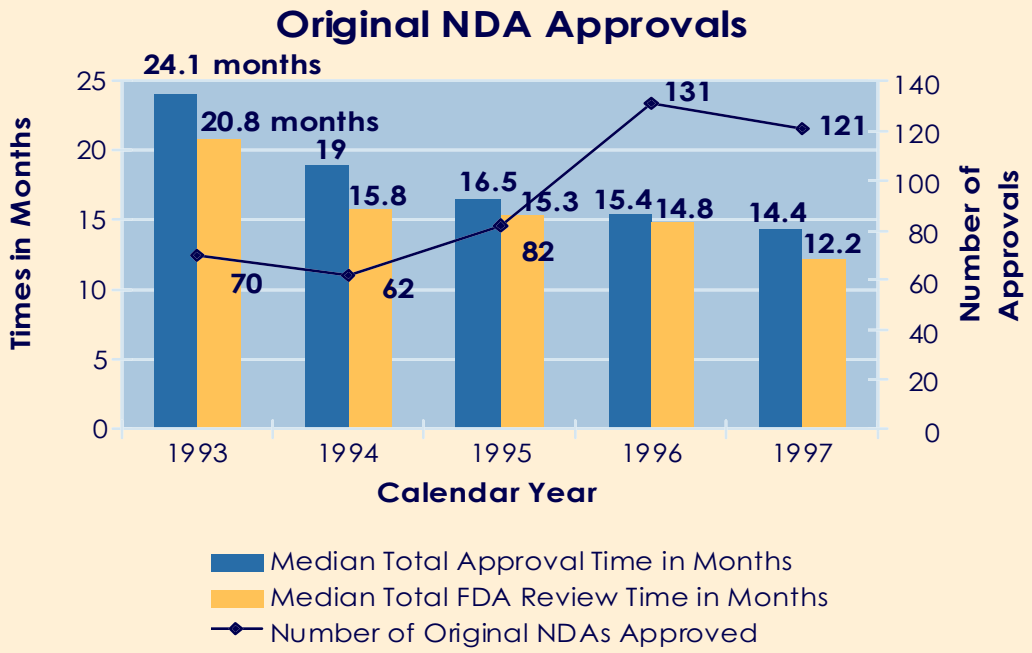
Application Approvals

performance, predictability and accountability have significantly improved as a result of:

- Additional human and financial resources.
- Significant investment in improved information technology.
- The use of project management methodology to guide the review process and monitor the increasing workload.
- The elimination of backlogs.
- The increased emphasis on timeliness as a performance measure.

Total Original NDA Approvals

Of these 235 actions, 121 were approvals of original NDAs. This represents a 75 percent increase in the annual number of NDAs approved over the Center's performance level in 1993.



Application Approvals

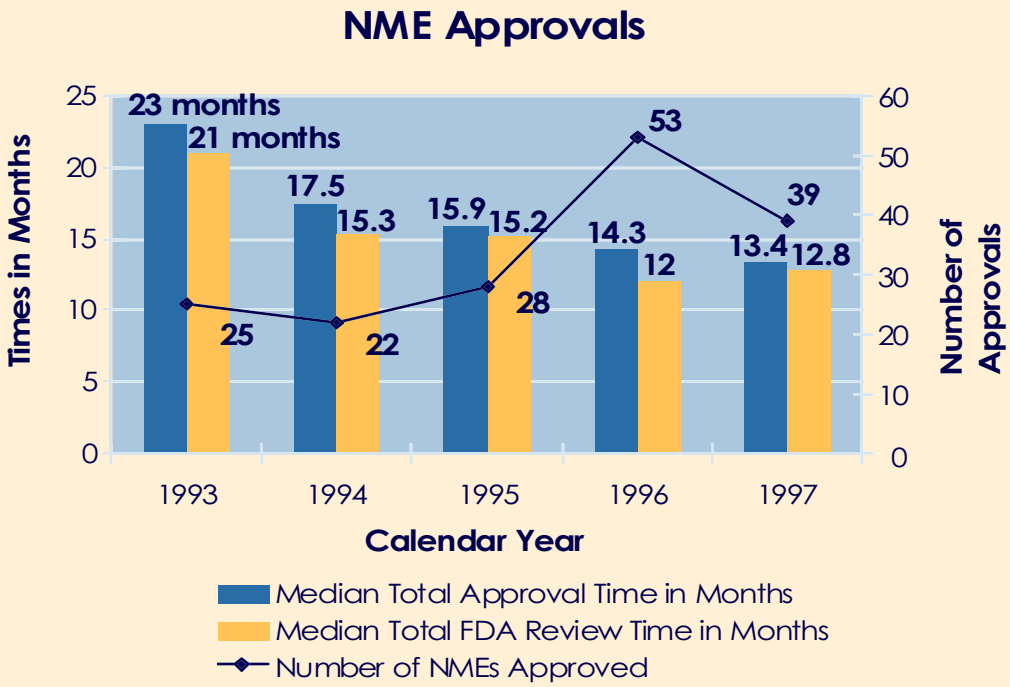
The median total FDA review time for these products was 12.2 months, 18 percent shorter than the year before. The median total FDA review time for these applications has fallen 41 percent from the performance level at the beginning of the PDUFA program.

In addition, the median total time to approval (total FDA review time plus industry response time to agency "approvable" or "not approvable" letters) was 14.4 months, 6 percent less than the 15.4 months for those products approved in calendar year 1996. The median total time to approval has fallen 40 percent from the performance level at the beginning of PDUFA.

Note: The median time is a value that falls in the middle of all times. It provides a truer picture of performance than average time, which can be unduly influenced by a few extremely long or short times.

New Molecular Entity Approvals

Of the 121 NDAs approved in calendar year 1997, 39 were new molecular entities. This represents a 56 percent increase in the annual number of NMEs approved compared with the Center's performance level at the beginning of



Application Approvals

the PDUFA program. In the 1960s, the average number of NMEs approved each year was 13.7. In the 1970s, that went up to 17.3. In the 1980s, the average was 21.7. In the first half of the 1990s, it stood at 25.6.

American consumers were the first in the world to have access to more than half of these NMEs, according to data from the Pharmaceutical Research and Manufacturers of America. In their report on the 39 NMEs approved in 1997, they found:

- 17 were first marketed in the United States.
- Three had not yet been marketed elsewhere in 1997.
- Seven were first marketed in other countries before U.S. approval but within 1997.

This is an improvement over 1996 when 17 of the 53 NMEs were first marketed in the United States. An additional eight were first marketed in other countries in the same year as U.S. approval.

The median total FDA review time for the NMEs approved in 1997 was 12.8 months, 38 percent faster than the Center's performance level for NME review at the start of the PDUFA program.

In addition, the median total time to approval for these 39 NMEs was 13.4 months, 6 percent faster than in 1996 and 42 percent faster than the performance level at the beginning of the PDUFA program.

Nine of the NMEs were priority drugs, which received an accelerated review because they represent a major advance in medical treatment. Viracept (nelfinavir mesylate), a new protease inhibitor for treatment of HIV infection, was reviewed and approved in 2.6 months. Evista (raloxifene hyrochloride), which is indicated for prevention of osteoporosis in postmenopausal women, Rezulin (troglitazone) and Prandin (repaglinide), both for treatment of patients with type II diabetes, were reviewed and approved in six months or less.

