

---

---

# **Food and Drug Administration**

# **Regulatory Primer**

**Office of AIDS  
and Special Health Issues**

---

---

# Office of AIDS and Special Health Issues

The FDA Office of AIDS and Special Health Issues, located within the Office of External Affairs, coordinates and provides technical support to all HIV/AIDS-related programs within the Food and Drug Administration.

The responsibilities of this Office include:

- Serving as the liaison between outside individuals/groups and the FDA for issues related to HIV/AIDS and other special health issues
- Serving as a resource for HIV/AIDS and other special health-related information within the Agency
- Providing FDA representation at a wide range of public and government meetings
- Assisting in the development of PHS and HHS policies and regulations that pertain to or impact upon HIV/AIDS, and other special health issues
- Providing policy advice to senior FDA staff.

For further assistance or information contact

Richard Klein

Food and Drug Administration  
Office of AIDS and Special Health Issues  
5600 Fishers Lane, HF-12  
Rockville, MD 20857  
(301) 443-0104  
FAX 443-4555

# **CONTENTS**

## **1 - What is FDA?**

Outline Profile of FDA -

Its Mandate, Its Role, Its People

Page 1

## **2 - How is FDA Organized?**

Organizational Chart & Component Descriptions

Page 10

## **3 - Drug Development**

Overview of New Drug Development & Approval

Page 19

Major Events and Milestones

Page 26

Currently Approved Drugs for HIV Infections and  
AIDS-related Conditions

Page 28

## **4 - Preclinical/Animal Studies**

The Beginnings: Laboratory and Animal Studies

Page 31

## **5 - Testing Drugs in Humans**

Testing in Real People

Page 35

Testing Drugs in People

Page 40

Drug Testing, Through a Patients Eyes

Page 44

## **6 - Protection of Human Research Subjects**

Protecting 'Human Guinea Pigs'

Page 46

FDA Informed Consent Regulation

Page 49

FDA Institutional Review Board (IRB) Regulation

Page 56

## **7 - Inclusion of Women in Clinical Trials**

Women in Clinical Trials of New Drugs

A change in Food and Drug Administration Policy

Page 66

Guideline for the Study and evaluation of Gender

Differences in the Clinical Evaluation of Drugs

Page 71

## **8 - FDA Review of New Drug Products for Approval**

Benefit vs. Risk: How FDA Approves New Drugs

Page 83

A Drug Review Glossary

Page 88

## **9 - Speeding Availability and Approval of Promising Therapies**

|  |          |
|--|----------|
| Experimental Drugs for the Desperately Ill   | Page 90  |
| FDA Finds New Ways to Speed Treatments to Patients   | Page 95  |
| Treatment IND Regulation   | Page 99  |
| Procedures for drugs intended to treat life-<br>threatening and severely debilitating illnesses<br>(Subpart E of the IND Regulation) | Page 112 |
| Parallel Track Policy  | Page 122 |
| Accelerated Approval Regulation<br>(Subpart H of the NDA Regulation)   | Page 131 |

## **10 - Access to Clinical Trials**

|  |          |
|--|----------|
| AIDS Clinical Trials Information Service | Page 151 |
|--|----------|

## **11 - Outside Advisory Panels**

|  |          |
|--|----------|
| Getting Outside Advice for 'Close Calls' | Page 153 |
| FDA Advisory Committee Information Line  | Page 157 |

## **12 - Post Marketing Monitoring of Drug Products**

|  |          |
|--|----------|
| Watching for Problems that Testing Might Have Missed | Page 158 |
| MedWatch - On the Lookout for Medical Problems       | Page 161 |

## **13 - Inspecting Manufacturing Establishments**

|                               |          |
|-------------------------------|----------|
| An Inside Look at FDA On-Site | Page 165 |
| FDA Field Offices             | Page 171 |

## **14 - Personal Importation Guidelines**

|  |          |
|--|----------|
| Guidance on Mail & Baggage importation of<br>personal use quantities of FDA-regulated products | Page 174 |
|--|----------|

## **15 - Medical Treatment**

|   |          |
|---|----------|
| An FDA Guide to Choosing Medical Treatments | Page 179 |
|---|----------|

# Section 1

What is FDA

# FDA's Mandate

---

FDA is responsible for ensuring that:

- Foods are safe and wholesome; human and veterinary drugs, human biological products, and medical devices are safe and effective; cosmetics are safe; and consumer products that give off radiation are safe.
- Regulated products are honestly, accurately and informatively represented.
- Regulated products are in compliance with FDA regulations and guidelines, noncompliance is identified and corrected, and any unsafe or unlawful products are removed from the marketplace.

# Major Laws Enforced by FDA

## **The Federal Food, Drug, and Cosmetic Act**

Enforcing the Federal Food, Drug, and Cosmetic Act, signed into law in 1938 and amended many times since, accounts for about 90 percent of FDA's workload. This statute and its amendments provide for the regulation of foods (including infant formulas and food and color additives), human and animal drugs, medicated animal feeds, medical devices, and cosmetics.

The law is intended to assure the consumer that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

## **The Fair Packaging and Labeling Act**

This statute, signed into law in 1966, affects the contents and placement of information required on product packages. FDA enforces provisions that affect foods, drugs, cosmetics, and medical devices.

## **Public Health Service Act**

FDA is responsible for enforcing sections of this act, signed into law in 1944, relating to biological products for human use and control of communicable diseases.

## **The Radiation Control for Health and Safety Act**

FDA enforces this act's provisions that cover electronic products that emit radiation, such as x-rays, lasers, microwave ovens, and TV sets. The act was signed into law in 1968, and Congress moved it to the Federal Food, Drug, and Cosmetic Act in 1990.

# Congressional Committees with FDA-Related Responsibilities

## Senate

- Committee on Appropriations, Subcommittee on Agriculture, Rural Development, and Related Agencies
- Committee on Labor and Human Resources
- Committee on Agriculture, Nutrition, and Forestry
- Committee on Governmental Affairs

## House of Representatives

- Committee on Appropriations, Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies
- Committee on Agriculture
- Committee on Energy and Commerce
- Committee on Government Operations
- Committee on Merchant Marine and Fisheries
- Committee on Science, Space and Technology
- Committee on Small Business

# Other Federal Agencies with FDA-Related Duties

## U.S. Department of Agriculture

- Meat and poultry
- Animal vaccines
- Grain inspection

## Consumer Product Safety Commission

- Consumer products such as household appliances (except those that emit radiation), baby furniture, toys
- Child-resistant packages

## Environmental Protection Agency

- Pesticides (sets tolerance levels for residues on feed crops and raw and processed foods)
- Municipal water supplies

## Bureau of Alcohol, Tobacco, and Firearms

- Alcoholic beverages, tobacco

## Drug Enforcement Administration

- Drugs of abuse

## Federal Trade Commission

- Nonprescription drug advertising

## National Marine Fisheries Service

- Voluntary seafood inspection program

## Occupational Health and Safety Ad- ministration

- Workplace safety standards

## U.S. Customs Service

- Imports

## Federal Bureau of Investigation

- Federal Anti-Tobacco Taxing Act

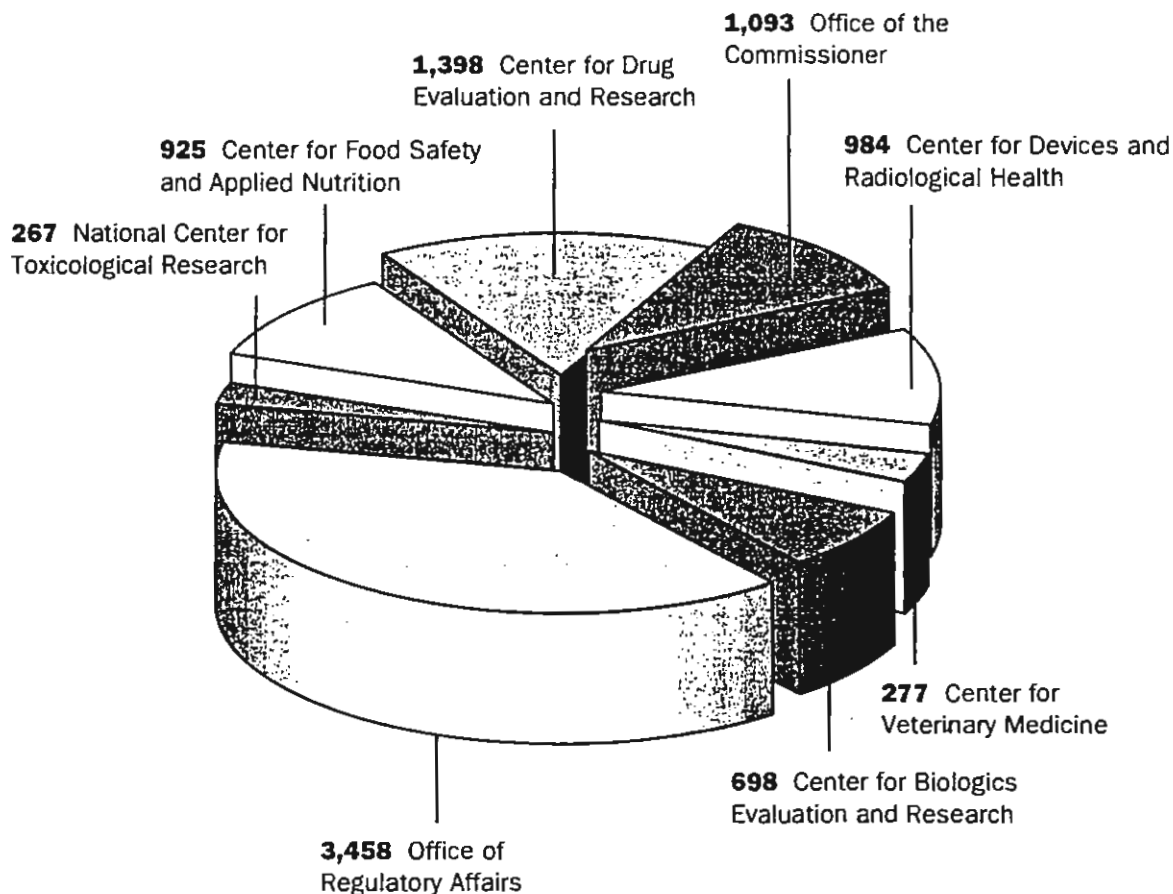


# The People of FDA Staffing by Program—FY 1993

During FY 1993, about 9,100 employees (FTE basis) carried out FDA's responsibilities. Those employees include physicians, attorneys, investigators, inspectors, biologists, toxicologists, chemists, nutritionists, veterinarians, pharmacologists, pharmacists, microbiologists, engineers, and other professionals.

About half of the agency's staff are located in the centers, and 11 percent are in the commissioner's office, which includes such functions as personnel, budget, and policy formulation. The field force composes slightly more than one-third of FDA's personnel.

The chart below shows the distribution of FDA full-time equivalent staffing for FY 1993.



# Science at FDA

About half of FDA's personnel are scientists in such diverse fields as chemistry, microbiology, nutritional science, and numerous medical specialties.

