Center for Drug Evaluation and Research

fact book 1997

Note: This publication is no longer current. It has been replaced by the yearly CDER Report to the Nation. The current issue of the Report is available at: http://www.fda.gov/cder/about/default.htm#What%20We've%20Accomplished

May 1997

I am pleased to present the 1997 Fact Book from the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA). This publication provides an overview of the diversity of activities and responsibilities within the Center.

CDER consists of 1,763 employees, working together as a strong and creative team to ensure that safe and effective drugs are available to the American public.

This booklet describes the organization and activities of CDER as we strive together with our partners—industry and trade associations, consumers, Federal, state and local government agencies, universities, hospitals, health care professionals, foreign governments, and manufacturers—to serve the public by making significant improvements in human health through excellence and innovation in drug regulation.

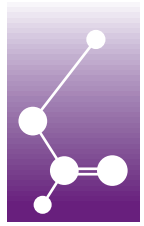
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Table of Contents

What Americans Expect

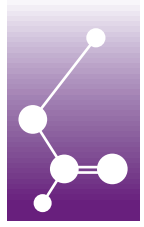
American consumers rely on the
U.S. Food and Drug Administration's
Center for Drug Evaluation and Research to:

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



CDER Mission

CDER assures that safe and effective drugs are available to the American people.



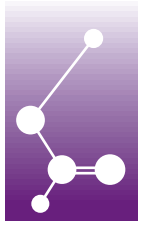
CDER Vision

CDER: A vital community serving the public by making significant improvements in human health through excellence and innovation in drug regulation.

Constituents in Drug Development and Review

CDER works closely with many organizations during the drug development and review process:

- *Industry and trade associations* - assisting personnel involved in developing new drugs;
- *Consumers and consumer groups* - seeking and providing information on new products for treating disease;
- *Universities, hospitals, and health care professionals* - offering guidance on conducting clinical trials and research on new products, and facilitating access, before general approval, to products to treat life-threatening diseases for which no satisfactory therapy is available;
- *Federal, state, and local government agencies* - providing information concerning the review of new drugs, product information, and their appropriate use; and
- *Foreign governments* - working together to ensure that harmonized requirements are met without sacrificing efficacy, safety, or quality standards.



Drug Review Team

CDER drug review team members apply their individual special technical expertise to review new drug applications:

- *Chemists* focus on how the drug is manufactured and whether the manufacturing controls and packaging are adequate to ensure the stability and purity of the product.

- *Pharmacologists/Toxicologists* evaluate the effects of the drug on laboratory animals in short-term and long-term studies, including the potential for drugs to induce birth defects or cancer in humans.

- *Physicians* evaluate the results of the clinical tests, including the drug's adverse and therapeutic effects, and determine if the product's benefits outweigh its known risks at the doses proposed.

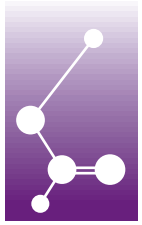
- *Project Managers* evaluate regulatory information to determine compliance with current policies and regulations. In addition, they orchestrate and coordinate the drug review team's interactions, efforts and reviews. They also serve as the CDER review team's primary contact for the drug industry.

- *Statisticians* evaluate the designs for each primary study and the validity of statistical analyses.

- *Microbiologists* evaluate the effects of anti-infectives (e.g. antibiotics, antivirals, antifungals) on germs. These drugs differ from others because they are intended to affect the germs instead of the patients.

- *Biopharmaceutists* evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized, and eliminated. They determine whether certain evidence supports the recommended dosing regimen and check for interactions with other drugs.

- All team members make sure the label is accurate and provides clear instruction to health care practitioners (if prescription) or to consumers (if OTC).



Early Access Programs

CDER has programs to ensure that patients with life-threatening conditions get the earliest possible access to promising new therapies. These programs include the "Treatment IND" (investigational new drug) program and "Parallel Track" program, as well as "Accelerated Approval."

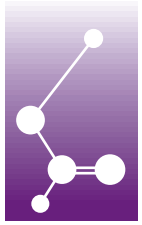
Treatment INDs are a means of facilitating—even before general marketing of the product—the availability of promising new drugs to desperately ill patients for whom no other therapy is available. A promising new drug can be distributed under a Treatment IND if:

- The drug is intended to treat a serious or immediately life-threatening disease;
- There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
- There is presumptive evidence that the drug may offer some benefit to certain patients; *and*
- Proper clinical trials are well underway to determine if the drug really does offer patients any benefit.

Drug manufacturers apply to CDER to obtain a Treatment IND while their product is still undergoing testing in humans—if the drug fits the criteria just mentioned. Once under a Treatment IND, the product may then be legally distributed to appropriate patients before general marketing is allowed. Manufacturers are permitted to charge for drugs distributed under a Treatment IND, although they usually do not. Treatment INDs also help the manufacturer obtain additional data on the drug's safety profile. Patients wishing to participate in a Treatment IND should speak with their physician because drugs under treatment INDs must be distributed from the manufacturer to a licensed physician.

Parallel Track expands the availability of promising investigational drugs to people with AIDS and other HIV-related diseases who have no therapeutic alternatives and cannot participate in clinical trials. Those wishing to participate in the Parallel Track program should call the AIDS Clinical Trials Information Service (ACTIS) at 1-800-TRIALS-A (1-800-874-2572). You can also access the ACTIS home page on the World Wide Web at http://www.actis.org.

Accelerated Approval is a mechanism through which a drug product for serious and life-threatening diseases for which no other alternative therapies are available can be approved for general marketing without having to show that it offers a clinically meaningful benefit to the patient. Instead, safety and effectiveness are determined by showing that the product has a positive effect on a laboratory finding or a patient's physical sign or symptom (also known as a "surrogate endpoint"). The surrogate endpoint is reasonably believed to predict an ultimate clinical benefit for the patient. Under this program, the manufacturer must continue with the clinical testing of the product after general marketing approval to validate whether the surrogate endpoint actually did predict a meaningful benefit for patients. If further testing does not validate the surrogate endpoint, FDA will remove the product from the market in an accelerated manner.



CDER Highlights

Office of the Center Director

Executive Operations Staff

The Executive Operations Staff provides support to the Office of the Center Director, including coordinating executive and legislative activities; managing the preparation and coordination of Center-level meetings; and responding to written correspondence from constituents. The Staff also provides project management support for Center- and Agency-wide initiatives to improve the quality and timeliness of regulatory reviews and improve team-based management practices. The Staff provides management support and advice to senior managers concerning Center programs such as contract and grant activities.

Regulatory Policy Staff

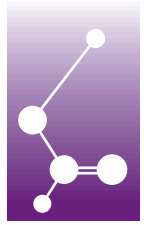
The Regulatory Policy Staff initiates, develops and reviews regulations, policies, procedures, and guidances that affect the drug review process. This includes creating and publishing CDER's Manual of Policies and Procedures to promote consistency and accountability throughout the Center, preparing Federal Register notices for publication, and responding to citizen petitions. In addition, the Staff serves as the Center's focal point for regulatory issues and provides advice and assistance on such matters as scope, applicability, and intent of the Food, Drug and Cosmetic Act and other laws, regulations, and policies. The Regulatory Policy Staff also serves as the coordinator for user fee billing activities.

Ombudsman

The primary mission of the Ombudsman is to receive complaints, investigate and act on them, mediate disputes, and in general attend to problems involving interpersonal working relationships. In CDER, the Ombudsman has responsibilities in addition to resolving disputes, such as getting feedback from inside and outside the Center about the effectiveness of programs and about problems that impede CDER's performance of its mission or conflict with its values and/or operating principles. The Ombudsman advises the Center Director on ways to correct such problems.

Equal Employment Opportunity and Diversity Management Staff

The Center's Equal Employment Opportunity and Diversity Management Staff advises and assists the Center Director and other management officials on equal employment opportunity and diversity activities that impact on policy development and program goals. The Staff also develops policies and procedures and establishes guidelines to assist supervisory personnel in implementing Affirmative Employment Plans; encourages and participates in the processing of informal resolution of discrimination complaints based on race, religion, sex, national origin, age, and other unmerited criteria; and identifies broad areas in which analytical studies would support changes in the overall diversity process.



CDER Highlights

Office of Pharmaceutical Science

The Office of Pharmaceutical Science provides scientific and regulatory support through:

- Developing and implementing review management and scientific policies pertaining to the generic drug review process. This includes evaluating and approving abbreviated new drug applications (ANDAs) and their amendments.

- Developing and implementing review management and scientific policies pertaining to the new drug review processes for chemistry, manufacturing controls, clinical pharmacology and biopharmaceutics. This includes performing scientific reviews on the applicable sections of investigational new drug applications (INDs) and new drug applications (NDAs).

- Developing and implementing policies and directing programs through applied regulatory research in consultation and collaboration with internal and external constituencies. This research provides a scientific basis for all aspects of drug review and postmarket surveillance.

- Performing drug testing and scientific evaluation of drug products in support of the regulatory components of FDA.

- Developing and implementing standards and policies for both generic drugs and new drugs that enhance the drug development and regulatory review processes.

- Providing scientific oversight, through the Center's Office of New Drug Chemistry, of chemistry and manufacturing controls (CMC) and the sterility sections of INDs, NDAs, and supplements. This oversight includes developing guidances for industry on particular technical issues and policies.