Other important priority drugs approved last year were Rescriptor (delavirdine mesylate), a combination therapy for HIV; Plavix (clopidogrel bisulfate), for the prevention of second stroke in patients with hardening of the arteries; Sclerosol (sterile talc powder), for the prevention of malignant

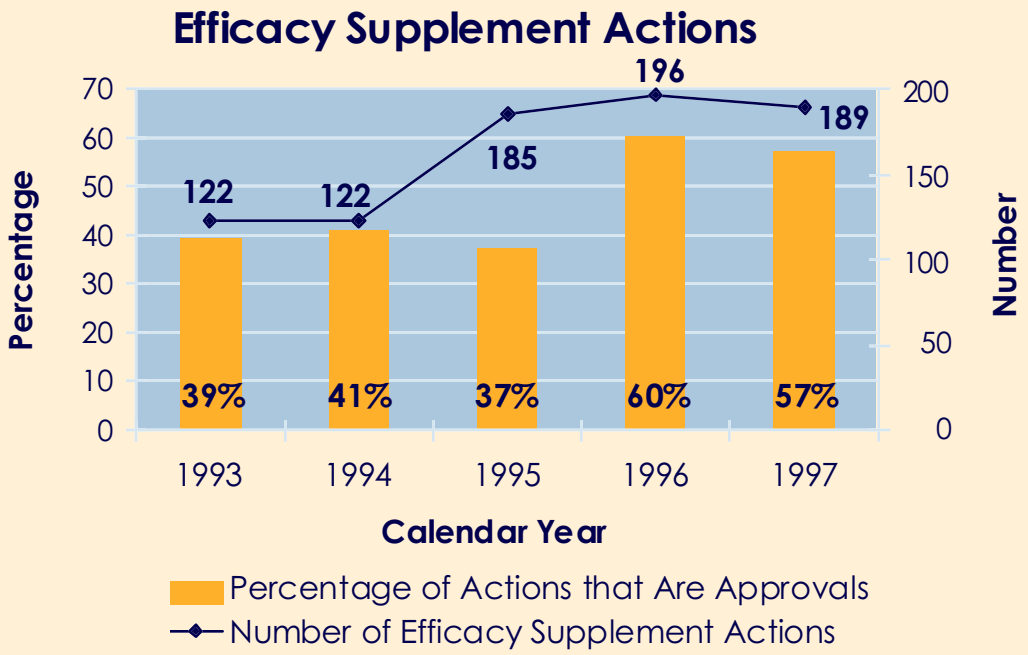
Application Approvals

secretions from the lung membrane; Agrylin (anagrelide hydrochloride), a blood thinner for patients with thrombosis; and PYtest (urea C-14), a breath test for the detection of *Helicobacter pylori,* a cause of stomach ulcers.

Noteworthy drug approvals in 1997 also included Tobi (tobramycin solution for inhalation), the first inhaled antibiotic for patients with cystic fibrosis, and Meridia (sibutramine hydrochloride), for the management of obesity.

Efficacy Supplement Approvals

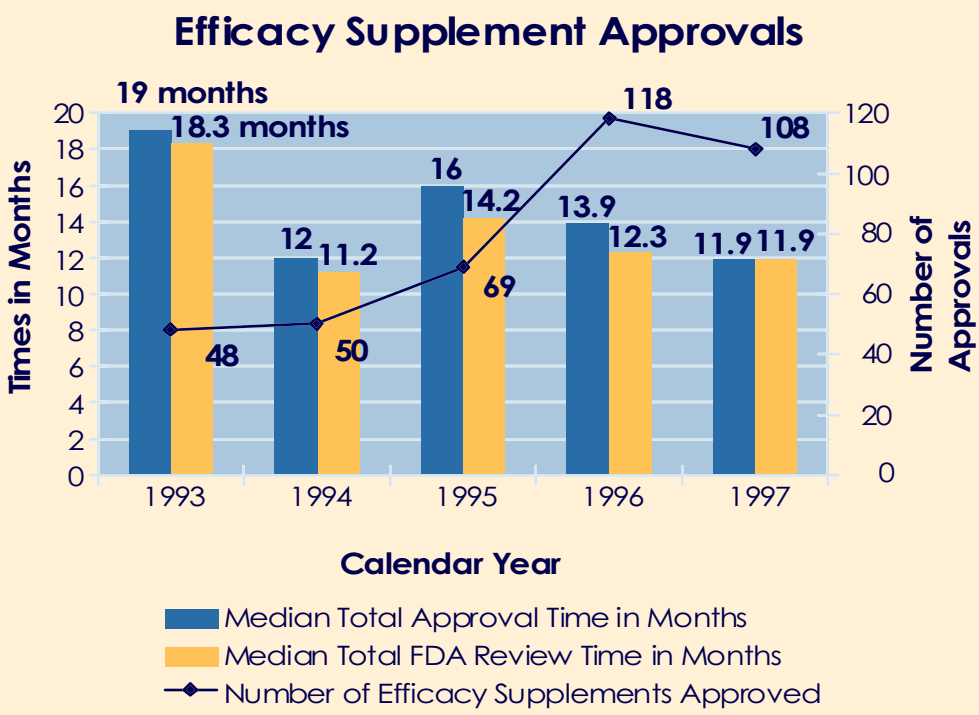
The Center took action on 189 efficacy supplements, of which 108 actions were approvals. Efficacy supplements are new uses for already approved drugs and often represent important new treatment options for American patients. The 1997 approvals represent a 125 percent increase in the annual number of approved efficacy supplements over the Center's performance level at the beginning of PDUFA. The annual average of 113 efficacy supplements approved in 1996 and 1997 is more than double the annual average of 55.7 for the three years 1993 to 1995.



Application Approvals

The median total FDA review time for these applications fell 35 percent from the Center's performance level at the start of the PDUFA program.

In addition, the median total time to approval fell 37 percent from the performance level at the beginning of the PDUFA program.

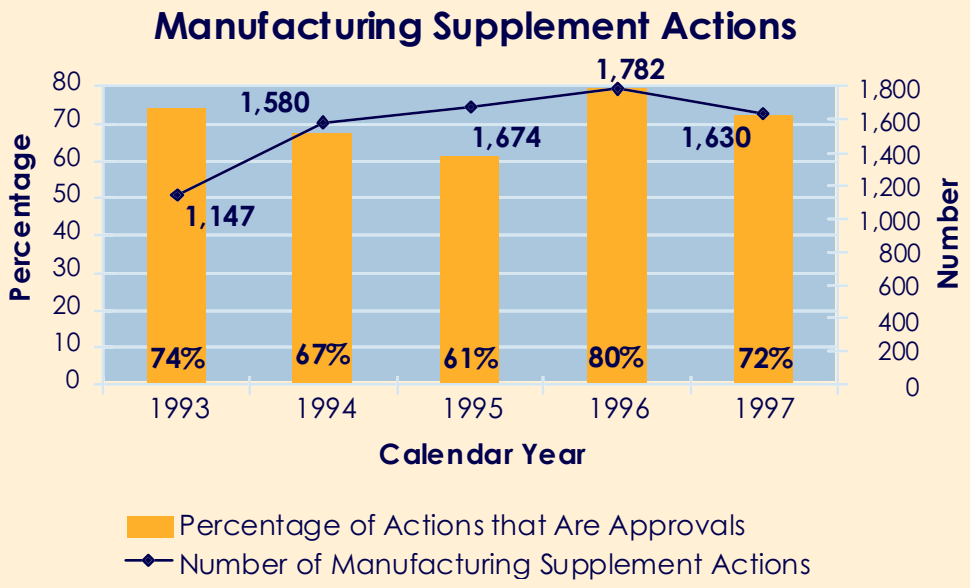


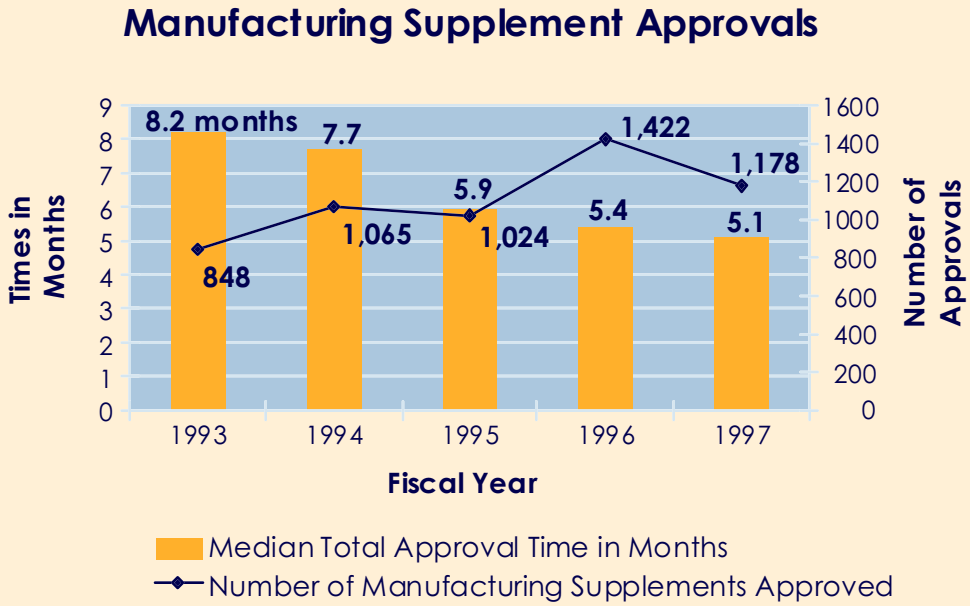
Manufacturing Supplement Approvals

In fiscal year 1997 (from Oct. 1, 1996, to Sept. 30, 1997), the Center took action on 1,647 manufacturing supplements, of which 1,178 were approvals. Manufacturing supplements are only tracked on a fiscal year basis. In many cases, manufacturing supplements represent the industry's efforts to modernize plants and equipment or to make manufacturing of already approved products more efficient. The approvals in 1997 are a 39 percent increase in the annual number of approved manufacturing supplements compared with the performance level at the beginning of PDUFA.