The senior advisor for science advises the commissioner on ways to strengthen and improve the quality of science and scientific research at FDA. To assist the senior advisor in this capacity, three groups have been established:

- Science Board to the Food and Drug Administration—A standing advisory committee of experts from academia and industry who specialize in the scientific disciplines relevant to FDA.
- Senior Science Council—One senior scientist from each FDA center and the Office of Regula-

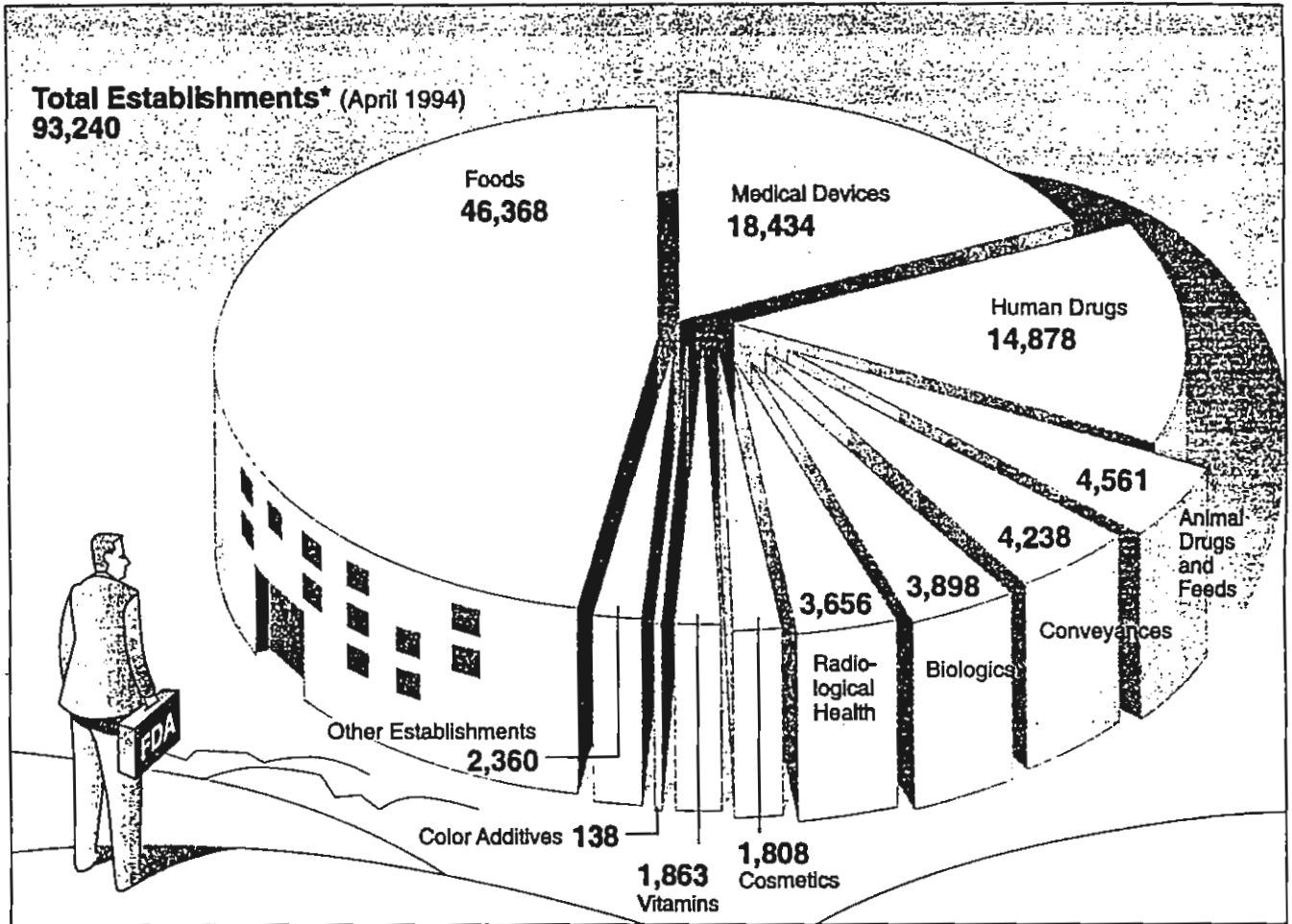
tory Affairs established to advise the senior advisor for science on science issues throughout FDA.

- Consultants to the Senior Advisor for Science—Two scientists from each FDA center and the Office of Regulatory Affairs who have worked at FDA between three and 10 years.

The council and consultants have made recommendations regarding staff development, recruitment and retention, and enhancement of FDA's scientific infrastructure.

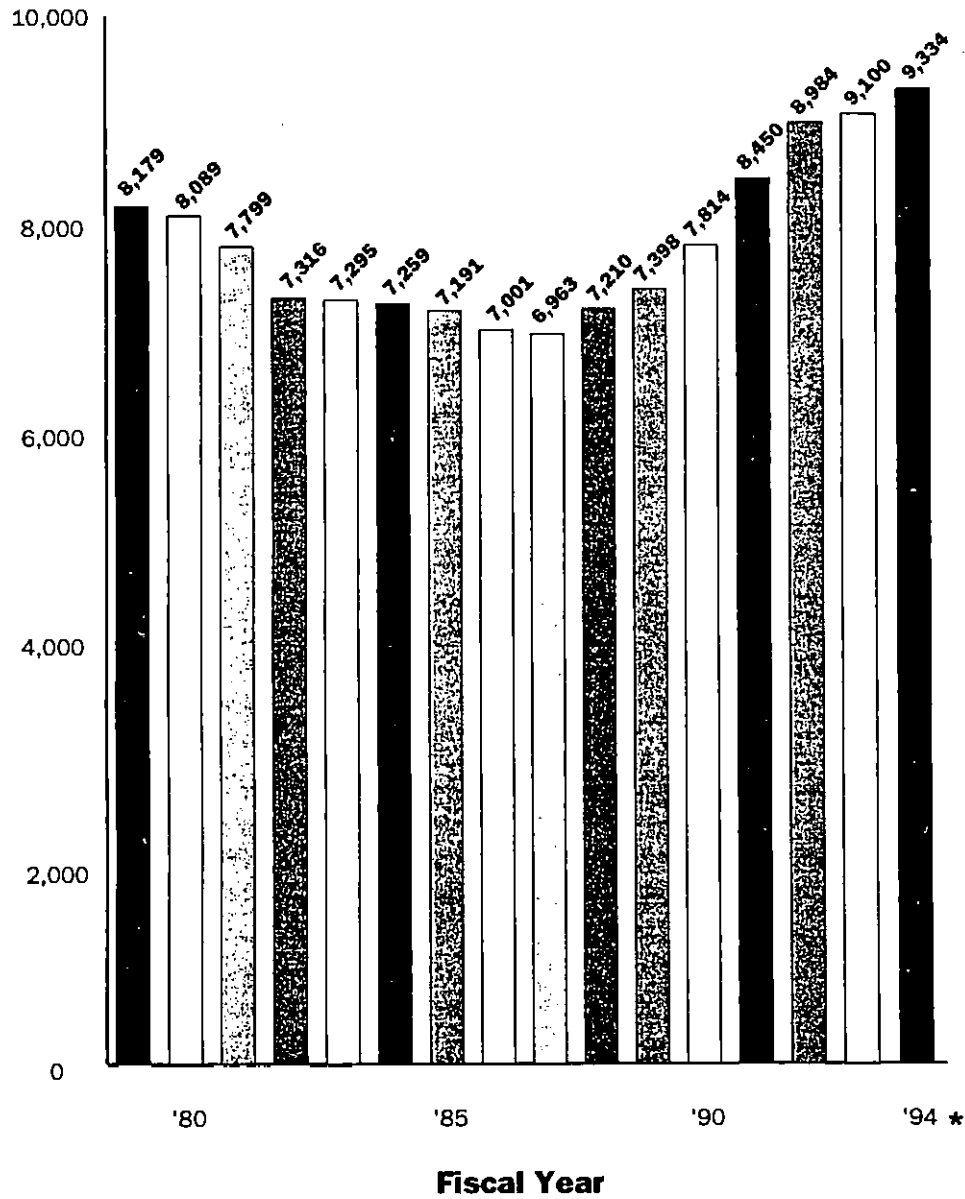
In addition to these three groups, the Office of Small Business, Scientific and Trade Affairs provides outreach and assistance to scientific associations to enhance their understanding of FDA's programs and policies.

# FDA Inspection Responsibilities



\* FDA defines establishment as a business or other facility under one ownership and at one geographic location or address that processes, manufactures, labels, repacks, stores, distributes, tests, or otherwise manipulates products under the jurisdiction of FDA. In addition, certain individuals or groups of individuals whose activities fall under the jurisdiction of FDA are also establishments. The sum of all categories is greater than the total because some establishments do business in more than one category.

**Staffing Levels**  
**FY 1979-1994**  
 (Full-Time Equivalents)



\* Estimated.

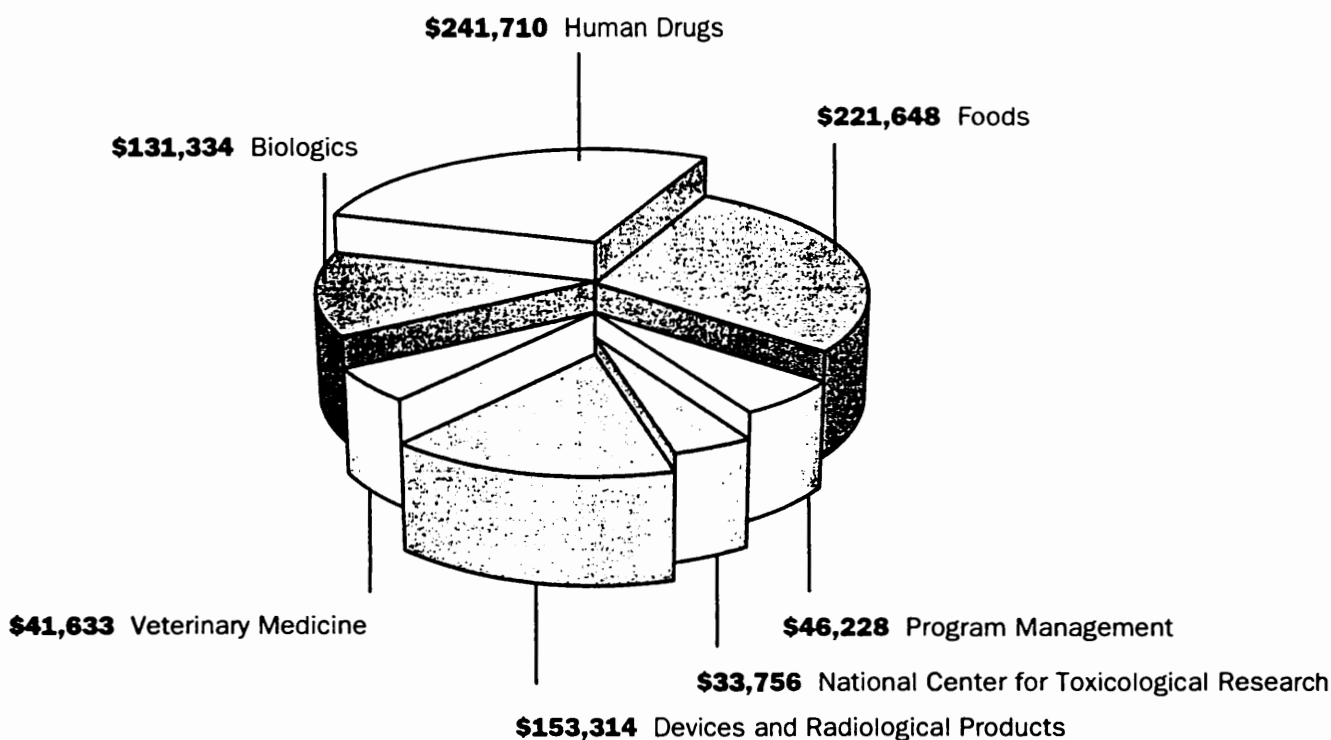
# Resources/Budget FDA FY 1994 Budget by Program Area

Total \$870 million

Total HHS: \$736 billion

FDA's FY 1994 budget totals \$870 million. This means FDA provides consumer protection over a vast array of products (worth over \$960 billion) at a cost of less than \$3 per American per year.