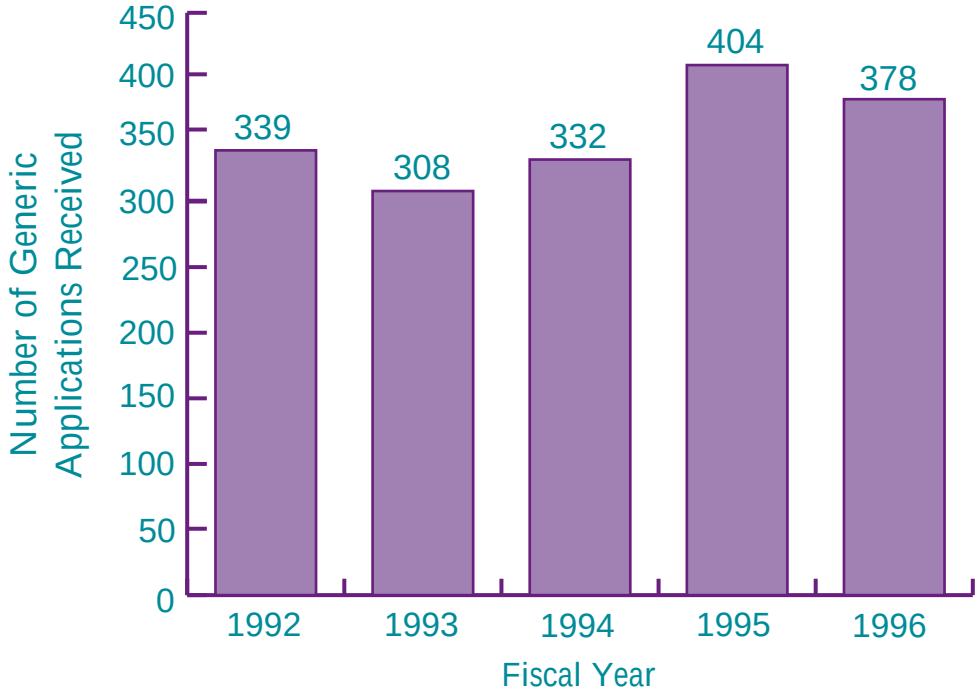
- Providing scientific oversight, through the Center's Office of Clinical Pharmacology and Biopharmaceutics, of microbiology, biopharmaceutics, and clinical pharmacology aspects of INDs, NDAs, and supplements. This oversight includes validating the comparability of clinical safety and efficacy studies conducted during the IND phase of drug development, and evaluating the impact of drug-to-drug interactions and population characteristics on the safety and efficacy of drug products.

Office of Pharmaceutical Science (cont.)

Generic Drug Review

In addition to regulating new prescription and over-the-counter drugs, CDER also regulates their generic counterparts. The abbreviated mechanism for approving generic copies of drug products (first approved after 1962) was established by the Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman-Hatch Act). This Act requires that companies wishing to obtain approval for generic drugs must demonstrate that their products are the same as the reference drugs in terms of active ingredients, strength, dosage form, route of administration, and labeling. In addition, bioequivalence—showing that the proposed generic and the reference drug can be expected to have the same therapeutic effect and safety profile if administered properly—must also be demonstrated. However, preclinical and clinical tests do not have to be repeated for each generic product.

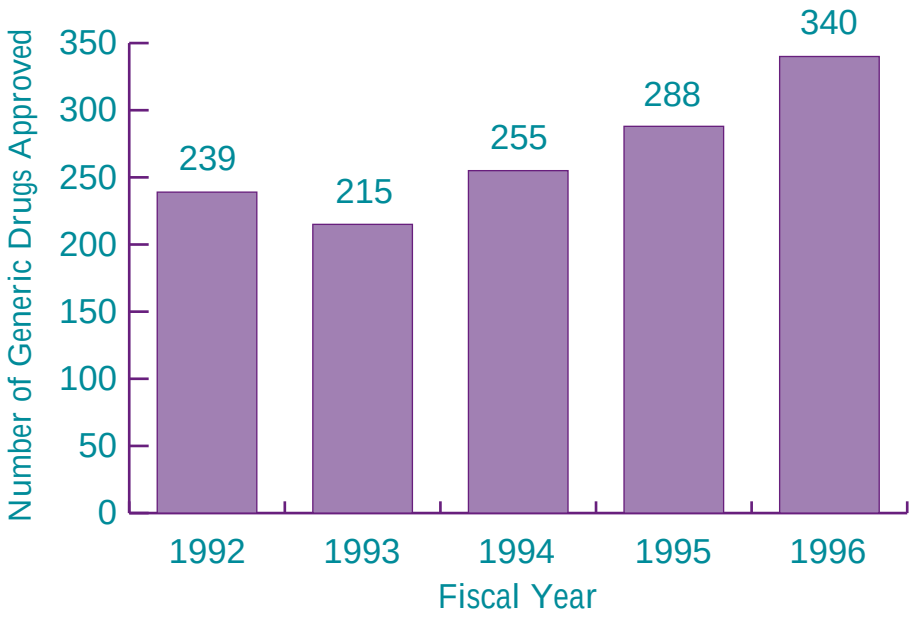
Generic Drug Applications



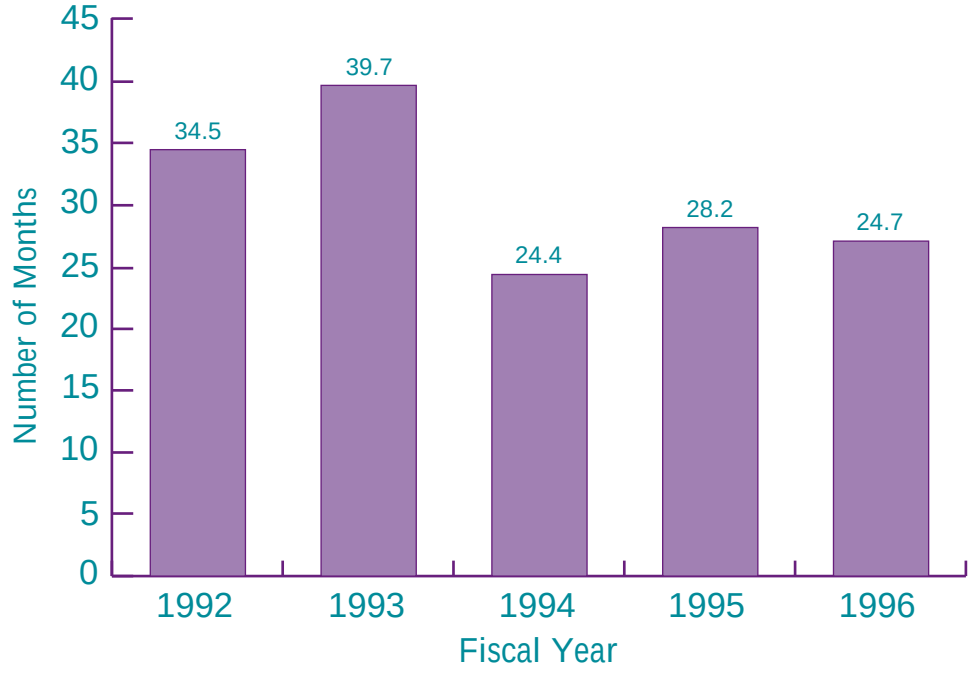
Office of Pharmaceutical Science (cont.)

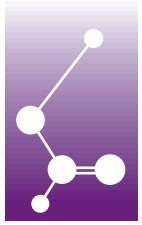
Generic Drug Approvals

Generic Drug Approvals



Median Total Times to Approval in Months





Office of Pharmaceutical Science (cont.)

Office of Testing and Research

CDER's Office of Testing and Research is responsible for conducting scientific research and development in support of the Center's drug application review responsibility. In 1996, the Office:

- continued developing a database containing over 700 drug listings and associated toxicological data identifying these products' cancer-causing potential, or carcinogenicity. This database has contributed to improved international guidances on toxicology testing of pharmaceuticals; a new International Conference on Harmonization (ICH) guidance on carcinogenicity testing; and an ICH guidance on pharmacokinetic alternatives in rodent carcinogenicity studies for pharmaceuticals.

- evaluated the adverse interactions of certain drugs when taken together. This evaluation contributed to withdrawal of terfenadine (the antihistamine Seldane) from the market; publication of an industry guidance that describes recommended data showing new drug metabolism and potential drug interactions; and a systematic examination of labeling for all pending new drug applications.

- created a scientific foundation of research data to support pharmaceutical industry guidances that will permit expeditious post-drug approval formulation and manufacturing changes. This research will result in regulatory guidances that can enable the industry to institute a change quickly, reduce the burden of in vivo bioequivalence evaluations, and allow the Center to reduce the number of Prior Approval Supplements reviewed.

- conducted in vitro and in vivo studies of mouse and human tumor cells after widely-heralded published reports indicated that certain approved antidepressants and antihistamines could stimulate tumor growth. CDER's research found that reported studies were incorrect and not reproducible and, as a result, averted a potential public health crisis over several FDA-approved and widely prescribed drugs.

- validated a test to detect the presence of human chorionic gonadotrophin (hCG), a frequently used birth control agent, in tetanus vaccines after Mexican, Nicaraguan, and Philippine authorities reported possible contamination of vaccines with the drug. CDER's research found no evidence of contamination. The Center reported these findings to the World Health Organization and public health authorities in the participating countries.

CDER Highlights

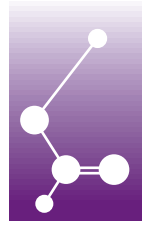
International Harmonization Activities

CDER's International Activities Coordinating Committee (IACC) plans the Center's international programs and facilitates information exchange and updates on international activities. In addition, IACC establishes areas of focus and subcommittees as appropriate. One such committee is the Joint Review Subcommittee that was charged by the Center Director to create a draft Manual of Policy and Procedures to facilitate interagency reviews.

A primary focus of CDER's international activities is the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, known simply as the International Conference on Harmonization (ICH). ICH is an international project that brings together the regulatory authorities of the European Union, Japan, and the United States, and experts from the pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product registration.

The CDER lead on ICH is the Deputy Center Director for Pharmaceutical Science. ICH makes recommendations on ways to harmonize the interpretation and application of technical guidelines and requirements for pharmaceutical product registration. By harmonizing these requirements, ICH is trying to reduce or eliminate duplicate testing that manufacturers perform during the research and development of new medicines. This harmonization will allow a more economical use of human, animal, and material resources, and eliminate unnecessary delays in the global development and availability of new medicines, while simultaneously maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect and promote public health.

In addition to its ICH involvement, CDER staff also meet regularly with international regulatory counterparts. Such meetings include a yearly Trilateral meeting with Canadian, Mexican, and U.S. officials, a yearly Tripartite meeting with Canadian, United Kingdom, and U.S. officials, and a yearly Bilateral meeting with European Union and U.S. officials.



CDER Highlights

Office of Review Management

CDER's Office of Review Management (ORM) develops and implements drug review management and scientific policies, including prescription drug user fee policies. With support from the Office of Pharmaceutical Science on chemistry and manufacturing controls and biopharmaceutical issues, this Office reviews all INDs and NDAs for human drugs, except generic drug applications.