Application Approvals

The median total approval time for these applications fell 38 percent from the Center's performance level at the start of the PDUFA program.



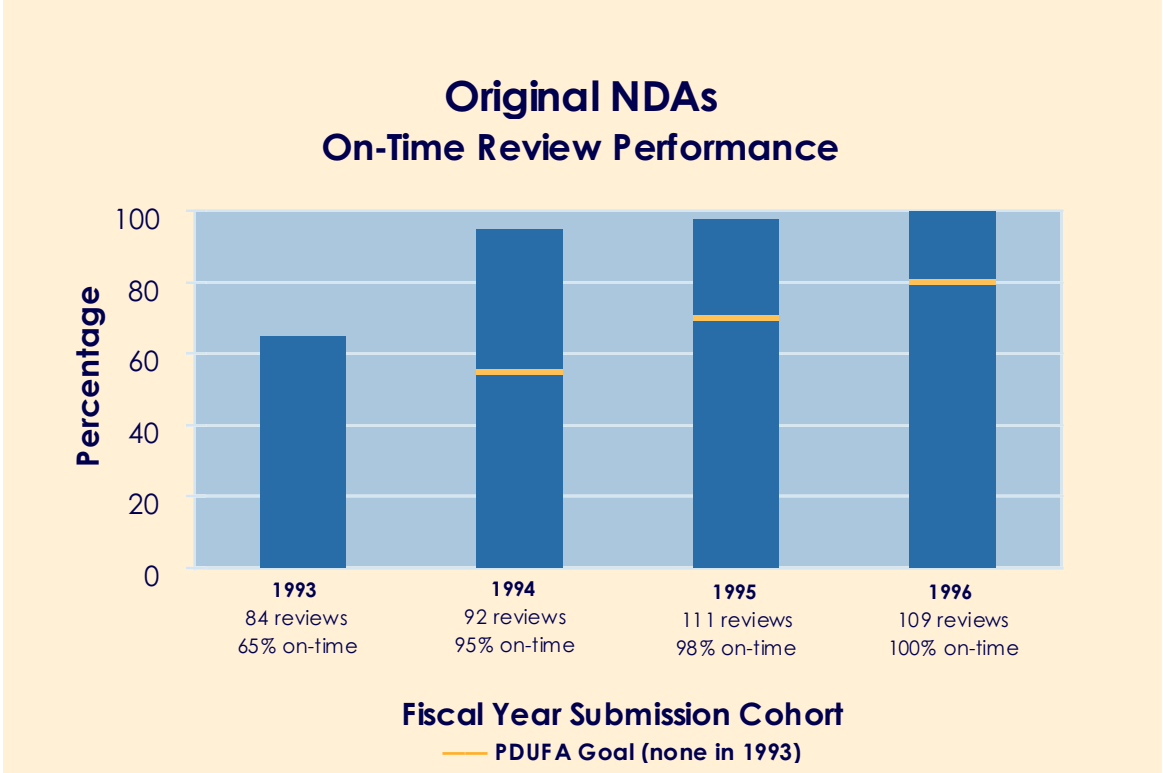


PDUFA Application Review Performance

The consistently high achievements of CDER's drug review program in recent years reflect the importance of the managerial reforms and additional resources provided under the Prescription Drug User Fee Act. Three unique features made PDUFA work:

- Mutually agreed-upon, prospective performance goals for drug reviews. These goals are time limits for a review based on submission cohorts, identified by the *fiscal year* in which the application is submitted.
- A provision that user fees were to be collected only if taxpayer dollars supporting the review program remained steady, making these truly additive resources.
- A sunset provision to allow stakeholders to assess results before program reauthorization.

By managing the review process to meet the PDUFA review performance goals, CDER has transformed the new drug review program into one that is

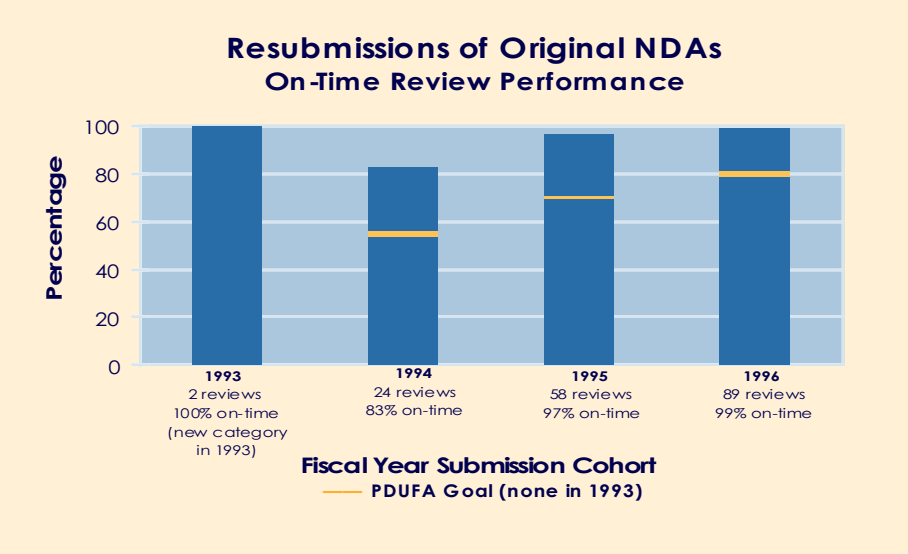


PDUFA Application Review Performance

not only thorough but also predictable and accountable. CDER's performance has established shorter review times and shorter total times to approval without sacrificing quality in the FDA application review process.

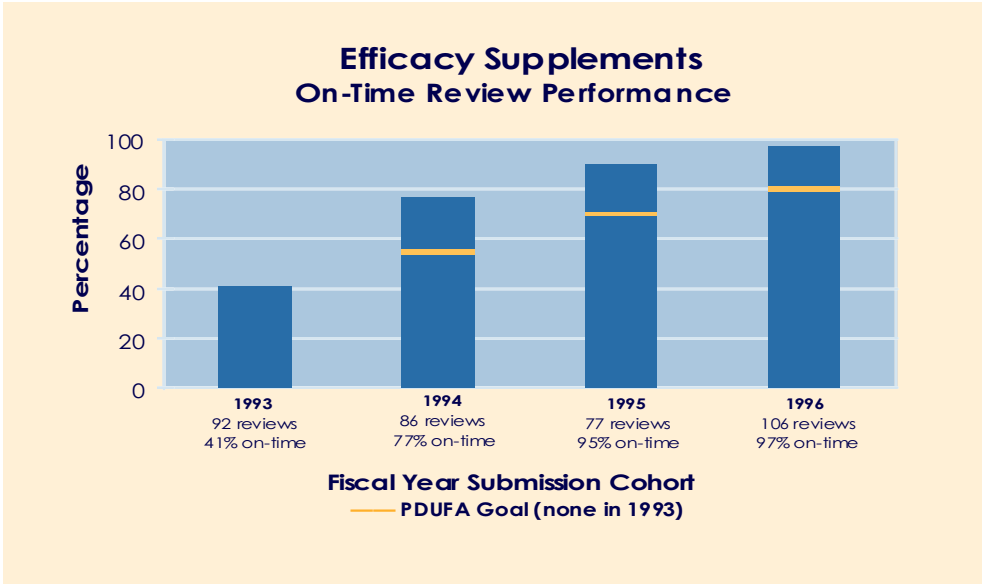
CDER's top priority has been to exceed the application review on-time performance goals established under PDUFA. For the first four years of PDUFA, an on-time review meant that the Center would completely review and act on original NDAs and efficacy supplements, priority and standard, within one year of submission. Manufacturing supplements and resubmissions of original NDAs would be completely reviewed and acted upon within six months of their submission to the FDA. In addition, CDER agreed to review and act on priority applications, both NDAs and efficacy supplements, in six months or less for the fiscal year 1997 submission cohort. A priority drug is one that appears to represent a major advance in therapy. A standard drug appears to have therapeutic qualities similar to those of an already marketed drug.