In recent years, the world has benefited from an explosion of U.S. investment in research and development (R&D) that, when successful, results in products that must be approved by FDA before reaching the public. For FDA to properly perform its evaluative function, the agency's resources must correspond in some meaningful way to the size of and growth in such R&D. Currently, however, the entire FDA budget is roughly 0.5 percent of R&D spending on FDA-regulated products, and increases in such spending do not translate into growth in the agency's budget. Our national blueprint for utilizing R&D as a means to improve national competitiveness will be furthered significantly if FDA resources are sufficient to allow timely and thorough review of regulated products on their way to the medical marketplace.



# FDA's International Role

FDA's international role grows as the world becomes a "global economy." As a world leader in food and drug regulatory science, FDA commits resources to information exchange, technical cooperation, scientific collaboration, and regulatory harmonization. Meeting this demand is the International Affairs Staff in the Office of Health Affairs, the International Program Staffs of the Centers, the Office of Small Business, Scientific and Trade Affairs, and the Office of Regulatory Affairs. Activities include:

## **International harmonization and trade**

- technical requirements for pharmaceuticals and biologicals
- international vaccine standards
- health and safety standards provisions in the General Agreement on Tariffs and Trade and the North American Free Trade Agreement
- U.S.-Canada Free Trade Agreement—technical working groups
- Codex Alimentarius Commission
- collaboration with the Commission of the European Communities

## **Technical cooperation**

- numerous projects and cooperative activities with Mexico
- vaccine needs assessment in Russia
- pharmaceutical quality programs in Saudi Arabia
- drug and nutrition programs in Egypt
- National Institute of Biologics in India
- cholera control in South America
- WHO consultation on Hazard Analysis and Critical Control Points (HACCP)

## **International Visitors Program**

- During FY 1992, over 700 regulatory officials and scientists from 67 countries visited FDA to discuss policy, regulatory and scientific issues, or to receive training.

## **Investigational drug export authorization**

- Manufacturers submitted to FDA almost 400 applications to export investigational drugs and biologicals for clinical trials or marketing in FY 1992.

## **Inspections of foreign manufacturers**

- In FY 1992, agency investigators inspected almost 450 foreign drug, medical device, biologic, and food production facilities that export products to the United States.

## **Information/Education**

- FDA participates in international training programs and conferences, and provides materials on its programs and activities to inform foreign industry about FDA regulations and policy.
- FDA regularly shares information on regulatory matters with counterpart foreign government regulatory authorities and international organizations.

## **International agreements**

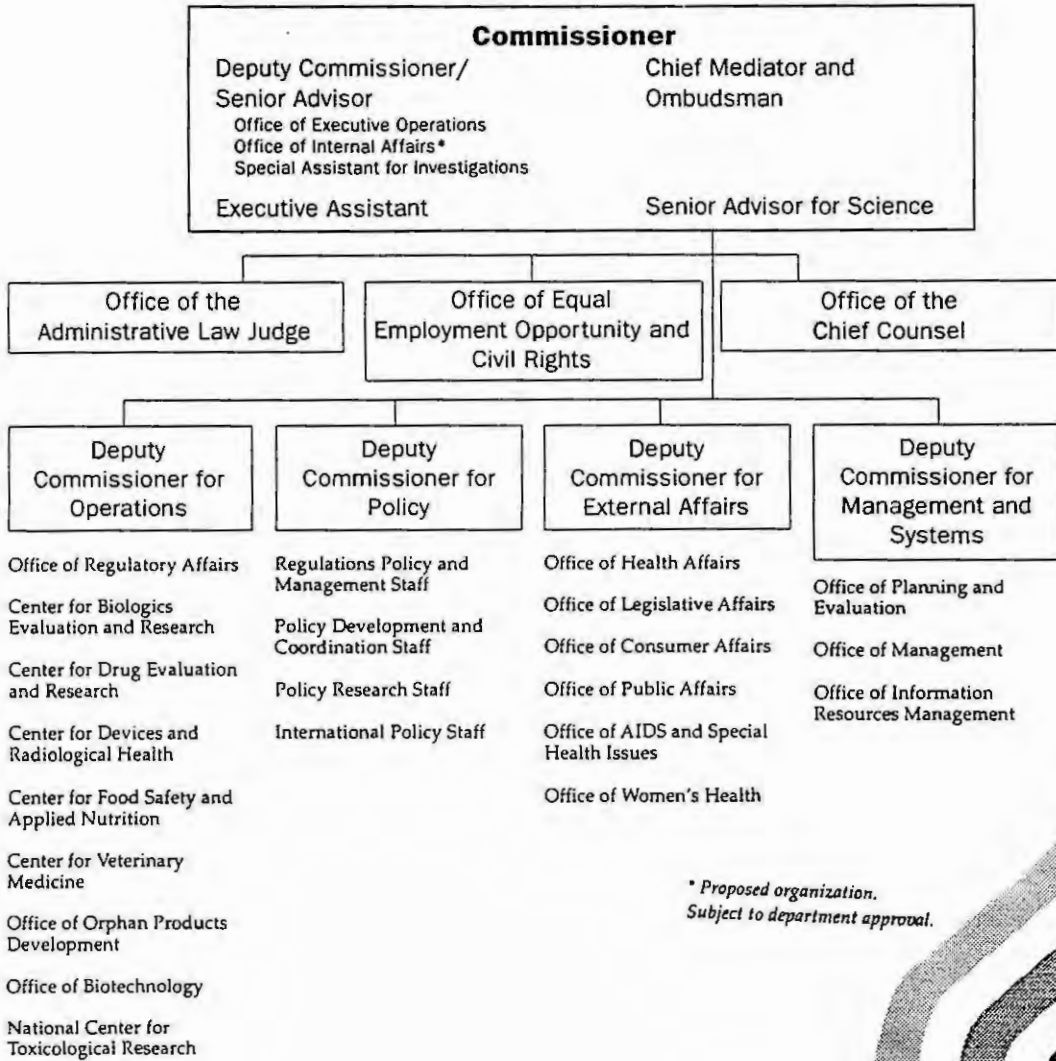
- FDA implements Memoranda of Understanding with foreign government counterpart authorities to help ensure the safety, quality and efficacy of FDA-regulated products exported to the United States.

# Section 2

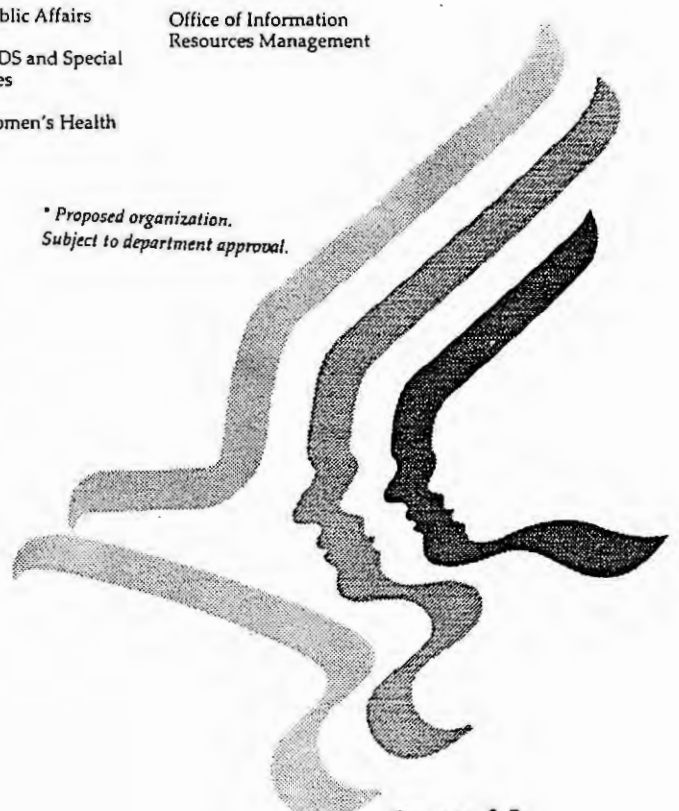
How is FDA  
Organized?

# DEPARTMENT OF HEALTH AND HUMAN SERVICES

## PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION



\* Proposed organization.  
Subject to department approval.





## **Office of AIDS and Special Health Issues**

On Aug. 18, 1993, the Office of AIDS Coordination was retitled the Office of AIDS and Special Health Issues, and its responsibilities were expanded to include cancer, Alzheimer's disease, and other special health issues. The objective for this new office is to provide a focal point for internal coordination and external communication of policy, agency activities, and new developments in these areas.

Additionally, the office has the following responsibilities:

- provides consultations and policy advice to senior FDA staff
- serves as a resource for AIDS and other special health issue related information within the agency
- ensures adequate and timely agency responses to AIDS and other special health related issues of importance
- provides FDA representation at a wide range of public and government meetings
- assists in the development of PHS and HHS policies and practices concerning AIDS and special health issues
- serves as a liaison between outside groups and FDA
- provides administrative and operational support for the National Task Force on AIDS Drug Development

# Office of Regulatory Affairs

## FDA's Enforcement Policy

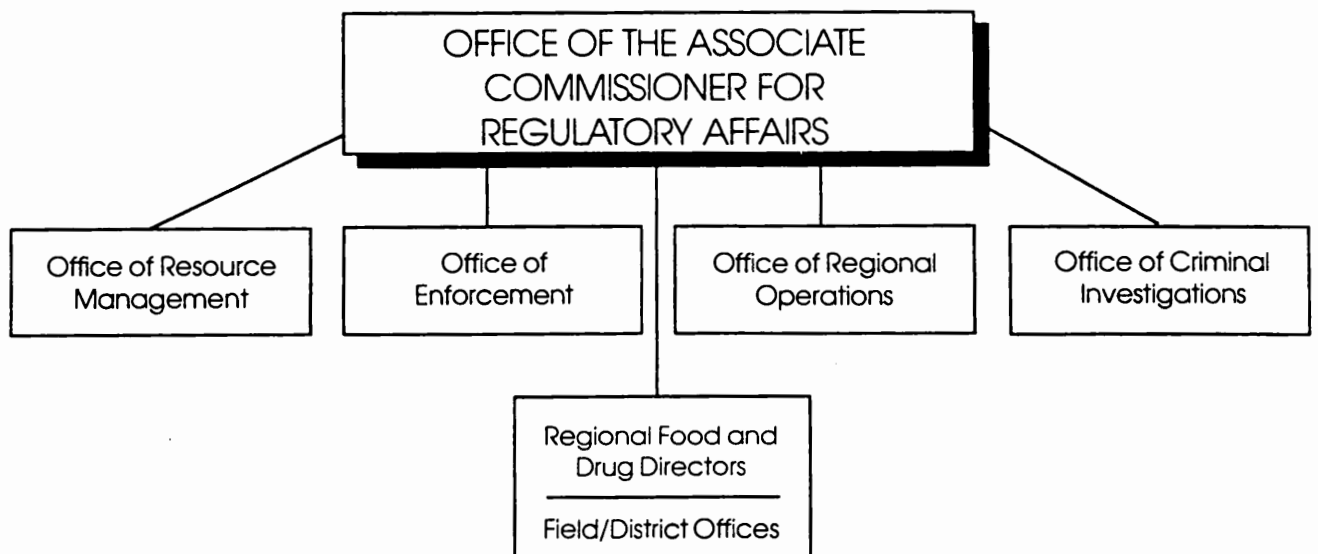
(Excerpted from 1990 Statement)

FDA is a scientifically based law enforcement agency. The enforcement function of FDA is twofold: to safeguard the public health and to ensure honesty and fair-dealing between the regulated industry and consumers.