In addition, ORM:

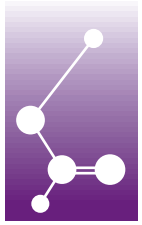
- Evaluates for safety and effectiveness NDAs for over-the-counter (OTC) drug products, OTC drug monographs, prescription drug switches to OTC drug status, and other OTC-related drug products;

- Develops and implements safety and effectiveness standards for prescription and OTC drug products;

- Oversees surveillance programs to collect and evaluate the adverse effects and use trends of marketed drug products;

- Provides Center direction and policy formulation for pharmacology and toxicology issues; and

- Cooperates with other FDA components, other Department of Health and Human Services (DHHS) organizations, government and international agencies, volunteer health organizations, universities, individual scientists, non-government laboratories, and drug manufacturers on matters related to drug development, post-marketing surveillance, and general drug regulatory oversight.



Office of Review Management (cont.)

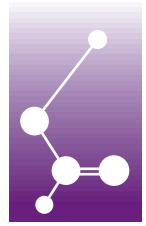
Prescription Drug User Fee Act

CDER's mission is to assure that safe and effective drugs are available to the American people as quickly as possible. This includes making timely decisions on new drug applications. In 1992, Congress, working with FDA and the pharmaceutical industry, enacted the Prescription Drug User Fee Act (PDUFA) to provide appropriate human and infrastructure resources to accelerate the review of drug applications, without compromising the safety and effectiveness standards that the American people expect.

This Act permits the Center to charge user fees to pharmaceutical manufacturers. These user fees were, in turn, spent to hire more reviewers and fund fundamental review management changes including the increased use of information technology. PDUFA has allowed the Center to fully eliminate review queues, to essentially eliminate all drug application and supplement backlogs, and to speed the review of new drug applications.

In return for the fees, PDUFA set ambitious review performance goals for the Center. CDER was tasked with clearing an overdue backlog equivalent to half a year of submissions, reviewing a pending workload equal to nearly 2 years of submissions, and building a review capability that could meet a phased schedule of substantially accelerated review performance goals for applications received in fiscal years 1994 to 1997.

To date, CDER has met all of its user fee goals and is reviewing 98 percent of all NDAs within the timeframes agreed to under PDUFA.



Office of Review Management (cont.)

Prescription Drug User Fee Act Update
Final Review Performance on Applications Filed in FY 1995

New Drug Applications - PDUFA Goal: Review 70 percent of filed applications within 12 months of receipt*

- 111 New Drug Applications filed
- 109 of 111 applications reviewed within goal (98 percent on-time)

Effectiveness Supplements - PDUFA Goal: Review 70 percent of filed applications within 12 months of receipt

- 77 filed
- 73 of 77 supplements reviewed within goal (95 percent on-time)

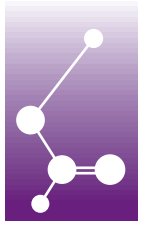
Manufacturing Supplements - PDUFA Goal: Review 70 percent of filed applications within 6 months of receipt

- 1,251 filed
- 1,123 of 1,251 supplements reviewed within goal (90 percent on-time)

Resubmissions - PDUFA Goal: Review 70 percent of filed applications within 6 months of receipt

- 58 filed
- 56 of 58 resubmissions reviewed within goal (97 percent on-time)

* Major amendments received within 3 months of the goal date will extend it one time by 3 months.



Office of Review Management (cont.)

Prescription Drug User Fee Act Update
Review Performance to Date on Applications Filed in FY 1996

Even more stringent performance targets for on-time application review took effect for applications filed in FY 1996. As of December 31, 1996:

New Drug Applications - PDUFA Goal: Review 80 percent of filed applications within 12 months of receipt*

- 115 New Drug Applications filed
- 47 applications already reviewed within goal
- 68 pending applications are still under goal (none have missed goal)

Effectiveness Supplements - PDUFA Goal: Review 80 percent of filed applications within 12 months of receipt

- 102 filed
- 51 supplements already reviewed within goal
- 50 pending supplements are still under goal (1 has missed goal)

Manufacturing Supplements - PDUFA Goal: Review 80 percent of filed applications within 6 months of receipt

- 1,220 filed
- 1,055 supplements already reviewed within goal
- 127 pending supplements are still under goal

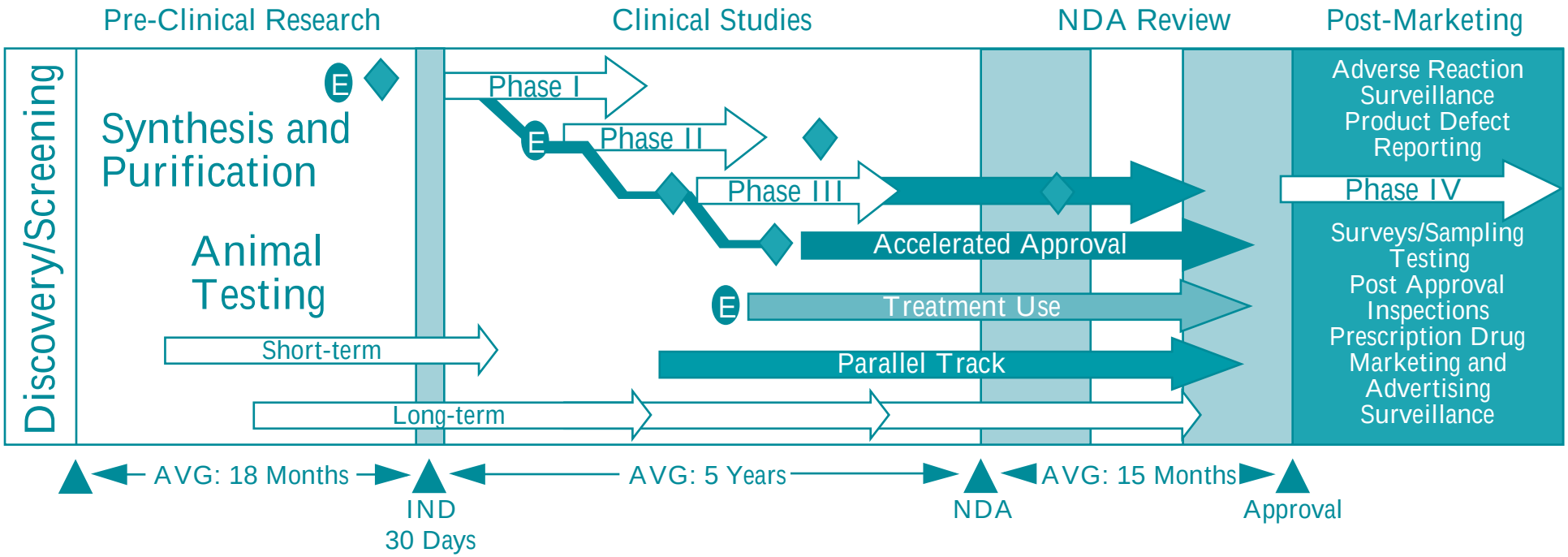
Resubmissions - PDUFA Goal: Review 80 percent of filed applications within 6 months of receipt

- 89 filed
- 79 resubmissions already reviewed within goal
- 9 pending resubmissions are still under goal (1 has missed goal)

* Major amendments received within 3 months of the goal date will extend it one time by 3 months.

Office of Review Management (cont.)

New Drug Development Process



FDA Time

Industry Time

FDA & Industry Time

Sponsor/FDA Meetings Encouraged

Accelerated Review:

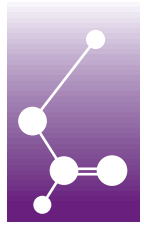
E Subpart E

Accelerated Approval

Expanded Access:

Treatment Use

Parallel Track

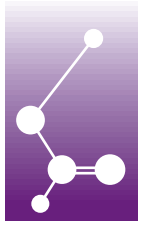


Office of Review Management (cont.)

New Molecular Entities Approved in 1996

New molecular entities (NMEs) - drugs distinctly different in chemical structure from those already on the market - approved by CDER from January 1, 1996, to December 31, 1996, include:

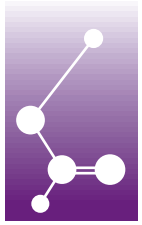
Product Name	Generic Name	Manufacturer	Indications/Use (general description)	Total time to approval in months	CDER review time in months
Myoview	technetium Tc99m tetrofosmin	Medi Physics	radiographic agent for x-rays	32.1	30.8
Norvir	ritonavir	Abbott	HIV infection	2.3	2.3
Crixivan	indinavir sulfate	Merck	HIV infection	1.4	1.4
Visipaque	iodixanol	Nycomed	radiographic agent for x-rays	36.6	36.1
Mavik	trandolapril	Knoll	hypertension	18.9	13.2
Buphenyl	sodium phenylbutyrate	Ucyclyd	urea cycle disorders	14.4	12.2
Taxotere	docetaxel	Rhone Poulenc	breast cancer	21.6	20.4
Gemzar	gemcitabine HCl	Lilly	pancreatic cancer	15.4	15
Hycamtin	topotecan HCl	SmithKline Beecham	ovarian cancer	5.2	5.2
Differin	adapalene	Galderma	acne vulgaris	38.2	38.2
Xalatan	latanoprost	Pharmacia and Upjohn	glaucoma, ocular hypertension	11.7	11.7



Office of Review Management (cont.)

1996 NMEs (continued)

Product Name	Generic Name	Manufacturer	Indications/Use (general description)	Total time to approval in months	CDER review time in months
Albenza	albendazole	SmithKline Beecham	hydatid disease	6	6
Remeron	mirtazapine	Organon	depression	16.5	14.8
Humalog	lispro	Lilly	diabetes mellitus	15.1	15.1
Camptosar	irinotecan HCl	Pharmacia and Upjohn	colorectal cancer	5.6	5.6
Viramune	nevirapine	Boehringer Ingelheim	combination HIV treatment	3.9	3.9
Merrem	meropenen	Zeneca	meningitis	5.9 **	5.9
Vistide	cidofovir	Gilead	CMV retinitis in patients with AIDS	8.8	8.8
Ultiva	remifentanil HCl	Glaxo Wellcome	general anesthesia	9.9	9.9
Allegra	fexofenadine HCl	Hoechst Marion Roussel	seasonal allergic rhinitis	11.8	11.8
Cerebyx	fosphenytion sodium	Parke Davis	control of epileptic seizures	17.4	15.7
IVY-Block	bentoquatam	Enviroderm	skin protection against poison ivy, oak and sumac	22.9	17.9
Feridex	ferumoxides	Advanced Magnetics	detection of liver and spleen lesions	30.7	28.8
Alphagan	brimonidine tartrate	Allergan	glaucoma, ocular hypertension	12	12
Meretek UBT	urea, C-13	Meretek	H. pylori detection kit	16.3	14.6



Office of Review Management (cont.)