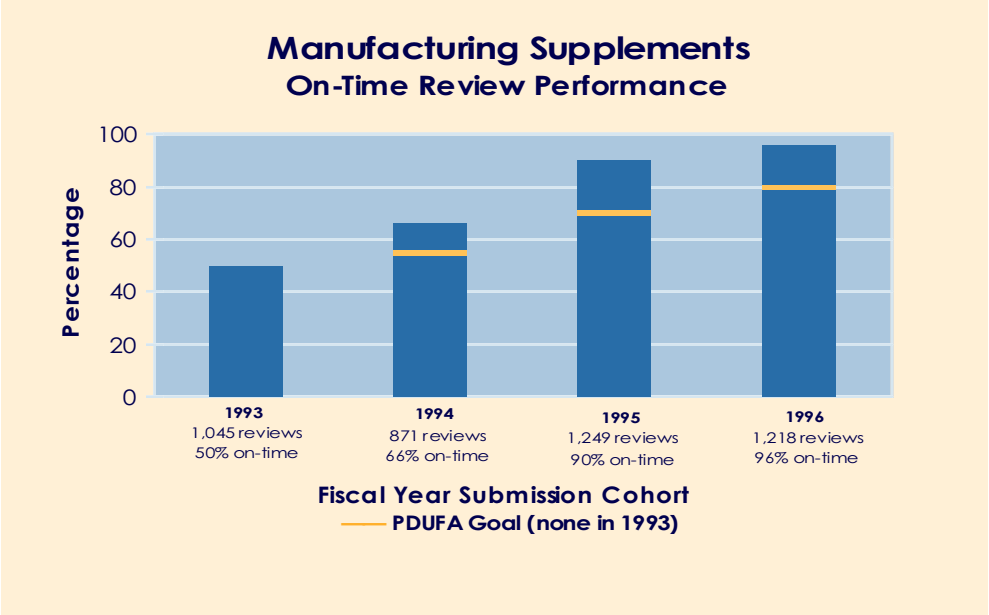
The review performance goals were predicated on the understanding that, over the five years of the program, CDER would increase the human resources available to perform reviews and install new management techniques for the review process. Therefore, it was agreed to phase in the percentage of applications that were expected to be reviewed on-time. Starting with a goal of 55 percent of the applications filed in fiscal year 1994 expected to be reviewed on time, the goal increased each year: 70 percent for fiscal year 1995, 80 percent for fiscal year 1996 and 90 percent for fiscal year 1997.



PDUFA Application Review Performance

The on-time review performance charts show CDER's results far exceeded the PDUFA review performance goals. When comparing the fiscal year on-time performance charts with the calendar year totals, remember that many applications in a fiscal year submission cohort are actually reviewed and acted on in the subsequent calendar year. So the results for the PDUFA fiscal year 1996 submission cohort substantially reflect the work effort of CDER in calendar year 1997.





PDUFA Reauthorization Goals

Recognizing PDUFA's major contributions to improving the drug review process and accelerating the delivery of new drugs to Americans, Congress, with the Center's and the industry's support, last fall further enhanced the user fee program and extended it for another five years. The act contains changes in how fees are assessed and collected. For example, fees are waived for first applications for small businesses, orphan products and pediatric supplements.

A phase-in to a 10-month review time by fiscal year 2002 for standard new drug applications and efficacy supplements highlights the expanded list of review performance goals. The Center's successes in meeting and exceeding the performance goals agreed to in 1992 give confidence that it can rise to these new challenges. Currently, CDER is reviewing more than 90 percent of priority drug applications in six months and standard drug applications in 12 months. Performance goals for priority drugs—those that appear to represent an advance over available therapy—will remain at six months for the five years of the reauthorization.

In addition to performance goals for standard and priority drug reviews, the Center has committed to goals that it believes will help speed the time it takes for drugs to be appropriately tested and developed before submitting those results for FDA review. These new performance goals include those related to meeting management, clinical holds, resolving major disputes and reaching agreement on certain protocols. In addition there are added expectations regarding electronic applications and submissions, simplification of action letters and expedited notification of deficiencies in applications.

Overdue Reduction

A primary goal of the PDUFA program was to reduce the overdue applications that existed in 1992 and to transform the CDER new drug review program into one that stays current with a minimum of overdue applications at any given time. On Dec. 31, 1997, the number of applications on hand in the Center, including those submitted but not yet officially filed, and the number overdue were:

- Original NDAs: 129 on hand, none overdue.
- Efficacy supplements: 103 on hand, five overdue.
- Manufacturing supplements: 575 on hand, five overdue.

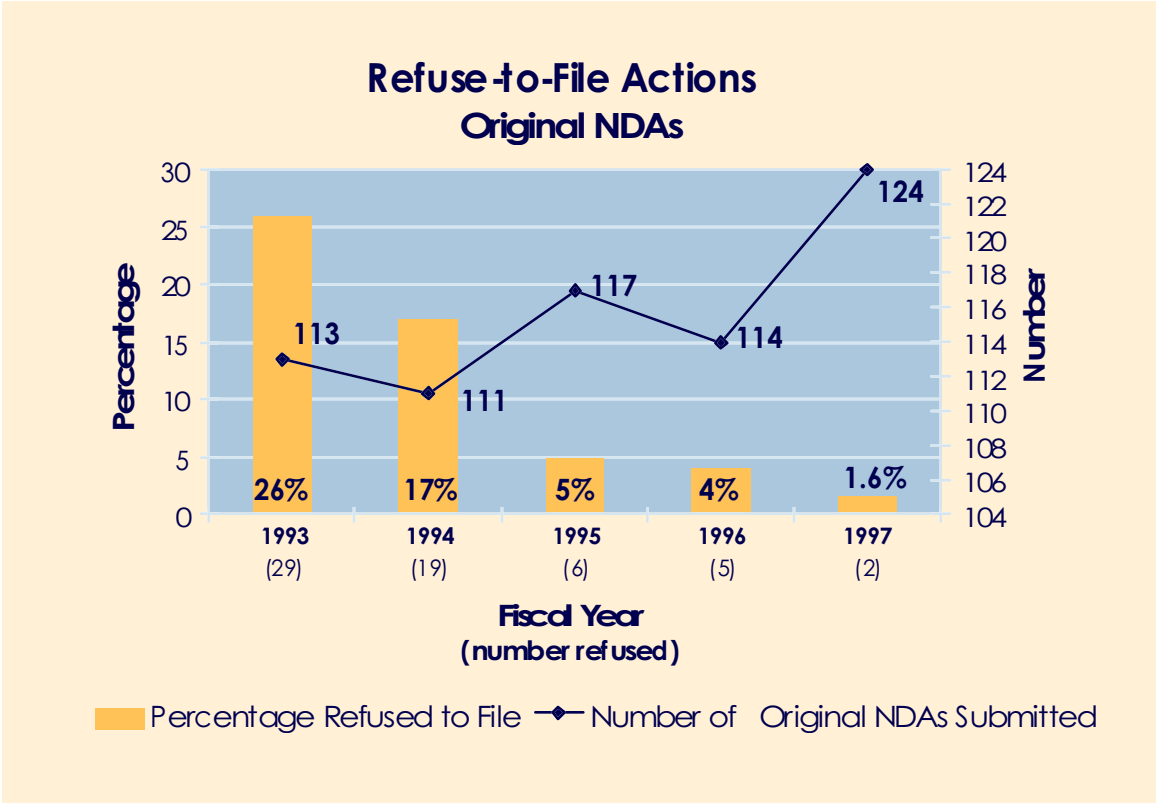
While CDER endeavors to avoid having any applications overdue, having only 1.2 percent overdue out of 807 applications pending on Dec. 31 is a significant improvement over the Center's performance prior to PDUFA.

Refusal to File an Application

Two remarkable successes of the PDUFA program have been the increased quality of applications submitted by industry and the Center's increased consistency in applying its authority to refuse to file an application. The Center refuses to file an application when it determines there is a significant omission of needed information.