- FDA encourages and expects compliance with the laws and regulations it enforces. To this end, the agency participates in cooperative and educational efforts designed to inform industry, health professionals, and the public of those legal requirements.
- FDA surveys and inspects regulated industry to assess compliance and discover noncompliance. Depending upon the nature of noncompli-

ance, FDA may afford an opportunity for correction by industry. If adequate correction does not occur within a reasonable period, FDA is committed to swiftly initiating action to obtain compliance. Legal remedies include injunction, seizure and prosecution.

- FDA does not tolerate fraud, intentional violations, or gross negligence, and promptly seeks prosecution to punish and deter whenever appropriate.
- FDA cooperates with . . . other federal, state and local agencies, and foreign governments and international organizations, to . . . increase the effectiveness of its consumer protection programs.



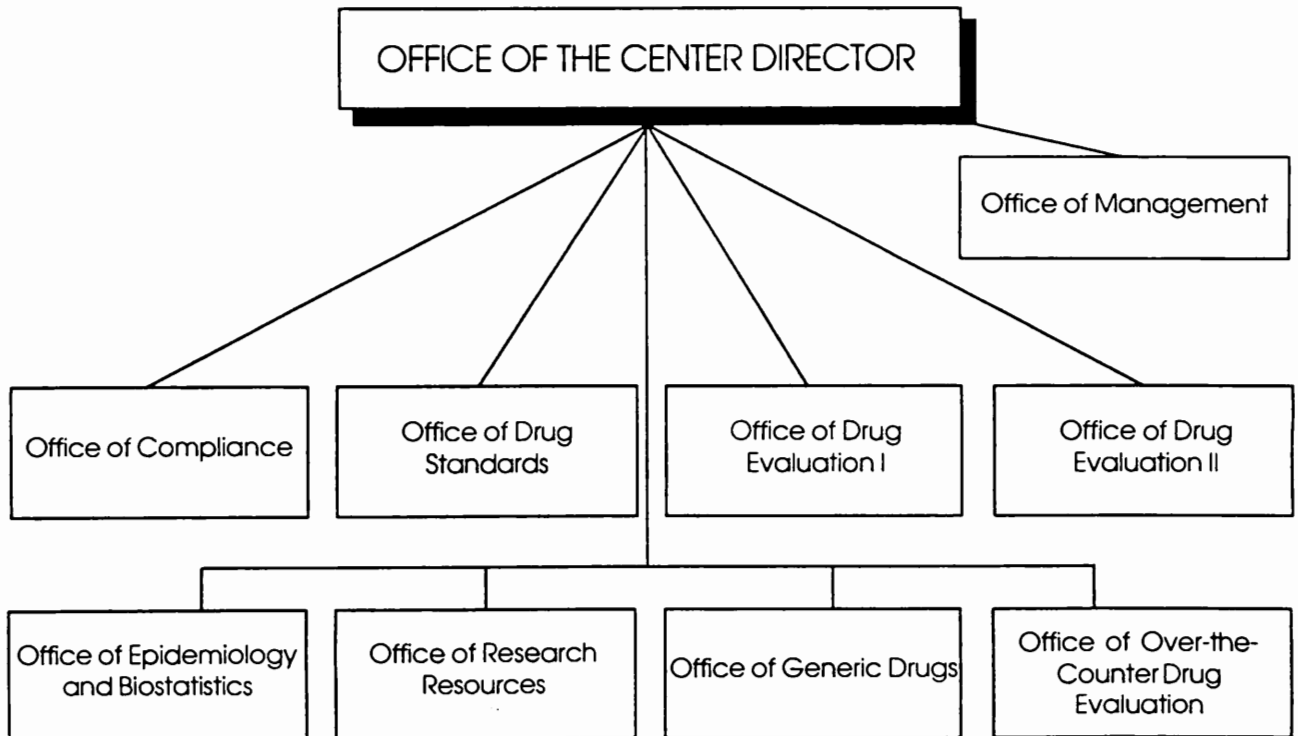
# Center for Drug Evaluation and Research

The center promotes, protects and enhances the health of the public through the drug development and evaluation process. The center's mission is to:

- approve drugs for marketing that are effective for their labeled indications, provide benefits that outweigh their risks, are of high quality, and have directions for use that are complete and honestly communicated
- facilitate early access to promis-

ing experimental drugs being developed for serious illnesses with no adequate therapy

- promote innovation and provide scientific leadership in the drug development process
- ensure that the safety and rights of patients in drug studies are adequately protected
- ensure that product quality and safety are maintained after marketing

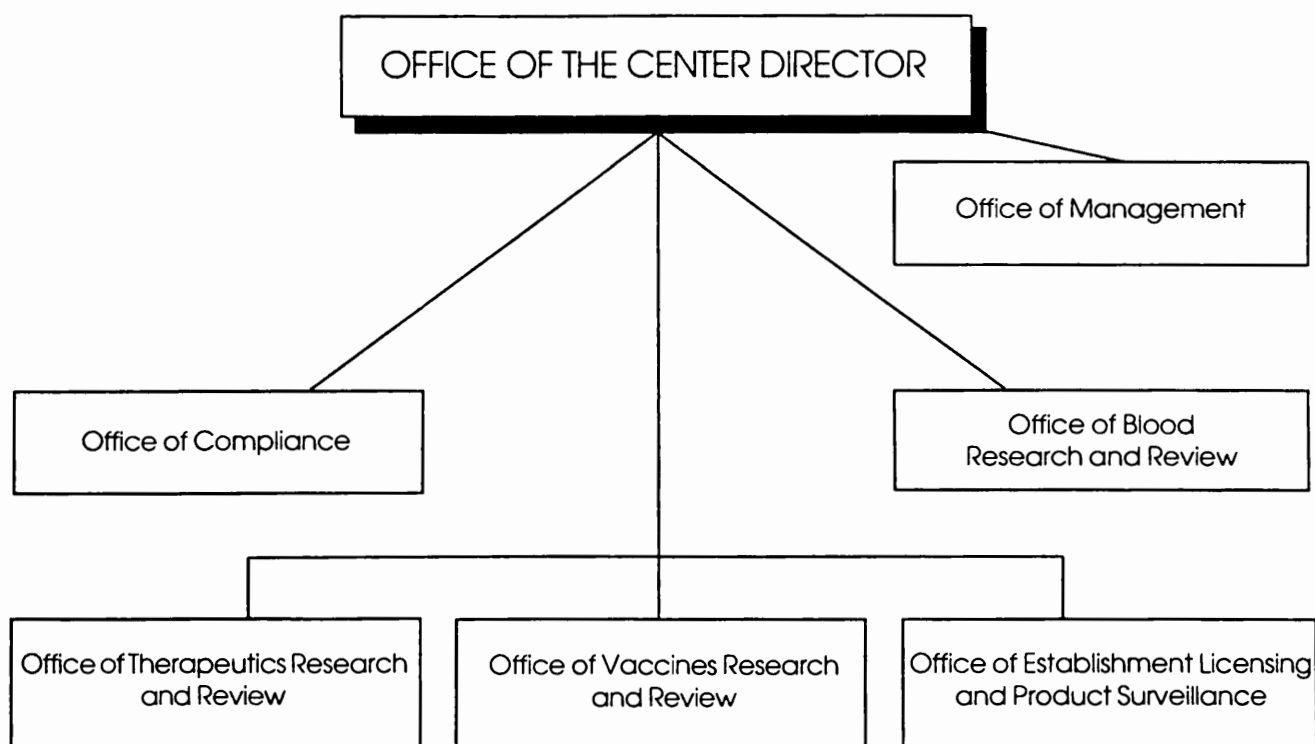


# Center for Biologics Evaluation and Research

The center's mission is to ensure the safety, efficacy, potency, and purity of biological products intended for use in the treatment, prevention or cure of diseases in humans. The primary responsibility of the center is to review the safety and efficacy of vaccines, blood products, certain diagnostic products, and other biological and

biotechnology-derived human products. The center also conducts mission-related research in areas such as:

- viral and bacterial vaccines
- immunology
- developmental biology
- parasitic diseases
- AIDS and related diseases

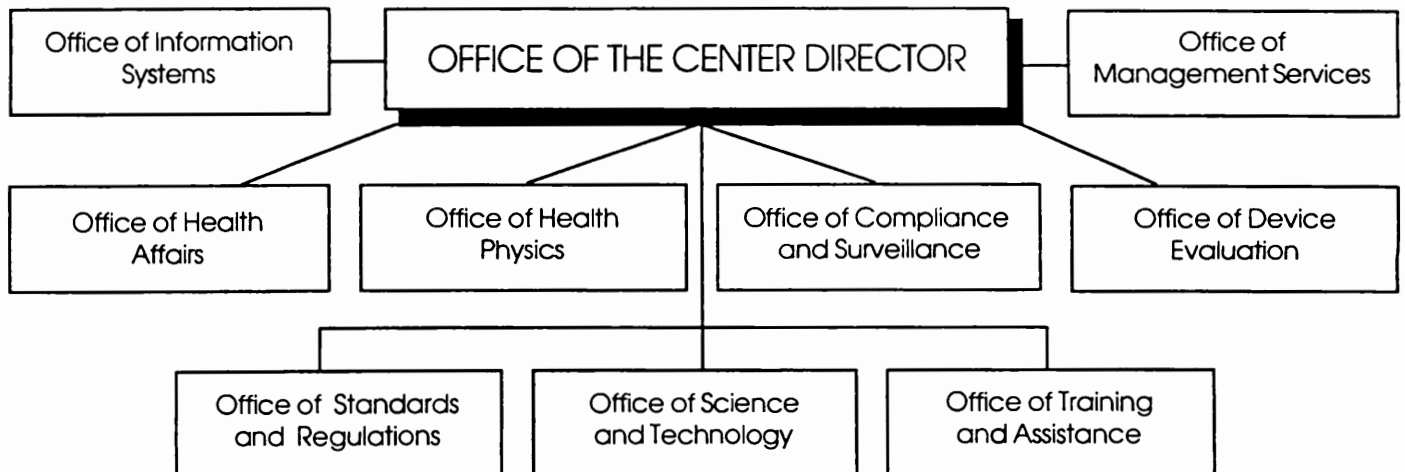


# Center for Devices and Radiological Health

The center is responsible for ensuring the safety and effectiveness of medical devices and eliminating unnecessary human exposure to man-made radiation from medical, occupational and consumer products. The center protects the public health by:

- reviewing and evaluating medical device premarket approval applications (PMAAs), product development protocols (PDPs), exemption requests for investigational devices (IDEs), and premarket notifications (510(k)s)
- collecting information about injuries and other experiences in the use of medical devices and

- radiation-emitting electronic products and using this information in center activities
- developing, promulgating and enforcing performance standards for radiation-emitting electronic products and medical devices and good manufacturing practice (GMP) regulations
- monitoring compliance and surveillance programs for medical devices and radiation-emitting electronic products
- providing technical and other nonfinancial assistance to small manufacturers of medical devices.