1996 NMEs (continued)

Product Name	Generic Name	Manufacturer	Indications/Use (general description)	Total time to approval in months	CDER review time in months
Nilandron	nilutamide	Roussel UCLAF	prostate cancer	30.5	24.1
Naropin	ropivacaine HCl monohydrate	Astra USA	surgical anesthesia	17.9	16.9
Denavir	penciclovir	SmithKline Beecham	herpes labialis	11.3	11.3
Accolate	zafirlukast	Zeneca	asthma	15	15
Zyprexa	olanzapine	Lilly	psychotic disorders	12.3	11.7
Mentax	butenafine HCl	Penederm	interdigital tinea pedis	18.5	17.3
Cystadane	betaine anhydrous	Orphan Medical	homocystinuria	12	12
Mectizan	ivermectin	Merck	intestinal strongyloidiasis	7.7	7.5
Aricept	donepezil HCl	Eisai America	dementia associated with Alzheimer's	7.7	7.2
Zanaflex	tizanidine HCl	Athena Neuroscience	management of muscle tone associated with spasticity	14.6***	8.1
Gastromark	ferumoxsil	Advanced Magnetics	magnetic resonance imaging contrast agent	36.5	34.8
Zyflo	zileuton	Abbott Labs	asthma	28.7	21
Aphthasol	amlexanox	Block Drug	aphthous ulcers	20	16.3

Office of Review Management (cont.)

1996 NMEs (continued)

Product Name	Generic Name	Manufacturer	Indications/Use (general description)	Total time to approval in months	CDER review time in months
Lipitor	atorvastatin calcium	Parke Davis	lower cholesterol	6	6
Glyset	miglitol	Bayer	non-insulin dependent diabetes mellitus	11.7	11.7
Patanol	olopatadine HCl	Alcon	allergic conjunctivitis	10.7	10.7
Zagam	sparfloxacin	Rhone Poulenc	pneumonia and chronic bronchitis	11.8	11.8
Monurol	fosfomycin tromethamine	Zambon	urinary tract infections caused by *Escherichia coli* or E*nterococcus faecalis*	5.7****	5.7
Copaxone	glatiramer acetate	Teva Pharmaceuticals	multiple sclerosis	14.3	13.2
Dostinex	cabergoline	Pharmacia and Upjohn	hyperprolactinemic disorders	11.9	11.9
Diovan	valsartan	Ciba Geigy	hypertension	11.9	11.9
Orgaran	danaparoid sodium	Organon	post-operative deep venus thrombosis in patients undergoing hip replacement	23.8	19.8
Topamax	topiramate	Johnson RW	partial onset seizures	23.8	17.9

**Significant new clinical data needed for approval was received for Merrem on Dec. 26, 1995; before this only partial clinical data had been received. This date was used to calculate total approval time and CDER time.

***Significant new clinical data needed for approval was received for Zanaflex on Sept. 11, 1995; before this only partial clinical data had been received. This date was used to calculate total approval time and CDER time.

****Significant new clinical data needed for approval was received for Monurol on June 28, 1996; before this only partial clinical data had been received. This date was used to calculate total approval time and CDER time.

Office of Review Management (cont.)

Pre-User Fee NMEs Approved in 1996

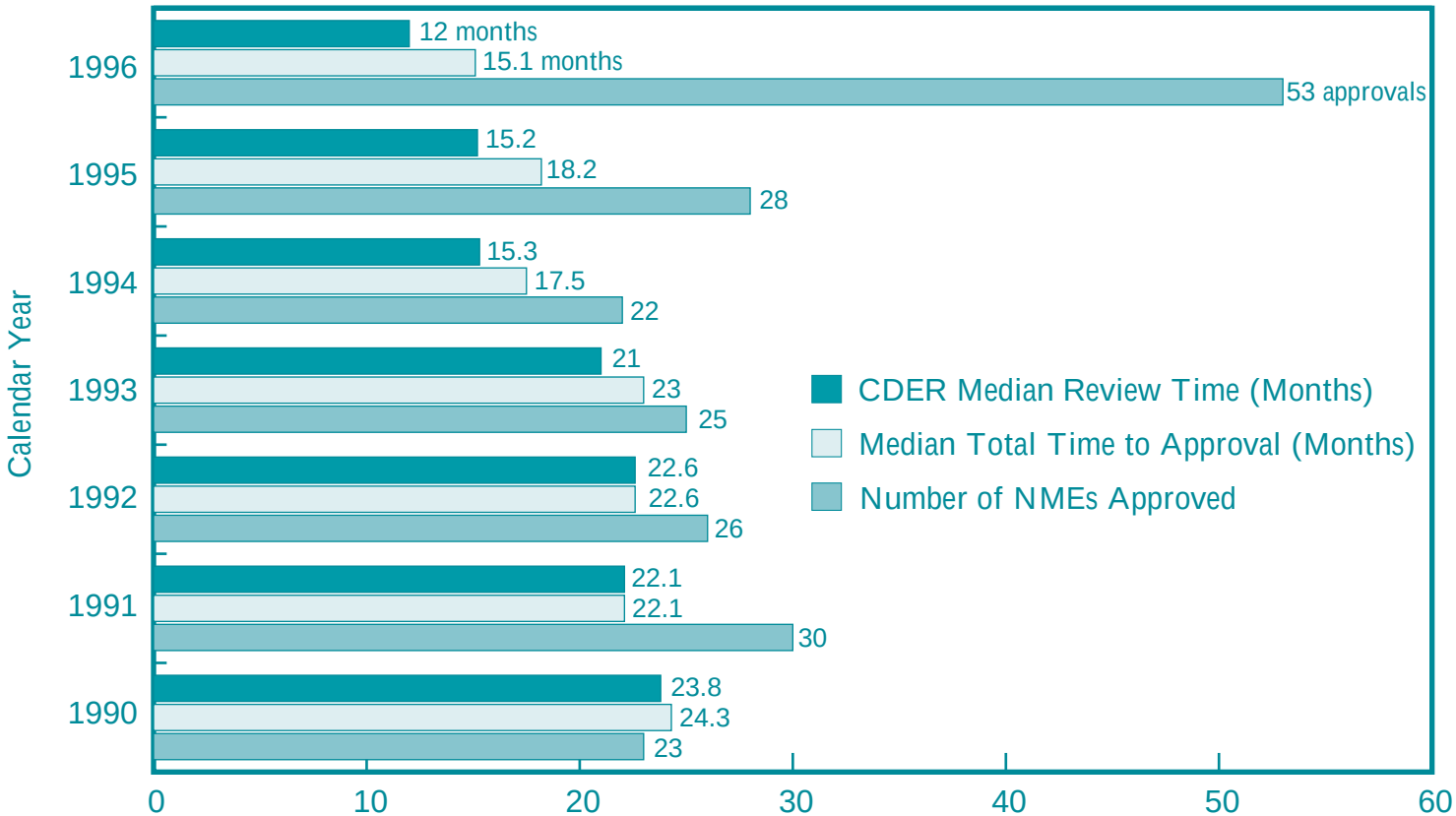
Product Name	Generic Name	Manufacturer	Indications/Use (general description)	Total time to approval in months	CDER review time in months
Maxipime	cefepime HCl	Bristol-Myers Squibb	urinary tract infections	42.6	37.3
Acthrel	corticorelin ovine triflutate	Ferring	diagnosing ACTH-dependent Cushing's syndrome	63.1	62.6
ProAmatine	midodrine HCl	Roberts Labs	orthostatic hypotension	11.4**	7.9
Elmiron	pentosan polysulfate sodium	Baker Norton	relief of interstitial cystitis pain	12.9***	11.5
Astelin	azelastine HCl	Wallace Labs	symptoms of seasonal allergic rhinitis	67.3	36.2

**Significant new clinical data needed for approval was received for ProAmatine on Sept. 25, 1995; before this only partial clinical data had been received. This date was used to calculate total approval time and CDER time.

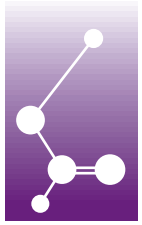
***Pivotal studies were not received for Elmiron until Sept. 1, 1995. This date was used to calculate total approval time and CDER time.

Office of Review Management (cont.)

New Molecular Entities
CDER Review Time and Total Time to Approval*



** Total Time to Approval is the time from submission of an NDA to the issuance of an approval letter. This encompasses both CDER review time plus company time to answer Agency questions generated during review.*



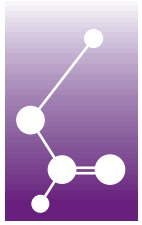
Office of Review Management (cont.)

Over-the-Counter Drug Review

CDER regulates over-the-counter (OTC) drugs, in addition to prescription drugs and generics. As Americans continue to participate more actively in their health care decisions, many medications purchased will be OTC drugs. Increasing this trend is the expanding availability of OTC drugs reclassified from prescription status. This offers consumers even greater choices.

Currently, there are more than 100,000 OTC products on the market. However, fewer than 1,000 active ingredients are used in all OTC products.

In addition to new drug approvals for OTC use, FDA has been evaluating the ingredients and labeling of OTC products that have been in the marketplace for a number of years as part of CDER's OTC Drug Review Program. The goal is to establish "OTC drug monographs" that contain acceptable ingredients, doses, formulations, and consumer labeling for these older active drug ingredients. This drug review ensures an ingredient's safety and effectiveness and helps consumers understand how to best use these products. Products that conform to a final monograph may be marketed without further FDA clearance, while those that do not, must undergo separate review under a new drug application.

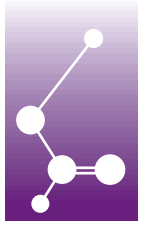


Office of Review Management (cont.)