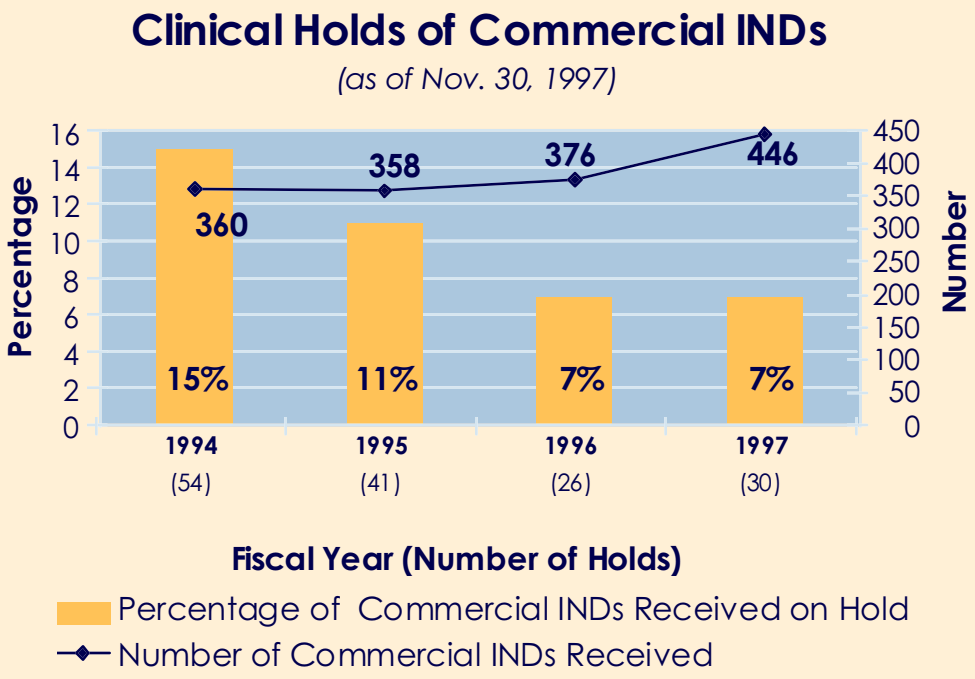
Before 1993, the Center was refusing to file approximately 25 percent to 30 percent of submitted original NDAs. The percentage of refused-to-file applications has dropped steadily to a low of less than 2 percent of the original NDAs submitted in fiscal year 1997.

This significant change ensures that CDER's review efforts are not expended on incomplete or low-quality applications.



Clinical Holds

By working with sponsors more closely, the percentage of commercial INDs put on clinical hold over the last five years has decreased by more than 50 percent. A clinical hold halts the testing of a drug in humans because of concerns about safety. The Center has developed and published procedures that outline specific responsibilities and time lines for handling clinical holds imposed on investigational new drugs (INDs).



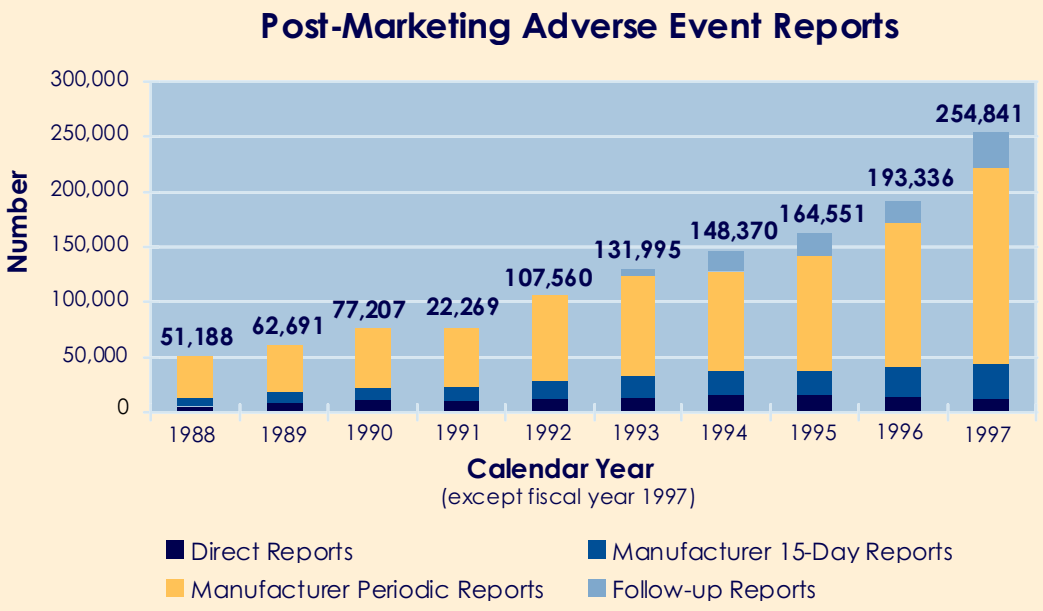
Post-Marketing Risk Assessment

Adverse Event Reporting

In the last fiscal year, the Center received 254,841 reports of suspected drug-related adverse events: 12,453 reports direct from individuals; 31,522 15-day manufacturer reports; 178,132 periodic manufacturer reports; and 30,737 follow-up reports.

The average number of reports received has jumped to more than 175,000 per year in the last five years from about 75,000 per year in the previous five years. This steep climb is due in part to PDUFA and the FDA's MedWatch program. The record number of 128 NMEs approved for the 1993 to 1996 PDUFA submission cohorts accounts for almost 10 percent of the adverse event reports. MedWatch, launched in 1993, solicits reports from individual health care practitioners and makes it easier to submit them.

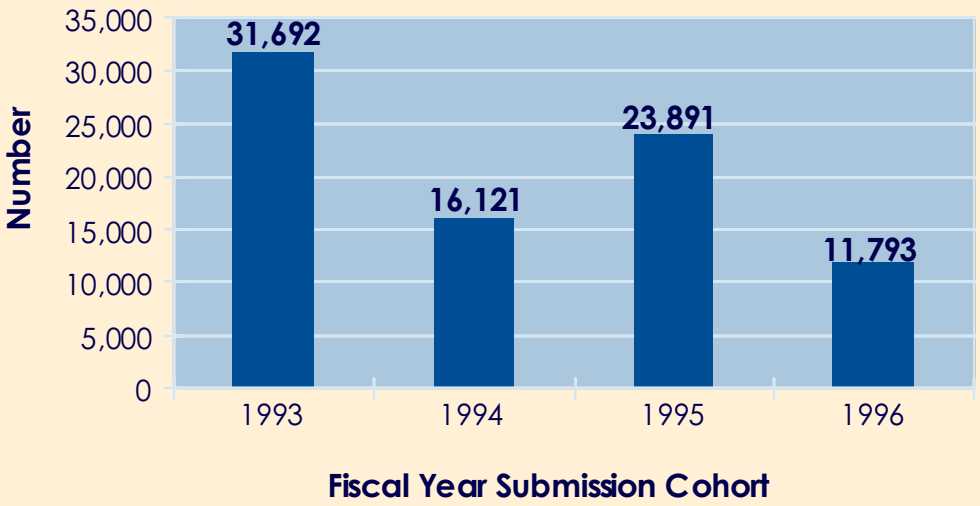
CDER has begun using a state-of-the art information technology system for receiving, storing and analyzing the more than a quarter million reports it receives each year. It is the first system in the world to implement the information technology and safety reporting requirements reached as part of the International Conference on Harmonization.



Post-Marketing Risk Assessment

Reports of suspected drug-related adverse events are:

- *Direct reports*. An individual, usually a health care practitioner, notifies the FDA directly of a suspected adverse event.
- *Manufacturer 15-day reports*. Drug manufacturers report serious and unexpected adverse events to the FDA as soon as possible and within 15 days of discovering the problem.



- *Manufacturer periodic reports*. Drug manufacturers periodically report all other adverse events, for example, those that are less than serious or described in the drug's labeling. Reports are submitted quarterly for the first three years of marketing and annually thereafter.
- *Follow-up reports*. When additional information is required, a follow-up report is submitted.

Post-Marketing Risk Assessment

Drug Safety Issues

As the Center discovers new knowledge about a drug's safety profile, it makes 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 include new labeling, "Dear Health Care Practitioner" letters, restricted distribution programs or product marketing termination. Highlights of the Center's drug risk assessment program in 1997 were:

- *Heart disease associated with diet drugs.* The Center's risk assessors participated in the initial review of adverse event reports of valvular heart disease in people treated with the appetite-suppressant drugs fenfluramine and dexfenfluramine. Using these reports, the Center then conducted an epidemiologic study in partnership with five investigators across the United States. The study uncovered a 30 percent rate of valvular disease, much higher than expected. The manufacturer voluntarily withdrew the products from the market.