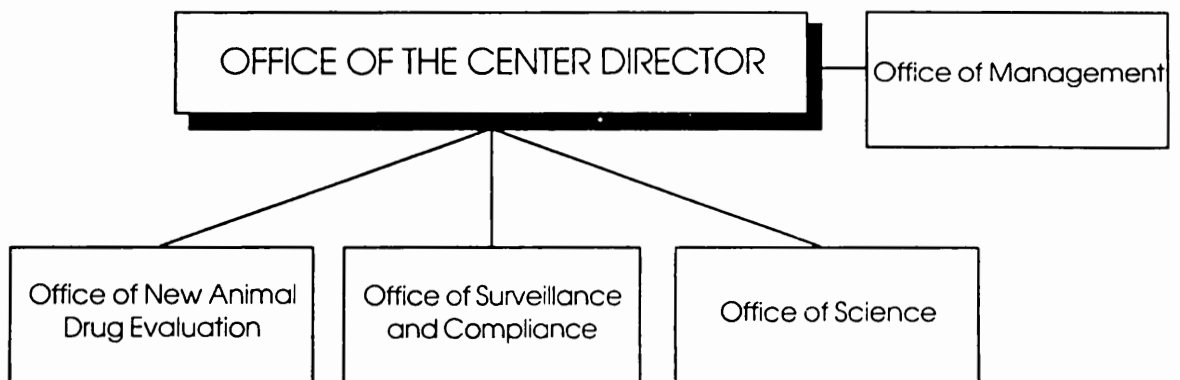
# Center for Veterinary Medicine

The Center for Veterinary Medicine's mission is to protect the public health through regulation of animal drugs, food additives, and devices. This mission is accomplished by:

- reviewing new animal drug applications, investigational new animal drug applications, abbreviated new animal drug applications, medicated feed applications, and food additive petitions

- assessing the environmental impact of product approvals
- surveillance of marketed products through review of drug experience reports and compliance programs.

Through these efforts, CVM ensures that animal drugs and medicated feeds are safe and effective and that food from treated animals is safe to eat.



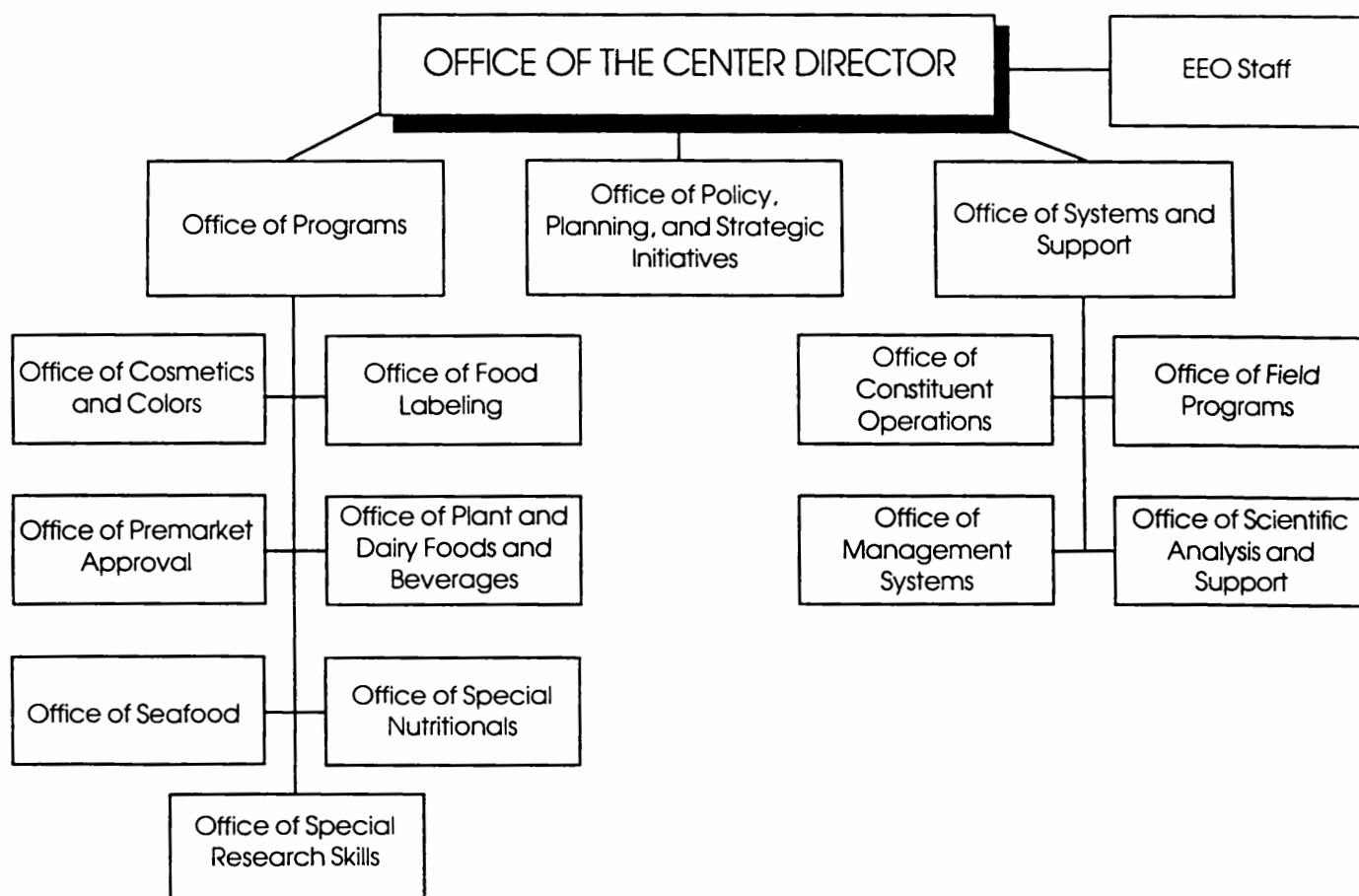
# Center for Food Safety and Applied Nutrition

The center is responsible for the regulation of foods for human consumption and cosmetics. All foods except meat and poultry products are FDA safety responsibilities. The mission of the center is to:

- be a leader in food safety
- protect consumers from economic fraud
- promote sound nutrition
- facilitate innovation

The center oversees a vast food industry that includes 46,000 U.S. food processors and warehouses. U.S. food

processors spend \$1.4 billion annually on research and development and introduce 10,000 new grocery products every year. Tens of thousands of pathogens, 450 pesticides (300 EPA approved), and 3,000 food additives require the center's attention to ensure that the public is protected from potential food safety problems. In addition, the center is responsible for handling issues involving imported foods and setting safety and sanitation standards for supermarkets, restaurants, and other retail food establishments.



# National Center for Toxicological Research

The National Center for Toxicological Research, located in Jefferson, Ark., pursues a research agenda with three major goals:

**Conducting integrated research with other centers to provide more effective risk measures for FDA-regulated products.** NCTR's role is to improve the standard bioassay through customized studies on:

- biochemical and molecular markers of carcinogenicity
- secondary mechanisms of toxicity
- solid-state toxicity (evaluation of potential toxicity of implanted materials used in medical devices)
- nutritional modulators of risk and toxicity
- quantitative risk assessment
- transgenics (mimicking human responses in animal models by insertion of human genes to a test animal or tissue culture)
- neurotoxicology
- developmental toxicology

**Supporting FDA enforcement through development of:**

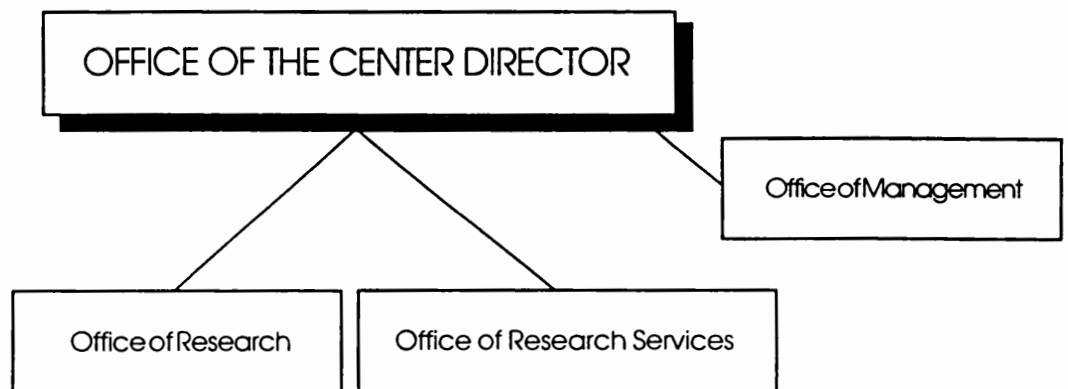
- sensitive methods to analyze

foods, drugs and cosmetics (analytical methods developments)

- improved information management systems for research/management decision-making
- exacting methods to measure compounds that adversely affect human health
- methods to determine the effects of novel food additives on human intestinal microflora and evaluate metabolic activation or detoxification of toxic chemicals (applied and environmental microbiology)

**Enhancing FDA's Life Science Education and Science Literacy Initiative by:**

- establishing and supporting an interdisciplinary toxicological program and regulatory science curriculum at two Arkansas universities
- maintaining 15 separate science education programs, from high school to postgraduate training, in an effort to increase the limited pool of qualified scientists.

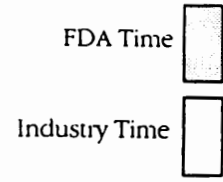




# Section 3

## Drug Development

# New Drug Development Timeline



**Pre-Clinical Testing, Research and Development**

**Clinical Research and Development**

**NDA Review**

**Post-Marketing Surveillance**

Range: 1-3 years  
Average: 18 months

Range: 2-10 years  
Average: 5 years

Range: 2 months-7 years  
Average: 24 months

Initial Synthesis

Phase 1

Adverse Reaction Reporting

Phase 2

Surveys/  
Sampling/  
Testing

Animal Testing

Short-Term

Phase 3

Inspections

Long-Term

30-Day Safety Review

NDA Submitted

NDA Approved

# Testing in Humans

|                | <b>Number of Patients</b>           | <b>Length</b>             | <b>Purpose</b>                                   | <b>Percent of Drugs Successfully Tested*</b> |
|----------------|-------------------------------------|---------------------------|--|--|
| <b>Phase 1</b> | 20-100                              | Several months            | Mainly safety                                    | 70 percent                                   |
| <b>Phase 2</b> | Up to several hundred               | Several months to 2 years | Some short-term safety, but mainly effectiveness | 33 percent                                   |
| <b>Phase 3</b> | Several hundred to several thousand | 1-4 years                 | Safety, effectiveness, dosage                    | 25-30 percent                                |

\* For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 will successfully complete phase 1 trials and go on to phase 2; about 33 of the original 100 will complete phase 2 and go to phase 3; 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

# Drug Development Timelines

(Two Case Studies)

## DDC (zalcitabine)

(AIDS Treatment)

|                     |   |
|---------------------|---|
| <b>1987</b>         | Preclinical tests begin for use in combination with AZT (zidovudine) to treat adults with advanced HIV infection or with clinical or immunological deterioration. |
| <b>April 1989</b>   | Investigational new drug (IND) exemption submitted to FDA.  |
| <b>July 1989</b>    | Phase I tests begin.  |
| <b>January 1991</b> | Phase II tests begin.   |
| <b>January 1991</b> | Phase III tests begin.  |
| <b>May 1991</b>     | Treatment IND approved.*  |
| <b>July 1991</b>    | New drug application (NDA) submitted.   |
| <b>June 1992</b>    | NDA approved.**   |

## TAXOL

(ovarian cancer treatment)

|                       |   |
|-----------------------|---|
| <b>1971</b>           | Taxol isolated from the bark and needles of the Pacific yew tree. |
| <b>1977</b>           | Preclinical studies begin.  |
| <b>September 1983</b> | Investigational new drug (IND) exemption submitted to FDA.        |
| <b>April 1984</b>     | Phase I studies begin.  |
| <b>August 1986</b>    | Phase II studies begin.   |
| <b>April 1990</b>     | Phase III studies begin.  |
| <b>July 1992</b>      | Treatment IND approved.   |
| <b>July 1992</b>      | New drug application (NDA) submitted.                             |
| <b>December 1992</b>  | NDA approved.   |

\*Treatment protocol that allows access to the new drug before approval for marketing for patients who meet the medical criteria of the study protocol.