1996 OTC Approvals

In fiscal year 1996, 19 new drugs or new indications for existing drugs were approved for over-the-counter (OTC) marketing. Approvals include:

Product Name	Indications/Use	Date Approved
Ocuhist Ophthalmic	Ocular itching, redness	01-31-96
Brompheniramine & Pseudoephedrine	Allergy relief	03-29-96
Tavist-D	Allergic rhinitis	08-09-96
Zantac	Heartburn	12-19-95
Axid AR	Heartburn	05-09-96
Actron-ketoprofen	Pain relief/fever reducer	10-06-95
Orudis-ketoprofen	Pain relief/fever reducer	10-06-95
Childrens' Motrin Oral	Pain relief/fever reducer	06-10-96
Jr Strength Motrin	Pain relief/fever reducer	06-10-96
Childrens' Advil	Pain relief/fever reducer	06-27-96
Ivy-Block	Poison ivy/oak prevention	08-26-96
Nicorette	Stop smoking aid-gum	02-09-96
Nicorette DS	Stop smoking aid-gum	02-09-96
Nicotrol	Stop smoking aid-patch	07-03-96
Nicoderm	Stop smoking aid-patch	08-02-96
Rogaine	Hair growth treatment	02-09-96
Monistat-3 Vaginal Dual-Pak	Vaginal antifungal	04-16-96
Gyne-Lotrimin 3	Vaginal antifungal	07-29-96



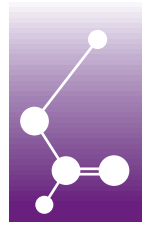
CDER Highlights

Office of Compliance

The Center's Office of Compliance monitors the quality of marketed drugs, including nontraditional drugs, through product testing, surveillance, and other compliance programs. In addition, the Office develops policies and standards for drug labeling, current good manufacturing practices, clinical and good laboratory practices, postmarketing surveillance, and industry practices to demonstrate the safety and effectiveness of human drug products.

This Office also:

- Develops and directs drug product quality enforcement programs; post-marketing drug quality surveillance programs; and compliance programs for OTC, non-traditional, and other drug monographs;
- Directs the Center's bioresearch monitoring program for human drug products;
- Initiates surveillance assignments to monitor research data submitted as part of premarketing applications;
- Coordinates preapproval inspections as part of the product approval process;
- Provides support and guidance to regional investigators on legal actions, case development, and contested cases; and reviews and decides disposition of regional submissions involving deviations from standards;
- Evaluates, classifies, and recommends human drug recalls and coordinates with regional recall activities;
- Monitors the resolution of all drug shortages involving compliance issues;
- Coordinates international inspections, results, and communications with other nations; and
- Participates in international standards-setting activities.



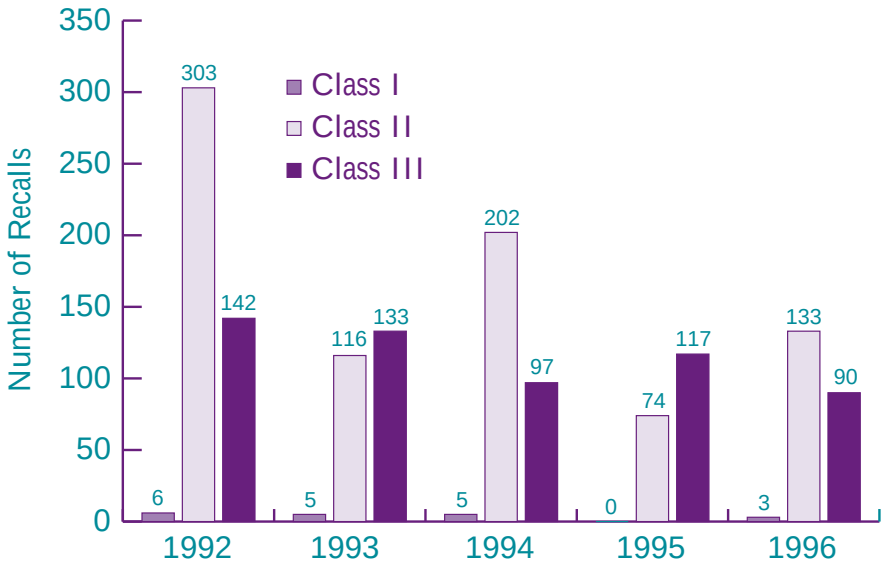
Office of Compliance (cont.)

Top 10 Reasons for Human Drug Recalls - Fiscal Year 1996

1. Current Good Manufacturing Practice deviations
2. Subpotent products
3. Product failed U.S. Pharmacopeia (USP) dissolution test requirements
4. Product failed pyrogen/endotoxin test requirements
5. Presence of contaminants in product
6. Label mix-up on the product
7. Stability data do not support expiration date
8. Product lacks stability
9. Product failed content uniformity
10. Product failed pH test requirements

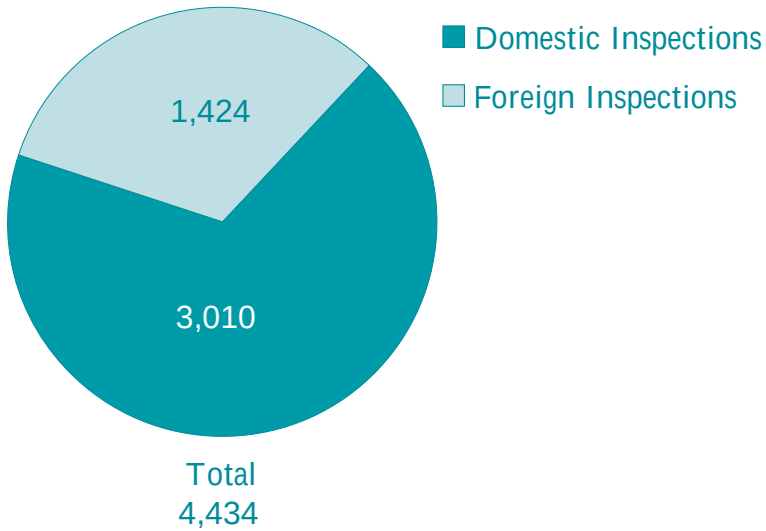
Office of Compliance (cont.)

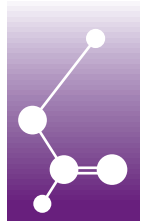
Prescription Drug Recalls by Fiscal Year



- A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- A Class III recall is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

Preapproval Inspections Accomplished in FY 1996





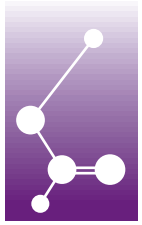
CDER Highlights

Office of Management

The Center's Office of Management monitors the development and operation of planning systems for CDER activities; monitors resource allocations; and offers guidance on administrative policies, guidelines, and information systems and services. In addition, this Office serves Center managers through program evaluation and technological forecasting.

CDER's Office of Management also:

- Plans and directs the Center's financial and personnel management operations;
- Directs Center organization, management, and information systems;
- Manages studies for improving processes and resource allocations;
- Advises Center managers on contract and grant proposals; and
- Provides coordination for receipt and distribution of initial drug applications and other related documents.



CDER Highlights

Office of Training and Communications

The Center's Office of Training and Communications (OTCOM) is responsible for a wide range of employee development, commun-ications, and information services. OTCOM prepares, develops, and coordinates responses to drug-related requests under the Freedom of Information Act, Privacy Act, and other statutes. In addition, the Office provides leadership and direction for all Center internal and external communications.

OTCOM also:

- Plans, coordinates, and evaluates policies, procedures, and programs for all communications and training activities;
- Provides scientific, technical, and other library resources to CDER, FDA and DHHS staff;
- Conducts new employee orientations and provides scientific and other training and education for all employees;
- Works with other Agency components to educate the public on Center and FDA policies and activities;
- Responds to the public's requests for information and answers over 50,000 calls annually;
- Coordinates state-of-the-art videoconferencing that allows CDER's geographically dispersed employees to easily communicate among themselves, with industry, and with health professional and consumer audiences;
- Coordinates CDER's World Wide Web site to provide millions of computer users with immediate access to CDER information; and
- Develops and coordinates communications outreach activities, such as public education campaigns, media relations, and information exchange programs.

Office of Training and Communications (Cont.)

Freedom of Information Act

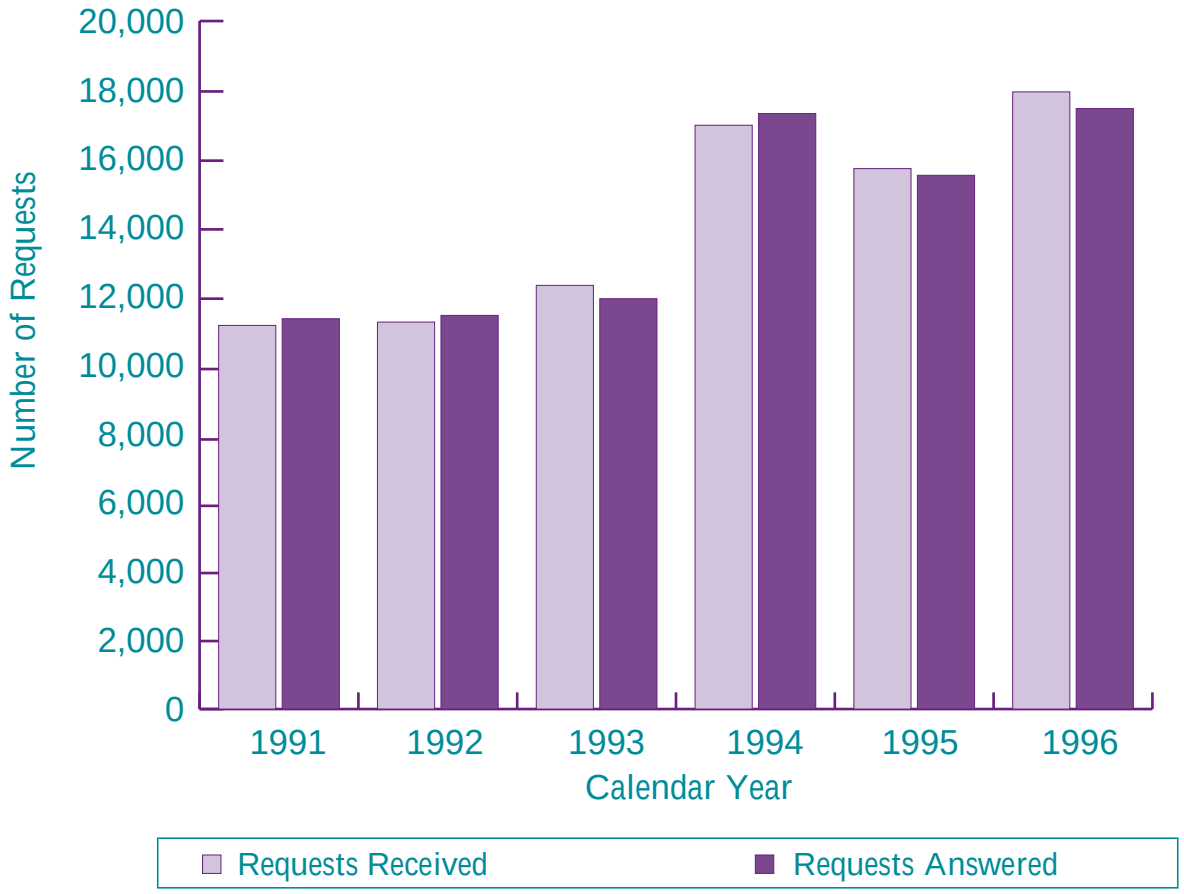
Through centralization of the Center's Freedom of Information Act (FOIA) responsibilities, OTCOM's Freedom of Information Staff has streamlined and significantly reduced the workload in many of CDER's offices.