- *Diabetes associated with protease inhibitors.* From reviewing MedWatch reports, Center risk assessors identified high blood sugar levels and diabetes as potentially serious adverse events associated with protease inhibitors used to treat HIV infection. This work formed the basis for a "Dear Health Care Practitioner" letter and an FDA Public Health Advisory.

- *Potentially fatal heart condition associated with an antihistamine.* Reports of irregular heartbeats associated with the use of the antihistamine terfenadine and the availability of a similar drug without the risk led to the Center's decision that products with terfenadine should be removed from the U.S. market.

OTC Update and Significant Switches

In January 1997, the Center consolidated administrative responsibility for over-the-counter drugs marketed under the authority of approved NDAs in the Division of OTC Drug Products. The responsibilities include postapproval regulatory oversight, such as the evaluation of postmarketing safety reports and the review of data submitted to provide for most changes to the approved NDA. Approximately 235 approved over-the-counter NDAs were involved in the transfer from the previous review divisions.

The Center approved eight new drugs or new indications for an existing drug for OTC marketing, including:

- A nasal spray to treat allergy symptoms.
- New drugs to treat heartburn.
- A new toothpaste for gingivitis.
- An antifungal for one-day treatment of vaginal infections.
- A hair growth treatment for hereditary pattern baldness in men.
- A product for dandruff control.

In addition, more than 50 labeling reviews of OTC drugs were performed.

CDER published 14 monograph and rulemaking documents related to over-the-counter drug products in the *Federal Register,* including:

- A proposed rule to increase the legibility and clarity of OTC labels in order to improve consumers' ability to understand important warnings and directions for use.
- A proposal to include a warning to heavy alcohol users about the risk of OTC internal analgesics.
- A proposal to remove the laxative ingredient phenolphthalein from the OTC market.
- New labeling for drug products containing the antihistamine diphenhydramine.

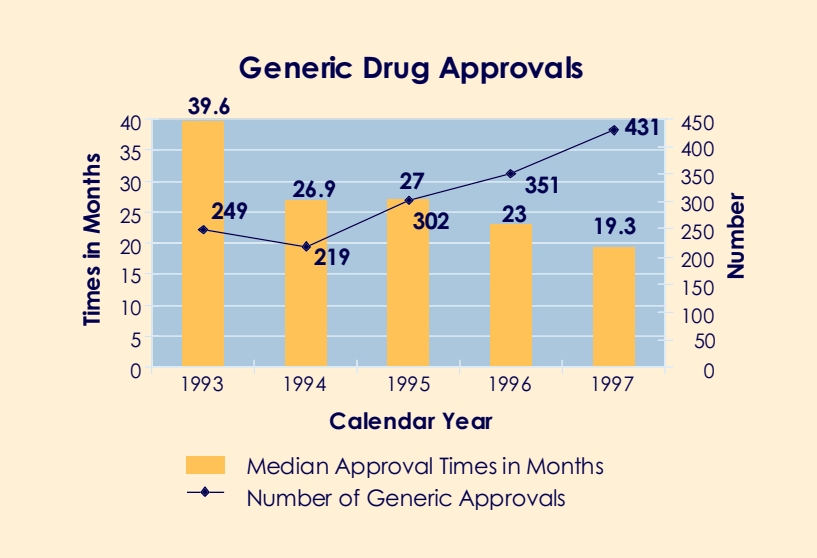
OTC Update and Significant Switches

Numerous OTC drug topics were discussed in public meetings. The Nonprescription Drugs Advisory Committee (NDAC), jointly with other FDA advisory committees and the Dental Panel, convened for a total of 12 days of meetings. The NDAC addressed a range of issues including the prescription drugs switches to OTC marketing and new indications for already marketed OTC products. In addition, the Dental Panel, previously a subcommittee of the Devices Advisory Committee, became a subcommittee of NDAC in the spring and continues to deliberate about remaining dental products for the OTC Review.

Other important public meetings were held between FDA, industry and interested professional and consumer groups. These meetings discussed new safety or efficacy issues concerning products that have long been marketed under OTC drug review procedures but are not yet covered under a final monograph.

Generic Drugs

The 431 generic drug approvals in 1997 represents a substantial increase over 302 approved in 1995 and 351 in 1996. This increase occurred despite a continuing growth in workload over the past three years. From 1991 to 1994, submissions remained relatively stable at approximately 323 applications each year. In each of the three years since, there has been an increase in submissions: 411 in 1995, 453 in 1996 and 464 in 1997.



Streamlining initiatives: CDER has undertaken several initiatives to make the generic drug review process more efficient, including:

- Faxing deficiency letters to applicants.
- Increasing communications with firms receiving major deficiency letters to help minimize review cycles.
- Making acceptable bioequivalence study protocols publicly available.
- Resolving simple refuse-to-file issues by telephone.
- Providing copies of currently approved labeling to applicants, thereby eliminating the lengthy delay in obtaining this information through the Freedom of Information process.

In addition, several other initiatives to streamline the review process—such as accepting the electronic submissions of bioequivalence data as well as chemistry, manufacturing and controls data—are being implemented or nearing implementation.

Export Certificates

In 1997, the demand for certificates by foreign governments remained high due to expanding world trade, ongoing international harmonization initiatives and international development agreements. The demand was met by the allocation of additional resources to the program, and CDER currently has no overdue requests for certificates.

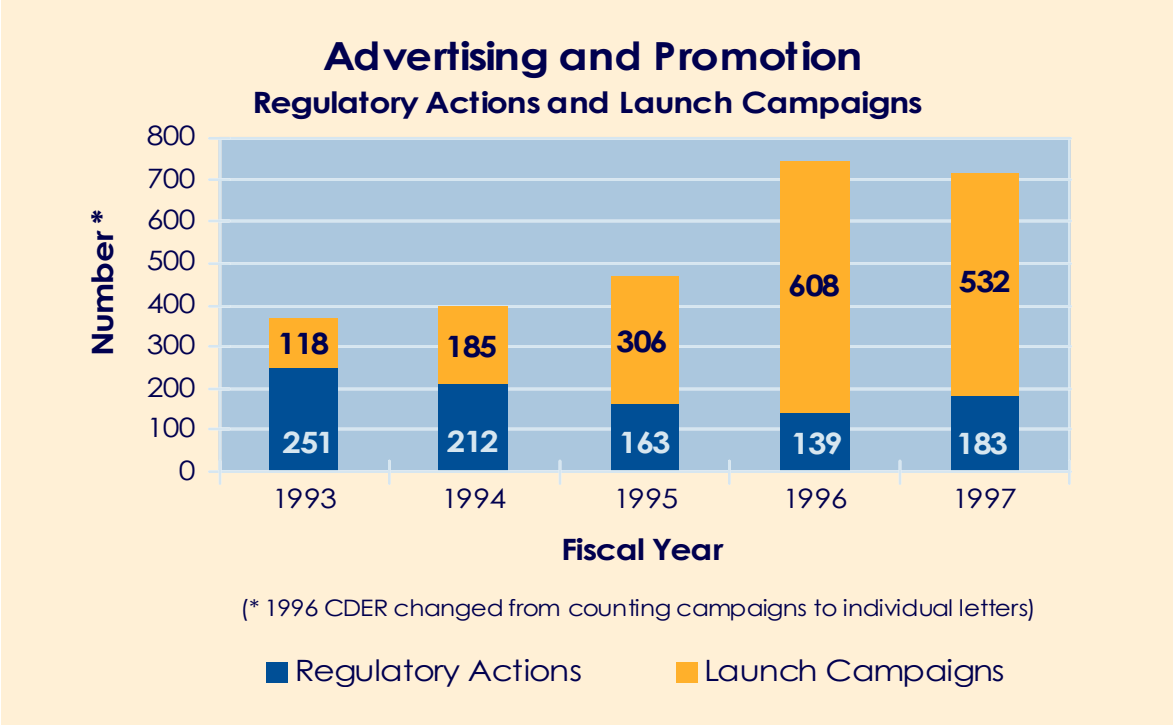
CDER processes nine different types of certificates to foreign governments. These certificates enable the manufacturers to export their products to foreign customers and foreign governments. The certificates attest that the drug products are subject to inspection by the FDA and are manufactured in compliance with current good manufacturing practices. In addition, they verify that the drug products being exported:

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

Drug Advertising and Promotion

CDER promotes and protects the health of Americans by ensuring that drug advertising and promotional materials are truthful and balanced. The Center operates a comprehensive program of education, surveillance and enforcement about drug advertising and promotion. Included in this program are:

- *Drug launch campaign advisories.* The Center reviews drug advertising and promotional materials before drug companies launch marketing campaigns that introduce new drugs or introduce new indications or dosages for approved drugs. In fiscal year 1997, the Center issued 532 advisory letters to companies regarding their promotional materials for launch campaigns.
- *Regulatory actions.* The Center issued 183 regulatory action letters to pharmaceutical companies for prescription drug promotions determined to be false, misleading or lacking in fair balance. These were either "untitled" letters for routine violations or "warning" letters for serious or repeat violations.
- *Other actions.* The Center also issued 555 other advisory, acknowledgment or closure letters to the industry regarding prescription drug advertising and promotion.