\*\*DDC is the first drug approved under FDA's accelerated drug review policy, which expedites approval of drugs for life-threatening illnesses.

# FDA Public Advisory Committees

FDA enlists the aid and expertise of outstanding scientists across the country to help the agency reach decisions, particularly concerning controversial issues or new and unusual products.

## **Office of the Commissioner**

Board of Tea Experts  
Science Board to the FDA

## **Center for Biologics Evaluation and Research**

Allergenic Products Advisory Committee  
Biological Response Modifiers Advisory Committee  
Blood Products Advisory Committee  
Vaccines and Related Biological Products Advisory Committee

## **Center for Drug Evaluation and Research**

Anesthetic and Life Support Drugs Advisory Committee  
Anti-Infective Drugs Advisory Committee  
Antiviral Drugs Advisory Committee  
Arthritis Advisory Committee  
Cardiovascular and Renal Drugs Advisory Committee  
Dermatologic Drugs Advisory Committee  
Drug Abuse Advisory Committee  
Endocrinologic and Metabolic Drugs Advisory Committee  
Fertility and Maternal Health Drugs Advisory Committee  
Gastrointestinal Drugs Advisory Committee  
Generic Drugs Advisory Committee  
Medical Imaging Drugs Advisory Committee  
Oncologic Drugs Advisory Committee  
OTC Drugs Advisory Committee  
Peripheral and Central Nervous Systems Drugs Advisory Committee  
Psychopharmacologic Drugs

Advisory Committee  
Pulmonary-Allergy Drugs Advisory Committee

## **Center for Food Safety and Applied Nutrition**

Food Advisory Committee

## **Center for Devices and Radiological Health**

Medical Devices Advisory Committee  
*Anesthesiology and Respiratory Therapy Devices Panel*  
*Circulatory System Devices Panel*  
*Clinical Chemistry and Clinical Toxicology Devices Panel*  
*Dental Products Panel*  
*Ear, Nose, and Throat Devices Panel*  
*Gastroenterology-Urology Devices Panel*  
*General and Plastic Surgery Devices Panel*  
*General Hospital and Personal Use Devices Panel*  
*Hematology and Pathology Devices Panel*  
*Immunology Devices Panel*  
*Microbiology Devices Panel*  
*Neurological Devices Panel*  
*Obstetrics-Gynecology Devices Panel*  
*Ophthalmic Devices Panel*  
*Orthopedic and Rehabilitation Devices Panel*  
*Radiologic Devices Panel*  
Device Good Manufacturing Practice Advisory Committee  
Technical Electronic Product Radiation Safety Standards Committee

## **Center for Veterinary Medicine**

Veterinary Medicine Advisory Committee

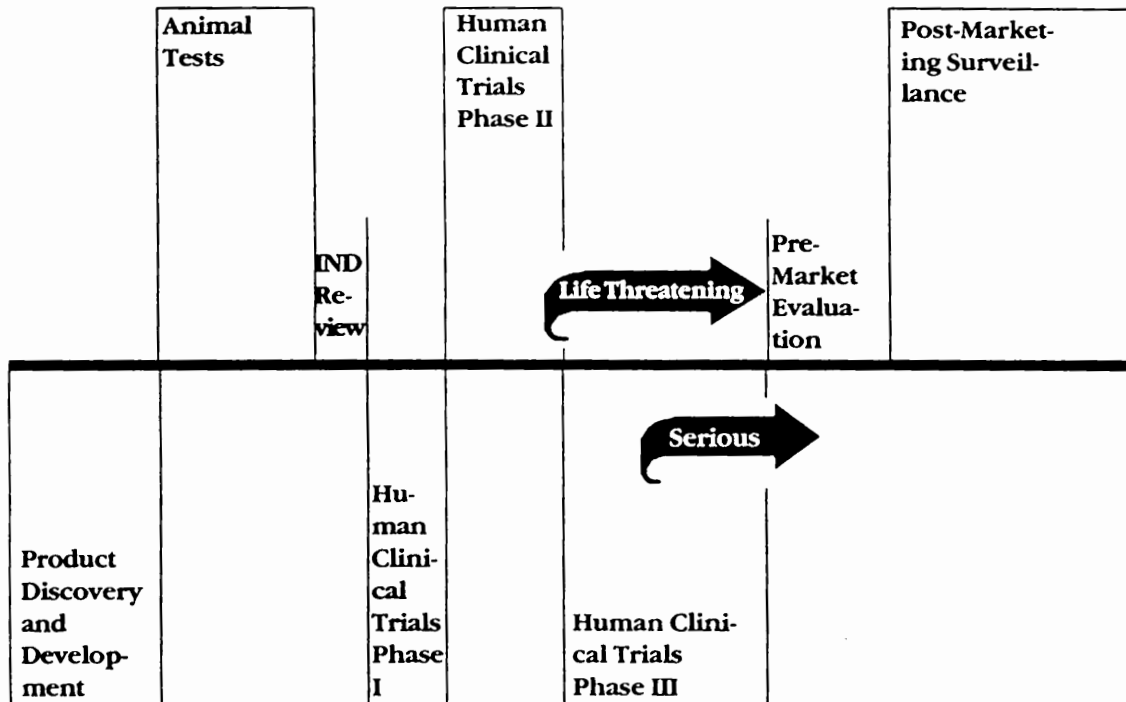
## **National Center for Toxicological Research**

Ranch Hand Advisory Committee  
Science Advisory Board

# Treatment IND Timeline

The arrows on this chart show when a promising experimental drug can be made available to additional desperately ill patients, under a rule FDA issued in 1987. With drugs for immediately life-threatening conditions, expanded availability can begin near the end of the second phase of human testing—that is, after the drug's initial safety testing has been done (phase I), and some evidence of therapeutic benefit has been obtained (phase II). For seri-

ous but not immediately life-threatening illnesses, approval for expanded treatment availability can occur sometime during the third and final phase of testing. During phase III, early evidence of safety and effectiveness is verified before marketing approval of the drug is sought from FDA. Once granted, FDA approval of an investigational drug for treatment use will normally continue until regular marketing of the drug begins.



# Product Submissions and Approvals

(Numbers in parentheses are  
non-add items.)

## New Drug Applications

|                             | FY 91 | FY 92 | FY 93 |
|-----------------------------|-------|-------|-------|
| Originals received          | 108   | 89    | 97    |
| Resubmissions               | 12    | 13    | 25    |
| Major amendments            | 436   | 411   | 423   |
| Final actions               |       |       |       |
| Approved                    | 63    | 86    | 83    |
| New Molecular Entities      | (26)  | (30)  | (26)  |
| Approvable <sup>1</sup>     | 54    | 37    | 45    |
| Not approvable <sup>2</sup> | 72    | 86    | 50    |
| Refusals to file            | 22    | 31    | 25    |
| Pending <sup>3</sup>        | 203   | 156   | 174   |

## Investigational New Drug Applications<sup>4</sup>

|                          | FY 91   | FY 92    | FY 93    |
|--------------------------|---------|----------|----------|
| Originals received       | 1,963   | 2,452    | 2,413    |
| Commercial               | (371)   | (371)    | (381)    |
| Research                 | (1,592) | (2,081)  | (2,032)  |
| Active INDs <sup>5</sup> | (9,958) | (10,261) | (10,682) |

## Abbreviated New Drug Applications<sup>6</sup>

|                                   | FY 91 | FY 92 | FY 93 |
|-----------------------------------|-------|-------|-------|
| Receipts <sup>7</sup>             | 1,453 | 1,789 | 1,593 |
| Original receipts                 | (300) | (339) | (308) |
| Actions <sup>8</sup>              | 1,097 | 1,499 | 1,177 |
| Approved                          | (141) | (239) | (215) |
| Withdrawals received <sup>9</sup> | 678   | 1,255 | 929   |
| Approved                          | (353) | (615) | (422) |
| Unapproved                        | (325) | (640) | (507) |

## **NDA Efficacy Supplements**

|                      | <b>FY 91</b> | <b>FY 92</b> | <b>FY 93</b> |
|----------------------|--------------|--------------|--------------|
| Received             | 47           | 57           | 76           |
| Approved             | 19           | 53           | 54           |
| Pending <sup>3</sup> | 119          | 103          | 102          |

## **Adverse Drug Reaction Reports**

|           | <b>FY 91</b> | <b>FY 92</b> | <b>FY 93</b> |
|-----------|--------------|--------------|--------------|
| Received  | 88,261       | 127,488      | 149,015      |
| Evaluated | 88,261       | 127,488      | 149,015      |
| Pending   | 0            | 0            | 0            |

1. An "approvable" action letter is issued by FDA when an application has substantially met FDA requirements but minor issues remain that still must be resolved before the application can be approved.
2. A "not approvable" action letter is issued by FDA when an application has major deficiencies. This action closes the file until the applicant makes significant amendments to the NDA, withdraws the application, or requests a hearing.
3. "Pending" refers to the pool of applications/supplements without final action at the end of the fiscal year. Any one application/supplement could have been in the pool for several years.
4. An investigational new drug (IND) is a new drug or antibiotic drug that is to be used in a clinical investigation. A commercial IND is submitted by a sponsor with the intent to gather data to eventually support a new drug application. A research IND is submitted by a sponsor whose main intent is to advance scientific knowledge by using the drug as a research tool for early clinical investigation.
5. Active INDs are those that are neither terminated nor discontinued but are still under active investigation.
6. Abbreviated antibiotic drug applications (AADAs) and ANDAs were combined beginning in FY 90.
7. Receipts include originals and resubmissions.
8. Actions include approvals.
9. Withdrawals reflect requests by applicants to "withdraw" their abbreviated applications from FDA either prior to approval (Unapproved) or subsequent to approval (Approved). The applicant will cease marketing the product when the application is withdrawn subsequent to approval.