The primary function of the Freedom of Information Staff is to handle the FOIA requests for CDER documents. This involves logging the requests into a computerized tracking system, interpreting the requests, locating correct response documents, or determining that none exist. In addition, staff review the response documents to ensure information is releasable and delete any trade secret, confidential commercial, or personal privacy information.

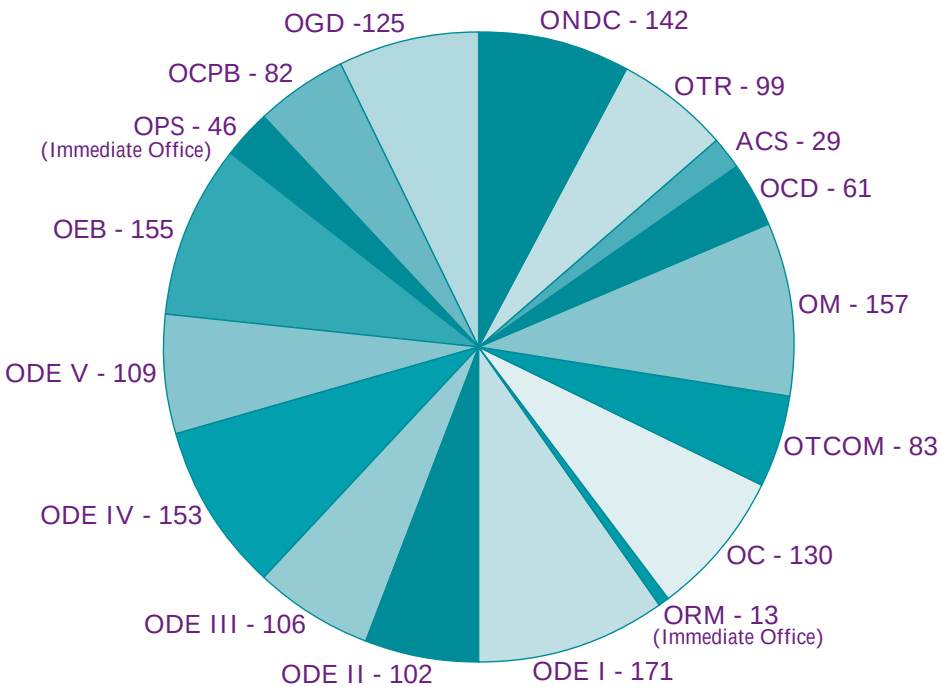
The centralization process began in July 1988 as a pilot study and then gradually evolved into a near-complete assumption of responsibilities from CDER offices. At that time, there were over 100 people throughout the Center working on FOIA requests, none working full time. Now, the 11-member Freedom of Information Staff handles the FOIA requests for most of the Center.

Office of Training and Communications (Cont.)

FOIA Requests and Responses



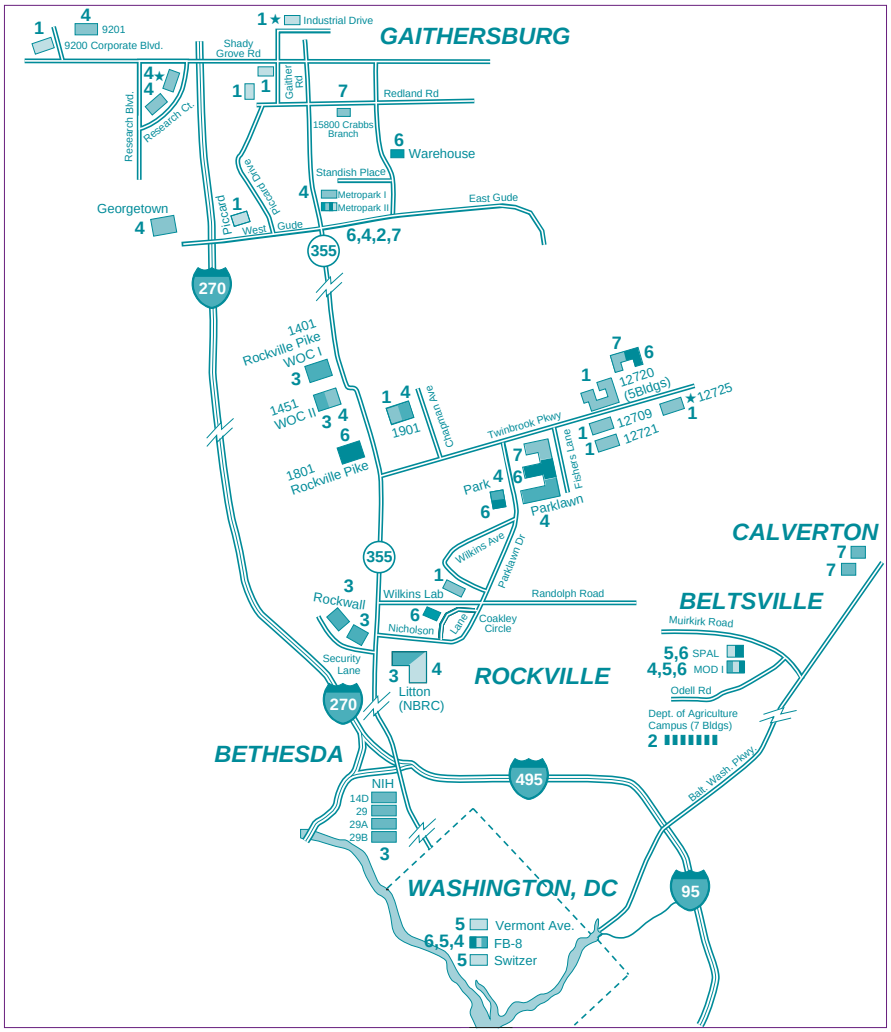
CDER's 1997 Full-Time Equivalent Level



Total 1,763

OCD - Office of the Center Director
OM - Office of Management
OTCOM - Office of Training and Communications
OC - Office of Compliance
ORM - Office of Review Management (Immediate Office)
ODE I - Office of Drug Evaluation I
ODE II - Office of Drug Evaluation II
ODE III - Office of Drug Evaluation III
ODE IV - Office of Drug Evaluation IV
ODE V - Office of Drug Evaluation V
OEB - Office of Epidemiology and Biostatistics
OPS - Office of Pharmaceutical Science (Immediate Office)
OCPB - Office of Clinical Pharmacology and Biopharmaceutics
OGD - Office of Generic Drugs
ONDC - Office of New Drug Chemistry
OTR - Office of Testing and Research
ACS - Advisory Committee Staff

Location of CDER Employees



FDA COMPONENTS SHOWN BY BUILDING

(as of 11/14/96)
Map Not To Scale

LEGEND

- 1 Center for Devices and Radiological Health
- 2 Center for Veterinary Medicine
- 3 Center for Biologics Evaluation and Research
- 4 Center for Drug Evaluation and Research
- 5 Center for Food Safety and Applied Nutrition
- 6 Office of the Commissioner
- 7 Office of Regulatory Affairs
- ★ Future Locations

Food and Drug Law History

People have long been concerned about the quality and safety of foods and medicines. In 1202, King John of England proclaimed the first English food law, the Assize of Bread, which prohibited adulteration of bread with such ingredients as ground peas or beans. Regulation of food in the United States dates from early colonial times. Federal controls over the drug supply began with inspection of imported drugs in 1848. The following chronology describes some of the milestones in the history of food and drug regulation in the United States.

1785
MASSACHUSETTS enacts the first general food adulteration law in the United States.

1820
Eleven physicians meet in the Capitol at Washington to establish the U.S. PHARMACOPEIA, first compendium of standard drugs for the United States.

1848
DRUG IMPORTATION ACT passed by Congress requires U.S. Customs inspection to stop entry of adulterated drugs from overseas.

1850
CALIFORNIA passes a pure food and drink law, one year after the gold rush.

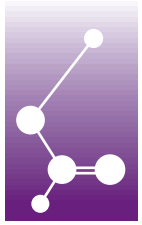
1862
PRESIDENT LINCOLN appoints a chemist, Charles M. Wetherill, to serve in the new Department of Agriculture. This was the beginning of the Bureau of Chemistry, now the Food and Drug Administration in the Department of Health and Human Services.

1898
PURE FOOD CONGRESS in Washington focuses attention on the growing national movement to secure a Federal law against the misbranding and adulteration of foods and drugs. Its leader is Dr. Harvey W. Wiley, chief chemist of the USDA.

1902
The BIOLOGICS CONTROL ACT is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.

1906
The original FOOD AND DRUGS ACT of 1906 is passed by Congress and signed by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs. No government pre-approval was granted under this system. Federal government could act only after products were on the market.