Drug Advertising and Promotion

- *Direct-to-consumer advertising.* CDER issued 240 letters in all categories regarding direct-to-consumer advertising.
- *Improved patient information for prescription drugs.* The Center continued its research, education and outreach activities in support of the public-private plan to provide consumers with easy-to-read information about their prescription drugs. CDER and other FDA components have been working with industry, non-profit agencies and academic groups to ensure that useful drug information reaches 75 percent of patients by the year 2000.
- *Improved drug label testing.* In February 1997, CDER proposed standardized over-the-counter drug label formats and is developing proposed regulations for the professional labeling that accompanies prescription drugs. To support these efforts, the Center continues to test label prototypes.
- *Risk vs. benefit communications research.* The Center is conducting research to assess the public's ability to understand risk vs. benefit information. The goal is to develop useful and meaningful ways of presenting important information about a drug's known risks and benefits.

International Harmonization

Harmonization—making the drug regulatory process more efficient and uniform—is an issue that is important not only to CDER, but to drug regulatory agencies and pharmaceutical companies throughout the world. During the last seven years, 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.

Although drug regulatory systems in all three regions share the same fundamental concerns for the safety, efficacy and quality of drug products, many time-consuming and expensive technical tests have had to be repeated in all three regions. To reduce, minimize and even eliminate unnecessary duplicate testing during the research and development of new drugs, the ICH process results in documents that recommend ways to find consistency in the implementation and application of technical guidances and requirements for product registration. ICH has four areas of focus: efficacy (human clinical trials), safety (animal pharmacology/toxicology), quality (manufacturing) and regulatory communication.

Highlights from the fourth biennial meeting, ICH 4, held in July 1997 in Brussels, Belgium, included finalization of 10 harmonized guidances and announcement of the next phase—the start of work on a Common Technical Document that can be used in all three ICH regions.

The results in Brussels mean that work on more than three-quarters of the guidances has been completed. After having made so much progress during this first phase, the ICH steering committee agreed to launch a second phase that will maintain the existing documents and develop a Common Technical Document. This represents a logical progression from a single, harmonized set of guidances for collecting the technical data to a common technical information package for presenting the data. The goal is to harmonize format so that essentially the same core submission could be provided to the regulatory authorities in all three regions.

ICH 4 also announced finalization of the Medical Dictionary for Regulatory Activities, which will provide a common terminology to facilitate regulatory communication. Also, the release for consultation of the consensus draft guidance, Specifications for New Chemical Drug Substances and Products (Q6A), represents a step toward the goal of having the same specifications

International Harmonization

for a drug product wherever it is marketed. The draft guidance has been developed in close collaboration with the pharmacopoeial authorities in each region.

Additional information on ICH activities may be found on the World Wide Web at **http://www.ifpma.org/ich1.html.** ICH guidances are available on CDER's Web site at **http://www.fda.gov/cder/guidance/index.htm.**

Applied Research

In 1997, CDER continued to support, facilitate and improve the drug development and review process through applied research. Research within the Center advances the scientific basis for regulatory policy and ensures that policy and decisions are based on the best available science. Some of the results of CDER's 1997 research included:

- Development of artificial intelligence software that will help assess the cancer causing potential of new drugs and aid in drug development and review.
- Implementation of a guidance describing data needed on drug metabolism and drug-drug interactions. This will help assure the safety of new drugs and aid in drug development and review.
- Development of a guidance that allows a short-term study in genetically altered mice in combination with a standard two-year rodent study to assess a drug's cancer causing potential. Continuing research will evaluate the potential of genetically altered mice to support other improvements in the requirements for animal testing.
- Assessment of near-infrared spectroscopy and development of a document for qualifying such equipment. This will provide FDA and industry with a common base for accepting data from this new technology and will eventually contribute to improved product quality.
- Development of additional guidances that allow manufacturers to make certain changes in equipment and production without requiring prior approval from the Center.

CDER's applied research was expanded in 1997 through development of external collaborations with industry, academia, professional societies and other government laboratories, including:

- The *Product Quality Research Initiative (PQRI)* to focus on research to support improvements in the area of drug quality and production.
- The *Collaboration for Drug Development Improvement (CDDI)* to support scientifically sound approaches for expediting drug development.

Additional information on research is available on CDER's Web site at **http://www.fda.gov/cder/otr/index.htm.**

Communications

CDER's evolution into an open and accountable organization within the FDA has relied heavily on improved communications.

Dissemination Activities

The Center has invested heavily in the technology to make information about its activities widely available to individuals, the media and industry. The Center has made extensive use of traditional methods of communication as well as the World Wide Web.

- The Center Internet Web site, **http://www.fda.gov/cder,** has grown by nearly 100 megabytes of information a week. Use has exploded from about 30,000 hits a month in late 1996 to nearly 2 million hits a month currently.
- CDER's Electronic Freedom of Information Reading Room provides Internet users ready access to its most frequently requested documents.
- CDER's Drug Information Branch answered more than 36,000 telephone inquiries and 17,500 written requests from pharmacists, doctors, nurses, pharmaceutical and insurance companies, consumers, Federal agencies and others. They were provided the most current drug information.
- CDER scientists and regulatory experts participated in the development of 15 Department of Health and Human Services press releases and 26 FDA talk papers. They took part in numerous media interviews related to these activities. In addition, more than 1,000 interviews were conducted for specialized publications serving the pharmaceutical industry.

Consumer and Industry Outreach Efforts

The Center cooperates with consumer health organizations, professional societies and industry associations to help their members better understand CDER's policies and actions.

- The Center in cooperation with FDA's Office of External Affairs implemented "Hot Topic" briefings for health associations to explain in detail actions with a high degree of public health impact.
- CDER engaged in a partnership to co-sponsor a 2½-hour live satellite broadcast to industry about the Center's developments in adverse event reporting.

Communications

- The Center's scientists and regulatory officials routinely make presentations to and participate in association conferences and workshops.
- The International Conference on Harmonization product quality guidances were subject of a day-long CDER-sponsored training session held for industry representatives.
- CDER's exhibit and information program completed successful showings at three national health care conferences.
- The Center conducted about 150 domestic and foreign videoconferences for academia, industry and associations.

Public Participation

CDER has expanded its efforts to obtain outside expertise and opinion to help formulate policies and procedures that affect the public and industry.

- Panels of outside experts confer with CDER about difficult scientific issues. These advisory committees met about 50 times a year during the five years of PDUFA, compared with about 30 times a year in the preceding five years.
- The Center has expanded its use of open public meetings to obtain input on important public health policy issues.
- In addition to analyzing required public comments on proposed new rules, the Center sought and received comments on its non-binding guidances to industry.

Ombudsman's Activity

In its second year of operation, the Center Ombudsman's office doubled its activity to more than 200 interactions. The goal of the Ombudsman is to provide a mechanism for people inside and outside the Center to seek solutions to problematic interactions and to suggest better ways for CDER to do its work. The ratio of external to internal cases rose from 2-to-1 in the first year to 3-to-1 in the second.

Improving Policy Consistency

New and Proposed Rules

In 1997, CDER published five proposed rules and 11 final rules. Some highlights are:

- *Electronic Records; Electronic Signatures Final Rule* (62FR13430, March 20, 1997). New regulations that provide criteria for FDA acceptance, under certain circumstances, of electronic records, electronic signatures and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper.

- *National Environmental Policy Act (NEPA) Final Rule* (62FR40570, July 29, 1997). Amendment to regulations governing compliance with NEPA that increase the efficiency of FDA's implementation of the act and reduce the number of evaluations by providing for categorical exclusions for additional classes of actions that do not individually or cumulatively have a significant effect on the human environment and for which neither an environmental impact statement nor environmental assessment is required.