# AIDS

## MAJOR EVENTS AND FDA MILESTONES

- 1981 AIDS first reported by CDC in Morbidity and Mortality Weekly (MMWR).
- 1982 FDA received first IND submission for treatment of AIDS.
- 1984 AIDS identified as being caused by a human retrovirus (HIV).
- 1985 FDA approved first enzyme linked immunosorbant assay (ELISA) test kit to screen for antibodies to the AIDS virus.
- 1987
  - AZT approved - the first drug approved for the treatment of AIDS.
  - Approved the first Western blot blood test kit - a more specific test. Currently there are eleven licensed manufacturers of in vitro test kits for the detection of antibodies to HIV-1 and one for the detection of antibody to HIV-2.
  - Approved the first human testing of a candidate vaccine against the AIDS virus. To date, eight IND applications have been received and several have been approved for Phase I clinical trials.
  - Published regulations which require screening all blood and plasma collected in the U.S. for HIV antibodies.
  - FDA completed studies demonstrating the safety of immune globulin products. The efficacy of viral inactivation and partitioning during manufacturing procedures was confirmed.
  - FDA revised its strategy for the regulation of condoms by strengthening its inspection of condom manufacturers and repackers, strengthening its sampling and testing of domestic and imported condoms in commercial distribution, and providing guidance on labeling of condoms for the prevention of AIDS.
- 1988
  - Trimetrexate was the first drug to be granted special status under the new Treatment IND regulations.
  - Human interferon Alpha 2 licensed for the treatment of Kaposi's Sarcoma, a cancer resulting from AIDS infection.
  - Injectable Pentamidine approved to treat Pneumocystis carinii pneumonia, an opportunistic infection of AIDS.
  - FDA doubled blood facility inspection effort with the inspection of 100 percent of FDA-regulated blood and plasma donor facilities.
  - FDA implemented new regulations designed to make promising therapies available sooner for patients with life-threatening and severely-debilitating diseases.
- 1989
  - Aerosolized pentamidine approved for the prevention of Pneumocystis carinii pneumonia.
  - Ganciclovir approved for use in the treatment of cytomegalovirus retinal infections in persons with AIDS.
  - Zidovudine in syrup formulation approved.
  - Licensed the first diagnostic kit to detect the presence of HIV-1 by directly detecting the proteins, or antigens, of the virus.
- 1990
  - Participated in the establishment of an AIDS Clinical Trial Information Service (ACTIS), a computerized listing of information on AIDS-related clinical trials available via toll free telephone service.
  - Fluconazole approved to treat two serious AIDS-related fungal infections.
  - Zidovudine approved in intravenous dosage form.
  - Expanded labeling for zidovudine approved, including dosage, for use in early HIV disease, and for use with children.
  - Approved erythropoietin for the treatment of zidovudine-related anemia.
  - FDA granted permission for expanded clinical testing of experimental inactivated virus vaccine being studied for its potential to counteract infections with HIV-1 through treatment mechanism.
  - FDA granted a license for the Recombigen (R) HIV-1 EIA AIDS antibody detection kit, designed for high volume screening sites.
  - Novopath HIV-1 Immunoblot test for the detection of antibodies to individual proteins of HIV-1 approved. This test is nearly 5 times faster than comparable tests using the same technology.
  - FDA published a final rule defining acceptable quality levels for medical gloves and establishing the sampling plans and test methods that FDA will use to determine whether gloves are adulterated.
- 1991
  - Didanosine (ddI) approved for the treatment of adult and pediatric patients (over 6 months of age) with advanced HIV infection. Approval result of historic joint review between officials at FDA and in Canada.
  - Foscarnet approved for use in the treatment of cytomegalovirus retinal infections in persons with AIDS.
  - The first combination test to detect HIV-1 and HIV-2 antibodies was licensed.
- 1992
  - On November 12 FDA authorized pre-approval distribution of atovaquone under a treatment IND protocol to patients who have Pneumocystis carinii pneumonia and cannot tolerate trimethoprim sulfamethoxazole, a standard treatment for this condition.
  - On March 6 FDA authorized pre-approval distribution of rifabutin under a treatment IND protocol for preventing or delaying the onset of Mycobacterium avium complex, a severe infection that often afflicts AIDS patients.
  - On May 27 FDA licensed SUDS HIV-1, a ten minute diagnostic test kit which can be used by health professionals to detect the presence of HIV-1.
  - On June 19 FDA approved zalcitabine, commonly known as ddc, for use in combination with zidovudine (AZT) as a treatment option for adult patients with advanced HIV infection who show signs of clinical or immunological deterioration. Zalcitabine, manufactured and distributed by Hoffmann La Roche under the trade name Hivid, was the first drug approved under the principles and procedures of FDA's proposed accelerated drug review policy.

- On September 11 FDA approved itraconazole for the treatment of blastomycosis and histoplasmosis in immunocompromised and non-immunocompromised patients.
- On September 25 FDA approved new labeling for ddI. The data demonstrated that the lower dose of ddI is equally efficacious and associated with lower rates of toxicity, especially pancreatitis.
- On October 5 d4T (stavudine) was the first drug made available for expanded investigational use under the parallel track policy.
- On October 8 FDA approved new labeling for nonprescription drugs for vaginal candidiasis. The revised labeling advised women that frequent or persistent cases of vaginal fungal infections may sometimes be an early warning of HIV infection.
- On November 25 FDA approved atovaquone for the treatment of mild to moderate PCP in patients who are intolerant of trimethoprim-sulfamethoxazole, the standard therapy.
- On December 22 FDA approved dronabinol (new indication) for anorexia and weight loss associated with AIDS.
- On December 23 FDA approved rifabutin for the prophylaxis against Mycobacterium avium complex, a severe infection that often afflicts AIDS patients.
- On June 17 Stavudine (d4T) was approved for treatment of adults with HIV infection who no longer respond to or are intolerant of other antiviral drugs.
- On August 5 FDA approved new labeling for ddC to include use as monotherapy for HIV-infection in adults.
- On August 8 FDA approved new labeling for AZT to include use in preventing vertical transmission of HIV from HIV-infected pregnant women to their babies.
- On November 7 FDA approved a polyurethane condom for use by individuals who are allergic to latex.
- On November 23 FDA approved new labeling for fluconazole to include pediatric patients with cryptococcal meningitis and candida infections.
- On December 20 Serostim, a mammalian derived recombinant human growth hormone, was granted a treatment IND.
- On December 22 FDA approved oral ganciclovir for the treatment of CMV retinitis in immunocompromised individuals.
- On December 23 FDA approved the first non blood-based collection kit utilizing oral fluid for use in the detection of the antibody to HIV-1.

• 1993

- On May 7 FDA approved the Reality Female Condom which offers women a barrier product to protect themselves without relying on the cooperation of their partner.
- On September 10 FDA approved megestrol acetate, (new indication), for anorexia, cachexia, or an unexplained weight loss in patients with AIDS.
- On December 14 an interim rule was published establishing a requirement for certain infectious disease testing, donor screening, and record keeping to help prevent the transmission of HIV and hepatitis b and C through human tissue used in transplantation.
- On December 17 FDA approved trimetrexate glucuronate for the treatment of moderate to severe Pneumocystis carinii pneumonia.
- On December 22 FDA approved clarithromycin (new indication), for the treatment of disseminated mycobacterial infections due to Mycobacterium avium and Mycobacterium intracellulare (Mycobacterium avium complex-MAC).
- On December 27 FDA licensed Immune Globulin Intravenous (Human) (IGIV), (new indication) for use in HIV-infected children to decrease the frequency of bacterial infections, increase the time free from serious bacterial infections, and decrease the frequency of hospitalizations.

• 1994

- On January 7 FDA approved trimethoprim/sulfamethoxazole, (new indication) for prophylaxis against Pneumocystis carinii pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing Pneumocystis carinii pneumonia.
- On February 4, Secretary Shalala announced the eighteen members of the National Task Force on AIDS Drug Development, which includes experts in AIDS drug development issues from academia, industry, medicine, the HIV/AIDS-affected communities, and Government. The Chairman of the Task Force is the Assistant Secretary for Health. FDA provides administrative and managerial support for the Task Force.
- On March 29 FDA asked condom manufacturers to begin using the air-burst test on all brands of latex condoms. This new test measures a condom's strength, and may be an indirect indicator of its resistance to breakage during use.

**DRUGS CURRENTLY APPROVED BY THE FDA FOR  
HIV INFECTION AND AIDS-ASSOCIATED CONDITIONS**

| <u>DRUG</u>   | <u>APPROVAL DATE</u> |
|---|----------------------|
| <u>Antiretroviral Drugs</u>   |                      |
| Retrovir Capsules<br>(zidovudine, AZT)  | 9 MAR 87             |
| Retrovir Syrup  | 28 SEP 89            |
| Retrovir Injection  | 02 FEB 90            |
| Videx<br>(didanosine, ddI)<br>(for advanced HIV infection<br>when there is intolerance to<br>or no response to zidovudine)                            | 09 OCT 91            |
| Hivid<br>(zalcitabine, ddC)<br>(for use in combination with<br>zidovudine for the treatment<br>of advanced HIV infection)                             | 19 JUN 92            |
| Zerit<br>(Stavudine, d4t)<br>(treatment of adults with advanced<br>HIV infection who no longer respond<br>to or intolerant of other anti-viral drugs) | 17 JUN 94            |
| <u>Drugs for AIDS-Associated Conditions</u>   |                      |
| Intron A<br>(interferon A injection)<br>(for Kaposi's Sarcoma)  | 21 NOV 88            |
| Roferon A<br>(interferon A injection)<br>(for Kaposi's Sarcoma)   | 21 NOV 88            |
| Cytovene<br>(ganciclovir)<br>(for CMV Retinitis)  | 23 JUN 89            |
| Cytovene Oral   | 22 DEC 94            |
| Diflucan Tablets<br>(fluconazole)<br>(for Cryptococcal meningitis,<br>candidiasis)  | 29 JAN 90            |

Currently Approved Drugs for AIDS  
-Page 2-

|  |            |
|--|------------|
| Diflucan Injection   | 29 JAN 90  |
| Nebupent<br>(aerosolized pentamidine)<br>(for prevention of PCP)   | 15 JUN 89  |
| Epogen<br>(erythropoietin)<br>(for ZDV-related anemia)   | 31 DEC 90  |
| Foscavir<br>(foscarnet)<br>(for CMV retinitis)   | 27 SEP 91  |
| Sporanox<br>(itraconazole)<br>(for histoplasmosis and<br>blastomycosis)  | 11 SEP 92  |
| Mepron<br>(atovaquone)<br>(for mild to moderate PCP<br>in patients intolerant of<br>TMP-SMX)   | 25 NOV 92  |
| Mepron Suspension  | 08 FEB 95  |
| Mycobutin<br>(rifabutin)<br>(for <u>Mycobacterium avium</u><br>complex-[MAC])  | 23 DEC 92  |
| Marinol*<br>(dronabinol)<br>(for anorexia and weight<br>loss associated with AIDS)   | 23 DEC 92  |
| Megace*<br>(megestrol acetate)<br>(for anorexia, cachexia, or<br>an unexplained weight loss in<br>patients with AIDS)  | 10 SEPT 93 |
| NeuTrexin<br>(trimetrexate glucuronate<br>administered concurrently with<br>leucovorin)<br>(for moderate to severe<br>Pneumocystis carinii<br>pneumonia [PCP]) | 17 DEC 93  |

Currently Approved Drugs for AIDS

-Page 3-

Clarithromycin \* 23 DEC 93  
(for the treatment of disseminated  
mycobacterial infections due to  
Mycobacterium avium and Mycobacterium  
intracellulare [Mycobacterium avium  
complex-MAC])