The MEAT INSPECTION ACT is passed the same day, June 30. Shocking disclosures of unsanitary conditions in meat-packing plants, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines were the major problems leading to the enactment of these laws.



Food and Drug Law History

1911

In U.S. v. JOHNSON, the Supreme Court rules that the 1906 Food and Drugs Act did not prohibit false therapeutic claims but only false and misleading statements about the ingredients or identity of a drug. Congress enacts the SHERLEY AMENDMENT to overcome the ruling in U.S. v. Johnson. It prohibits labeling medicines with false therapeutic claims intended to defraud the purchaser, a standard difficult to prove.

1927

A separate law enforcement agency is formed, first known as the Food, Drug, and Insecticide Administration and then, in 1930, as the Food and Drug Administration (FDA).

1933

FDA recommends a complete revision of the obsolete 1906 Food and Drugs Act. The first bill is introduced into the Senate, launching a 5-year legislative battle.

1937

An ELIXIR OF SULFANILAMIDE containing a poisonous solvent kills 107 persons, mostly children, dramatizing the need to establish drug safety *before* marketing and to enact the pending food and drug law.

1938

THE FEDERAL FOOD, DRUG, AND COSMETIC (FDC) ACT of 1938 is passed by Congress, containing new provisions:

- Extending control to cosmetics and therapeutic devices.
- Requiring new drugs to be shown safe before marketing—starting a new system of drug regulation.
- Eliminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases.
- Providing that safe tolerances be set for unavoidable poisonous substances.
- Authorizing standards of identity, quality, and fill of container for foods.
- Authorizing factory inspections.
- Adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.

1940

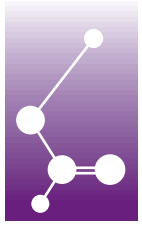
FDA TRANSFERRED from the Department of Agriculture to the Federal Security Agency, with Walter G. Campbell appointed as the first Commissioner of Food and Drugs.

1941

INSULIN AMENDMENT requires FDA to test and certify purity and potency of this life-saving drug for diabetes.

1944

PUBLIC HEALTH SERVICE ACT was passed, covering a broad spectrum of health concerns, including regulation of biological products and control of communicable diseases.



Food and Drug Law History

1945

PENICILLIN AMENDMENT requires FDA testing and certification of safety and effectiveness of all penicillin products. Later amendments extended this requirement to all antibiotics. In 1983, such control was no longer needed and was abolished.

1950

In ALBERTY FOOD PRODUCTS CO. v. U.S., the Court of Appeals rules that the directions for use on a drug label must include the purpose for which the drug is offered. Therefore, a worthless remedy cannot escape the law by not stating the condition it is supposed to treat.

1951

DURHAM-HUMPHREY AMENDMENT defines the kinds of drugs that cannot be safely used without medical supervision and restricts their sale to prescription by a licensed practitioner.

1952

In U.S. v. CARDIFF, the Supreme Court rules that the factory inspection provision of the 1938 Act is too vague to be enforced as criminal law (see Factory Inspection Amendment, 1953).

1953

FEDERAL SECURITY AGENCY becomes the Department of Health, Education, and Welfare (HEW).

FACTORY INSPECTION AMENDMENT clarifies previous law and requires FDA to give manufacturers written reports of conditions observed during inspections and analyses of factory samples.

1960

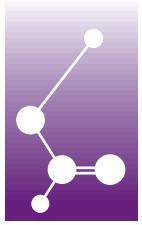
COLOR ADDITIVE AMENDMENTS enacted, requiring manufacturers to establish the safety of color additives in foods, drugs, and cosmetics.

1962

THALIDOMIDE, a new sleeping pill, is found to have caused birth defects in thousands of babies born in western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation.

KEFAUVER-HARRIS DRUG AMENDMENTS passed to ensure greater drug safety. For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them. The amendments also exempt from the Delaney proviso animal drugs that are shown to induce cancer.

CONSUMER BILL OF RIGHTS is proclaimed by President John F. Kennedy in a message to Congress. Included are the right to safety, the right to be informed, the right to choose, and the right to be heard.



Food and Drug Law History

1965

DRUG ABUSE CONTROL AMENDMENTS are enacted to deal with problems caused by abuse of depressants, stimulants, and hallucinogens.

1966

FDA CONTRACTS with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4,000 drugs approved on the basis of safety alone between 1938 and 1962.

FAIR PACKAGING AND LABELING ACT requires all consumer products in interstate commerce to be honestly and informatively labeled, with FDA enforcing provisions on foods, drugs, cosmetics, and medical devices.

1968

FDA BUREAU OF DRUG ABUSE CONTROL and Treasury Department Bureau of Narcotics are transferred to the Department of Justice to consolidate policing of traffic in drugs that are abused.

REORGANIZATION of Federal health programs places FDA in the Public Health Service.

1970

In UPJOHN v. FINCH, the Court of Appeals upholds enforcement of the 1962 drug effectiveness amendments by ruling that commercial success alone does not constitute substantial evidence of drug safety and efficacy.

1972

OVER-THE-COUNTER DRUG review begun to enhance the safety, effectiveness, and appropriate labeling of drugs sold without prescription.

REGULATION OF BIOLOGICS including serums, vaccines, and blood products - is transferred to FDA.

1973

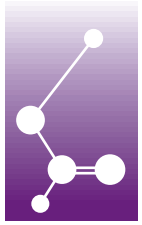
THE SUPREME COURT upholds the 1962 drug effectiveness law and endorses FDA action to control entire classes of products by regulations rather than to rely only on time-consuming litigation.

1976

VITAMINS AND MINERALS AMENDMENTS stop FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.

1982

TAMPER-RESISTANT PACKAGING REGULATIONS issued by FDA to prevent poisonings such as deaths from cyanide placed in Tylenol capsules. The Federal Anti-Tampering Act passed in 1983 makes it a crime to tamper with packaged consumer products.



Food and Drug Law History

1983

ORPHAN DRUG ACT enables FDA to promote research and approval and marketing of drugs needed for treating rare diseases, which otherwise would not be profitable.

1984

DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective. At the same time, the brand-name companies can apply for up to 5 years longer patent protection for the new medicines they developed to make up for time lost while their products were going through the development and review process.

1986

CHILDHOOD VACCINE ACT requires patient information on vaccines, gives FDA authority to recall biologics, and authorizes civil penalties.

1987

THE PRESCRIPTION DRUG MARKETING ACT bans the diversion of prescription drugs from legitimate commercial channels. Congress finds that the resale of such drugs leads to the distribution of mislabeled, adulterated, subpotent, or counterfeit drugs to the public. The new law requires drug wholesalers to be licensed by the states; restricts reimportation from other countries; and bans sale, trade, or purchase of drug samples, and traffic or counterfeiting of redeemable drug coupons.

1988

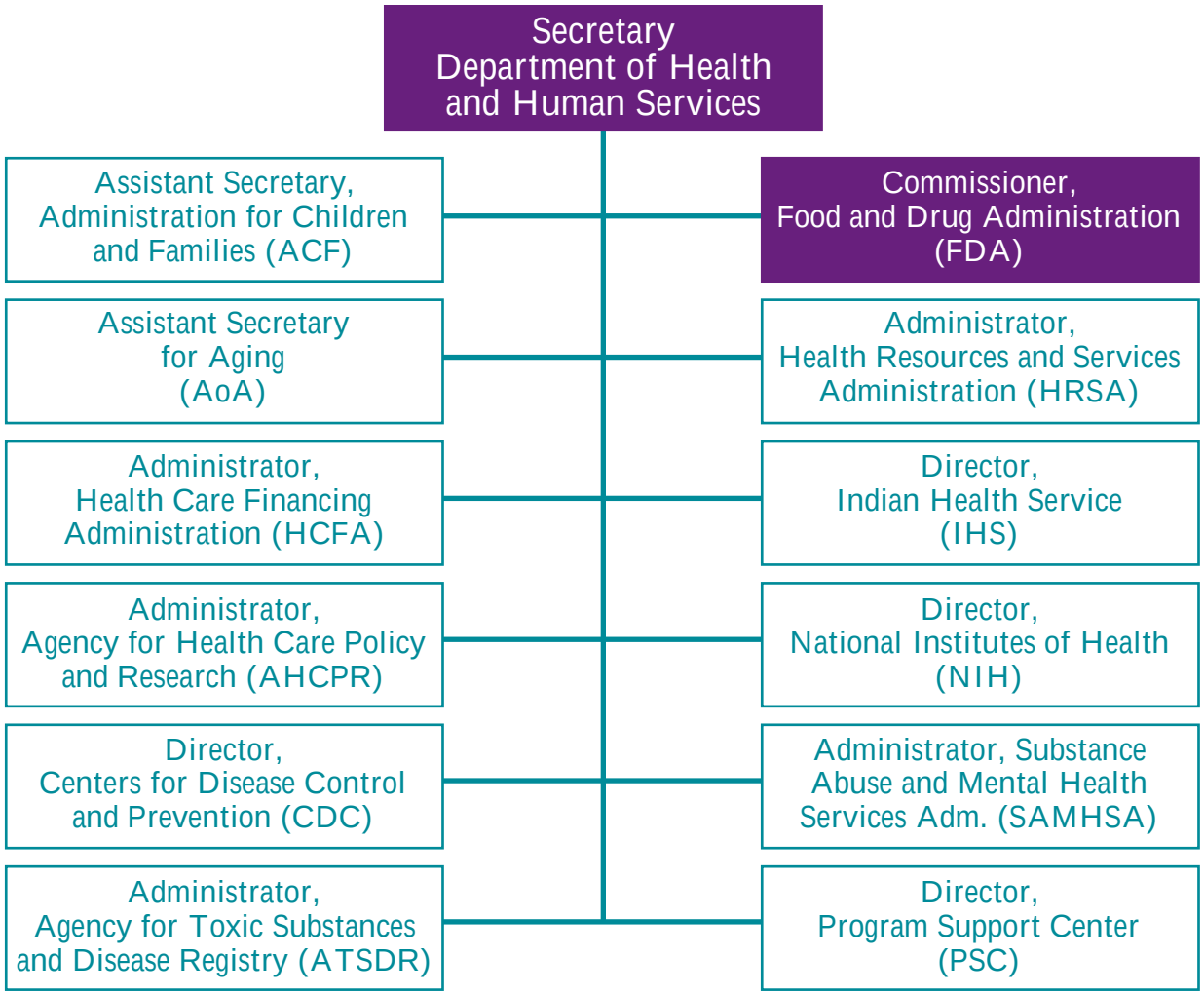
FOOD AND DRUG ADMINISTRATION ACT of 1988 officially establishes FDA as an agency of the Department of Health and Human Services with a Commissioner of Food and Drugs appointed by the President with the advice and consent of the Senate, and spells out broadly the responsibilities of the Secretary and the Commissioner for research, enforcement, education, and information.