- *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling Final Rule* (62FR45313, Aug. 27, 1997). Amendment to regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling.

- *Expedited Safety Reporting Requirements for Human Drug and Biological Products Final Rule* (62FR52237, Oct. 7, 1997). Amendment to expedited safety reporting regulations to provide consistency with FDA's MedWatch program and with ICH guidances. The amendments include definition changes, for example, what constitutes a serious adverse reaction to a medication, and changes to reporting content, format and time frames. The final rule is the first of several proposed and final rules that CDER expects to publish during in the coming year to implement the ICH guidances and update the information technology used to report and record adverse events.

- *Over-the-Counter Human Drugs; Proposed Labeling Requirements* (62FR9024, Feb. 27, 1997). Proposed new regulations that standardize the format for OTC drug labeling to enable consumers to read and understand better OTC drug product labeling and to apply this information to the safe and effective use of OTC drug products.

Improving Policy Consistency

Guidances to Industry

During 1997, in accordance with the FDA's Good Guidance Practices (62FR8961, Feb. 27, 1997), 40 guidances for industry were issued either as draft or final documents. Of these, 22 were the result of ICH efforts. Guidance documents published during the last two years are available on the CDER Web site at **http://www.fda.gov/cder/guidance/index.htm.** The Center has undertaken a project to make all Center guidances available on its Internet site.

Among the documents completed this year are two of four guidances begun under the administration's Reinventing Government initiative. These guidances clarify how to make and document manufacturing scale-up and post-approval changes for non-sterile semisolid dosage forms and modified-release solid oral dosage forms. They were published in May and September 1997, respectively. Other guidances for industry completed in draft or final form in 1997 include:

- *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. This draft document is intended to provide guidance to applicants planning to file NDAs or efficacy supplements on what evidence should be provided to demonstrate effectiveness.
- *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products*. This draft guidance considers the quality and quantity of data that may be adequate to add a new use to the prescribing information for a product used in the treatment of cancer.
- *Post-Marketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*. This guidance clarified reporting requirements for adverse experiences.
- *Archiving Submission in Electronic Format—NDAs*. This is the first in a series that will provide guidance on how to submit applications in electronic format.

Improving Policy Consistency

MAPPs

During 1997, the Center continued its efforts to implement its Manual of Policy and Procedures (MAPP). More than 32 individual MAPPs were issued to CDER staff. MAPP development is part of a long-term Center effort to update the old staff directives. Old directives are being reviewed, revised and revoked when necessary. New MAPPs are being developed to help the Center better achieve its mission and to facilitate Center operational changes. All Center MAPPs are available on the CDER Web site under *Regulatory Policy* at: **http://www.fda.gov/cder.**

Organizational Changes

During 1997, the Center continued to fine-tune its organizational structure based on the major reorganization announced in November 1995. The new structure and the refinements made in 1997 helped improve management efficiency and processes, increase application review efficiency and consistency, improve policy decisions and reduce duplicative work. The 1997 organizational changes are partly responsible for the successes highlighted in this report and will play a role in enabling CDER to continue to exceed its user fee review performance goals in the future.

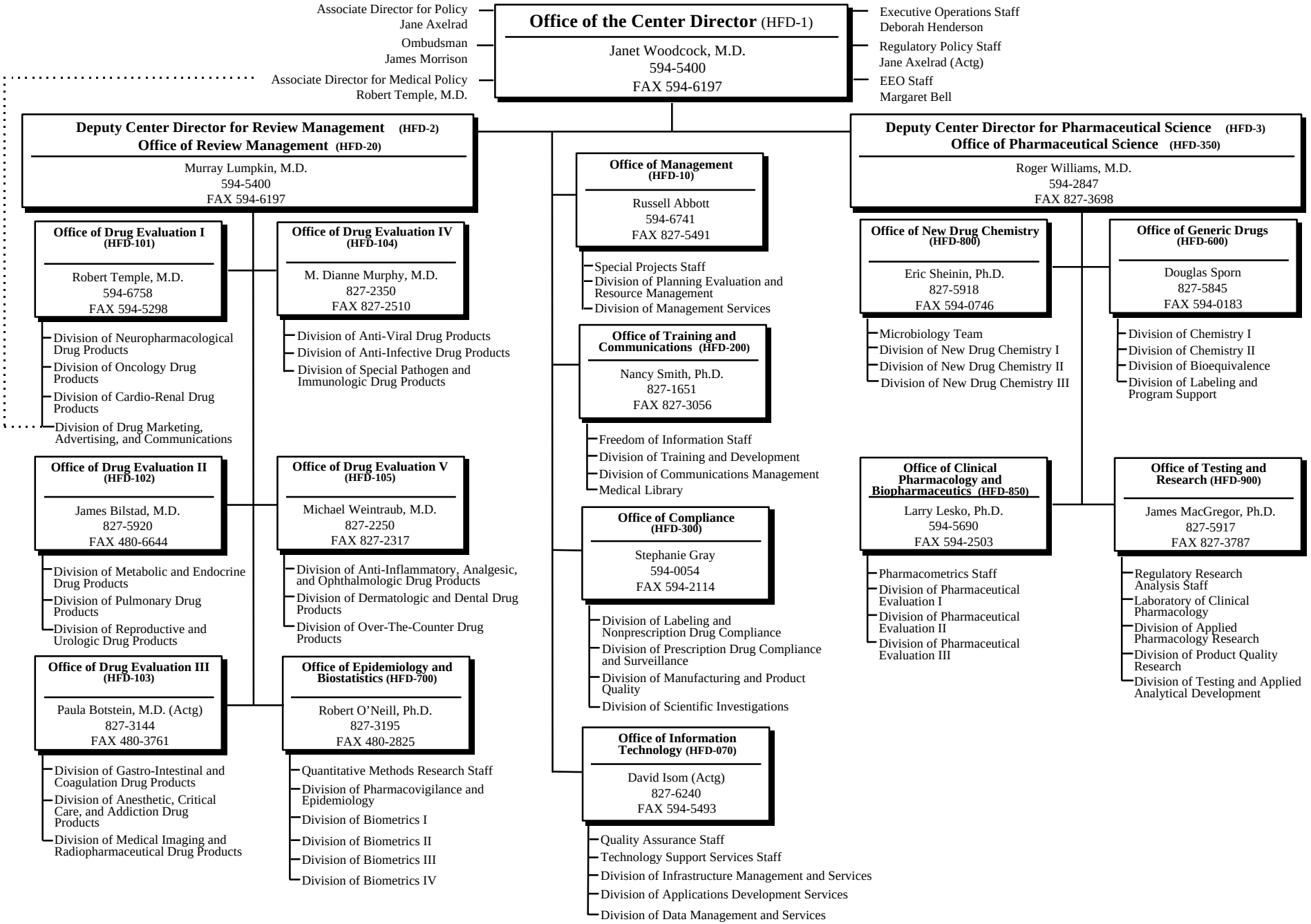
The formation of the *Office of Information Technology* in 1997 will provide a more focused approach to CDER-wide information technology support, services, investment management and strategic planning. Promoting these functions to office level will maximize CDER's efforts to comply with the Information Technology Management and Reform Act of 1996 and to implement an electronic regulatory submission and review environment—a major step toward the goal of accepting and reviewing electronic regulatory submissions by 2002. Elements of electronic regulatory submission and review are part of CDER's compliance with the 1997 PDUFA reauthorization, the National Partnership for Reinventing Government and the Government Performance and Results Act.

As CDER has grown, new divisions have helped better focus oversight responsibility and level workload. In 1997, the *Division of Special Pathogens and Immunologic Drug Products* was formed in response to the growth of both the Division of Anti-Viral Drug Products and the Division of Anti-Infective Drug Products. The new division will oversee, for example, products used to treat systemic fungal, mycobacterial or parasitic diseases; vaginal antifungal products; certain immunologic products; and the quinolones. It is the third division in the Office of Drug Evaluation IV.

Other initiatives included the reorganization of the *Office of Testing and Research* in the Office of Pharmaceutical Science and the formation of the *Special Projects Staff* located in the Immediate Office of the Director, Office of Management. The Special Projects Staff will facilitate the Center's strategic planning. (See CDER's organizational chart on the next page.)

AS OF: 3/24/98

CENTER FOR DRUG EVALUATION AND RESEARCH



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