1992

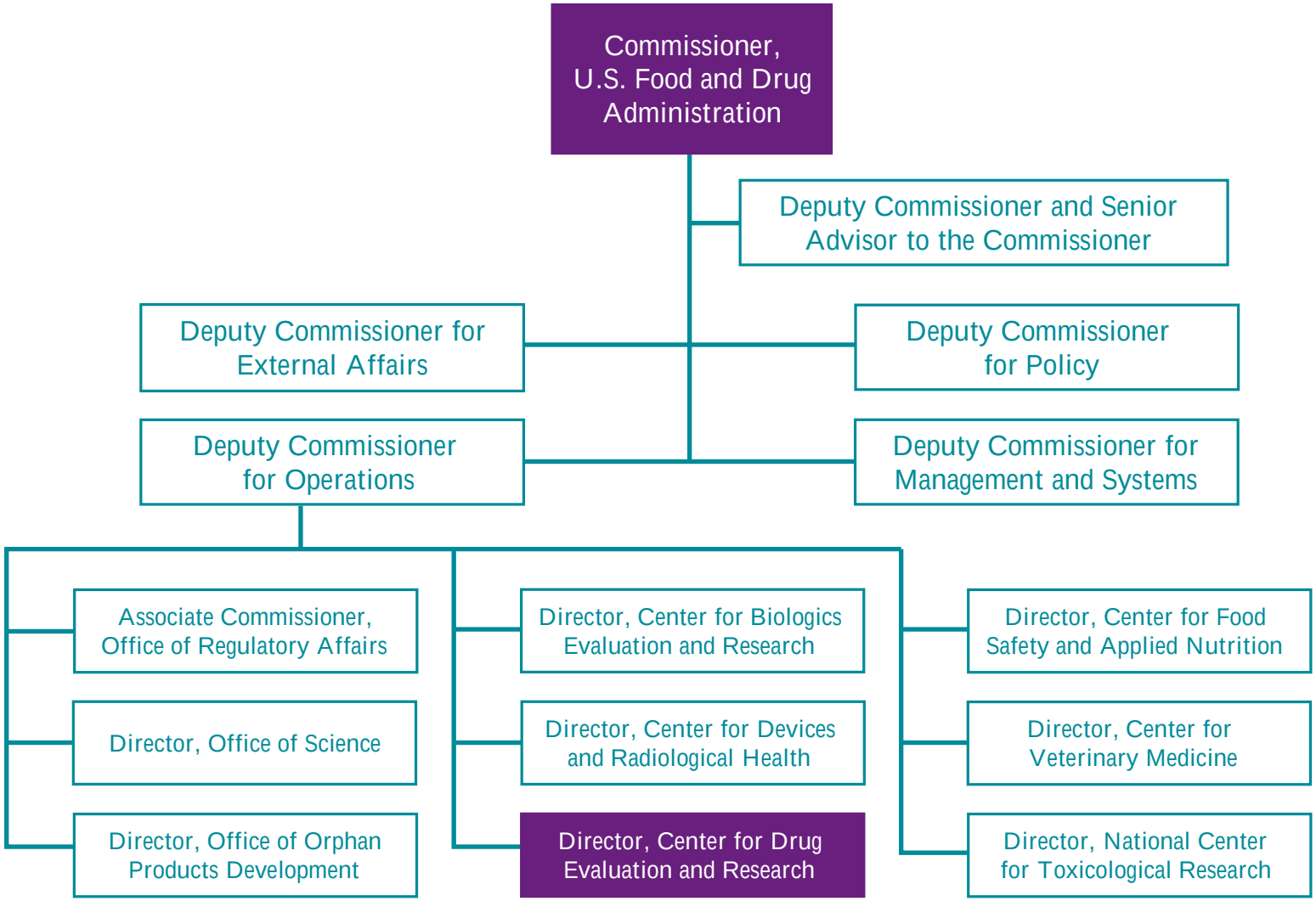
GENERIC DRUG ENFORCEMENT ACT imposes debarment and other penalties for illegal acts involving approval of abbreviated drug applications.

PRESCRIPTION DRUG USER FEE ACT OF 1992 requires drug and biologics manufacturers (not generic manufacturers) to pay fees for drug and biologics applications and supplements. In addition, these firms must pay annual establishment fees and annual product fees. FDA uses these funds to hire more reviewers and improve infrastructure to assess applications. Unless Congress renews the Act, the user fee law will expire at the end of FY 1997.

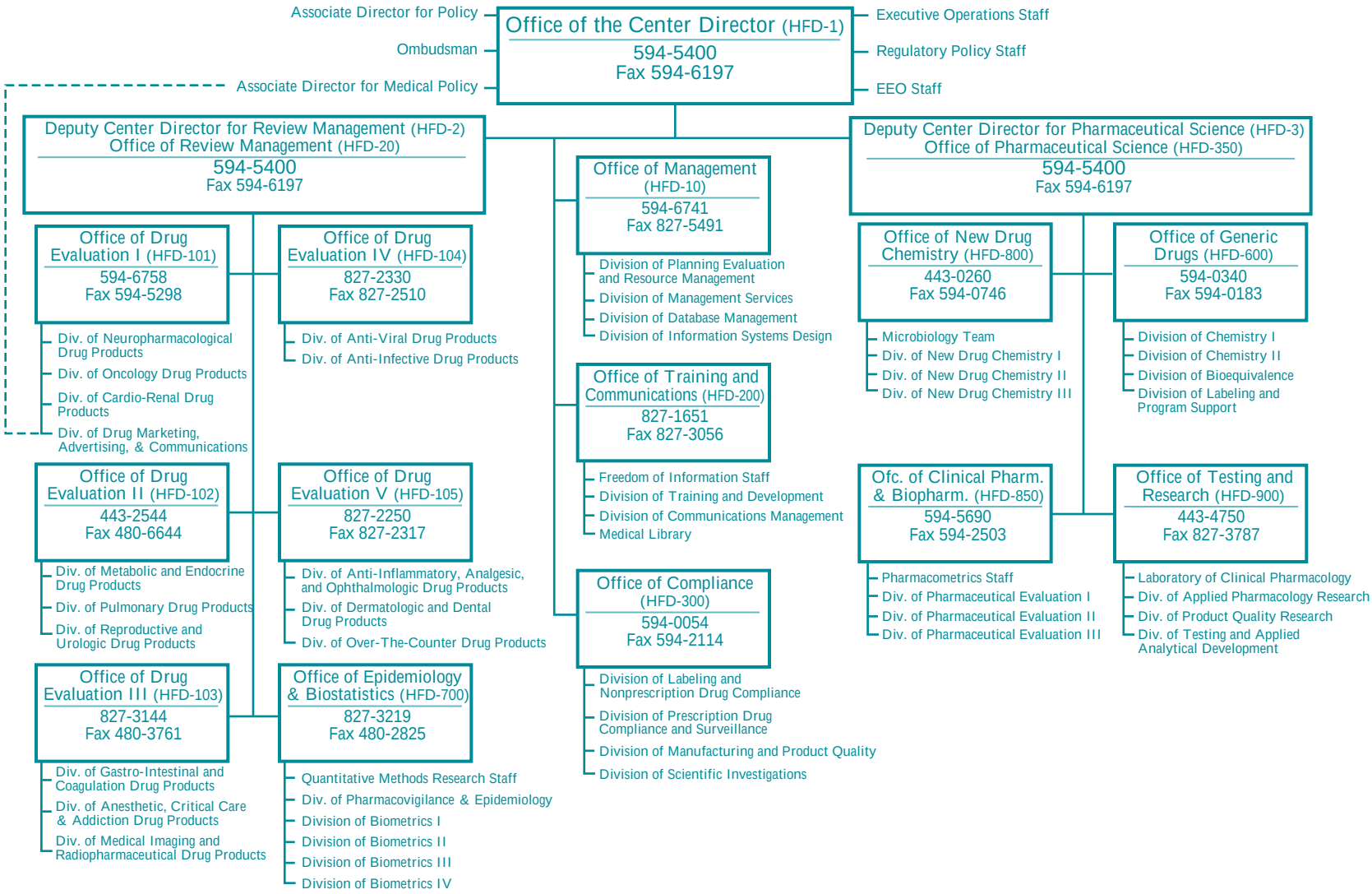
HHS Organizational Chart



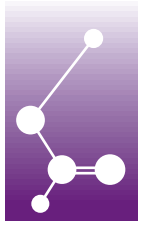
FDA Organizational Chart



CDER Organizational Chart



Note: Most of the contact information on this page is no longer current. Up-to-date contact information is available at: http://www.fda.gov/cder/about/default.htm#How%20to%20Contact%20Us



Drug Information

For additional information contact:

- CDER's World Wide Web home page at http://www.fda.gov/cder. Hard copies of guidances are also available by faxing a request to (301)827-4577 or by e-mailing to DIB@FDA.GOV.
- The Center's Fax-on-Demand system which contains literally hundreds of documents for anyone with questions about human drugs. The number is 1-800-342-2722.
- CDER's Drug Information Team, for more specific or complex questions, call (301) 827-4573.

Other sources of information include:

- FDA's Office of Consumer Affairs at 1-800-532-4440, or locally at (301) 827-4420;
- FDA's Office of Public Affairs at (301) 443-1130.

Additional sources of information or assistance include:

- CDER Ombudsman, (301) 594-5443;
- FDA Freedom of Information Staff, (301) 443-6310;
- AIDS Clinical Trials Information Service, 1-800-TRIALS-A or on the World Wide Web at http://www.actis.org.
- CDER's Executive Secretariat, (301)594-6740;
- National Cancer Institute, 1-800-4CANCER.

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