Immune Globulin Intravenous\* 27 DEC 93  
(Human) (IGIV)  
(for use in HIV-infected children  
to decrease the frequency of bac-  
terial infections, increase the  
time from serious bacterial  
infections, and decrease the  
frequency of hospitalizations)

Trimethoprim/Sulfamethoxazole\* 07 JAN 94  
(for the prophylaxis against  
Pneumocystis carinii pneumonia  
in individuals who are immuno-  
suppressed and considered to be  
at an increased risk of developing  
Pneumocystis carinii pneumonia)

\* New indication

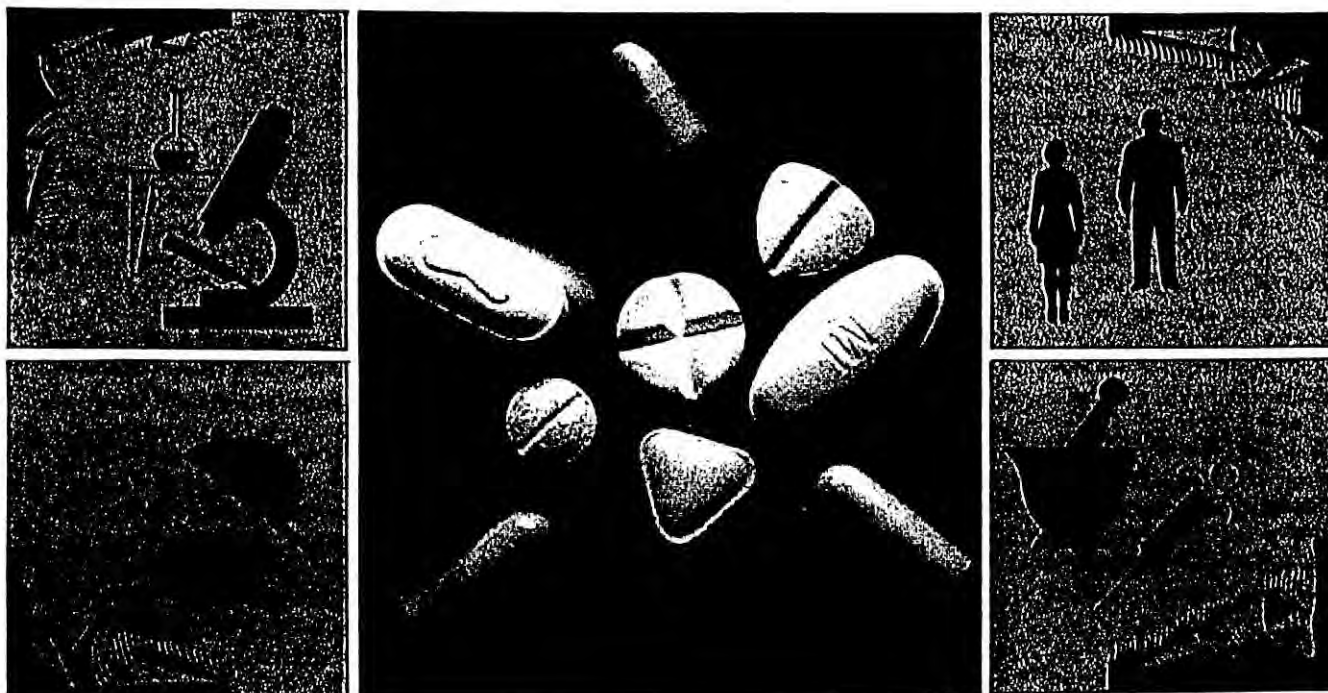
Prepared by  
Office of AIDS and Special Health Issues  
Food and Drug Administration  
April 13, 1995

# Section 4

## Preclinical/Animal Studies

# The Beginnings: Laboratory and Animal Studies

by Jeffrey P. Cohn



The scene is a typical one. A patient, perhaps you or I, goes to a doctor and gets a prescription. Then a pharmacist fills the prescription, with instructions to take the drug in the prescribed amount and manner over the following days, weeks or months. This scene is repeated millions of times across this country every day—some 1.6 billion prescriptions are filled every year in the United States, an average of seven for every man, woman and child. In fact, the process is so commonplace that the pills, tablets, capsules and other medications that virtually every one of us relies on to restore or maintain good health at some point in our lives come to be taken for granted.

Yet these drugs—and the improved quality of health they bring to the American people—are truly “miracles of modern science.” In fact, the process for discovering, developing and testing new drugs encompasses some of the most exciting areas of scientific discovery today. The endeavor runs the gamut from basic biomedical investigation of living cells and molecules to applied research that yields new consumer products to improve health care.

---

## THE CUTTING EDGE

---

“We are on the cutting edge of the biological sciences,” says Rhoda Gruen, a biochemist at Hoffmann-La Roche, Inc., a leading pharmaceutical research and manufacturing firm, head-

quartered in Nutley, N.J. “We suck up new information like a sponge. Everything we do is subject to change as new scientific information becomes known.”

The research process is a complicated, time-consuming, and costly one whose end result is never known at the outset. Discovering a new drug has been likened to searching for the proverbial needle in a haystack. Literally hundreds and sometimes thousands of chemical compounds must be made and tested to find one that can achieve the desirable result without too-serious side effects.

The complexity of the process can be gauged, in part, by the diversity of scientific disciplines engaged in finding new drugs. Traditional organic chemists, physiologists and statisticians have been joined in recent years by new kinds of specialists. Biochemists study the chemistry of life processes. Molecular biologists study the molecules that make up living matter. Toxicologists investigate chemicals’ potential for harm. Pharmacologists look at how drugs work. And computer scientists apply the power of their sophisticated machines to analyze and assess new chemicals. Each provides a different way of looking for that needle.

Such a complicated process costs vast amounts of time and money. The Pharmaceutical Manufacturers Association (PMA), a trade group of research-based drug makers, says 10 years or more are needed to study and test a new drug before

the Food and Drug Administration can approve it for the general public. That includes early laboratory and animal testing, the subject of this article, as well as later clinical trials using human subjects. (See page 10.)

Drug companies spend about \$65 million, on average, to develop a new drug, says economist Steven Wiggins of Texas A&M University. Actually, Wiggins, who conducted a study on the costs of drug development on behalf of PMA, says the real cost of bringing a drug to market is more like \$125 million. That includes what the economists call the opportunity cost of investing money in research whose payoff may be years away, instead of in a more immediate moneymaking venture. A company such as Hoffmann-La Roche, whose annual sales in the United States alone exceeds \$1 billion, spends about \$2 million each business day on research worldwide.

---

### **BUILDING ON GOOD SCIENCE**

---

There is no standard route by which the 2,400 drugs now sold in the United States were developed. "Each drug has its own way of being born," says Clement Stone, senior vice president for Merck, Sharp & Dohme research laboratories, West Point, Pa. "Often we consciously search for a drug for a specific use, but more often it is serendipity. What is required, though, is good science building on good science."

In some cases, a pharmaceutical company decides to develop a new drug aimed at a specific disease or medical condition. In others, company scientists may be free to pursue an interesting or promising line of research. And, in yet others, new findings from university, government or other laboratories may point the way for drug companies to follow in their own research.

Indeed, the process typically combines elements of all three avenues. "We let our scientists do and make use of the best research they can in their fields," says Ronald Kuntzman, vice president for research and development at Hoffmann-La Roche. "The only question we ask as a company is whether this research is leading toward development of a new drug."

New drug research starts by studying how the body functions, both normally and abnormally, at its most basic levels. The pertinent question, Kuntzman says, is: "If I change it [the body's functioning], will I have a useful drug?" That, in turn, leads to a concept of how a drug might be used to prevent, cure or treat a disease or medical condition. Once the concept has been developed, the researcher has a target to aim for, Kuntzman adds.

Gruen elaborates: "Disease processes are complex and involve a sequence of events. If you want to intervene in the disease process, you try to break it down into its component parts. You then analyze those parts to find out what abnormal events are occurring at the cellular and molecular levels. You would then select a particular step as a target for drug development with the aim of correcting the cellular or molecular dysfunction."

---

### **A NEW CHOLESTEROL DRUG**

---

Take cholesterol, a wax-like substance found naturally in the body. Too much cholesterol, either naturally or in the diet, can cause it to build up on the inside walls of blood vessels. This

can clog the arteries that deliver blood to the heart muscle, blocking the flow of oxygen and nutrients, causing a heart attack.

There have been few drugs that effectively cut cholesterol levels without either toxic or unpleasant side effects. This has limited their use. Others that were tested acted too late in the process by which the body makes cholesterol to lower its levels. What was needed, says Eve Slater, a cardiologist and Merck's director for biomedical research, was a drug that would act earlier in the cholesterol-making process.

To find one, scientists at Merck and elsewhere spent decades studying how the body makes and uses cholesterol. Along the way they identified more than 20 biochemical reactions necessary for the body to make cholesterol, along with the enzymes required at each step to turn one chemical into the next one in the chain.

The research problem, Slater says, was to find the step where interference by a drug would effectively lower cholesterol production. By the 1970s, scientists had found a possibility. They had isolated a chemical, mevalonic acid, that was an early link in the cholesterol chain and an enzyme called HMG-CoA reductase that produced mevalonic acid.

What was needed, then, was a drug that could either inhibit HMG-CoA reductase or prevent cells from correctly using the enzyme.

Sometimes, scientists are lucky and find the right compound quickly. More often, Gruen says, hundreds or even thousands must be tested. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which show some chemical effect. Some may not work well, but may hint at ways of changing the compound's chemical structure to improve its performance. The latter process alone may require testing dozens or hundreds of compounds.

---

### **COMPUTER CLUES**

---

A more high-tech approach is to use computers to simulate an enzyme or other drug target and to design chemical structures that might work against it. Enzymes work when they attach to the correct site on a cell's membrane. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there.

Nevertheless, "computers give chemists clues to which compounds to make, but they don't give any final answers," says Kuntzman. "You still have to put any compound you made based on a computer [simulation] into a biological system to see if it works."

Yet a third approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what they call a fermentation broth, one type of organism per broth. Sometimes 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

In the search for a new cholesterol drug, scientists found a fungus that inhibited the HMG-CoA reductase enzyme in a test





*Pharmaceutical firms conduct laboratory and animal research with new drugs before they can begin experiments with humans. Scientists at Hoffmann-La Roche conduct basic research into normal life processes (above) as well as studies targeted to developing specific new drugs. The investigator in the above right photo is studying obesity in laboratory rats, with the ultimate goal of developing medicines to control obesity in humans.*

*(Photos courtesy of Hoffmann-La Roche Inc., Nutley, N.J.)*

tube. Chemists then had to identify which of the fungus' dozens of chemical byproducts was actually inhibiting the enzyme. Once that was done, the chemical's structure was analyzed and improved on to enhance its effects.

To this point, the search for a new drug has been confined to a laboratory test tube. Next, scientists have to test those compounds that have shown at least some desired effects in living animals. "We have to find what the drug is doing on the down side," Kuntzman explains.

---

#### **ANIMAL TESTING**

---

In animal testing, Kuntzman says, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Two or more species are typically tested, since a drug may affect one differently from another. Such tests show whether a potential drug has toxic side effects and what its safety is at different doses. The results "point the way for human testing and, much later, product labeling," Kuntzman says.

So far, research has aimed at discovering what a drug does to the body. Now, it must also find out what the body does to the drug. So, in animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body. Sometimes such tests find a metabolite that is more effective than the drug originally picked for development.

Of particular concern is how much of the drug is absorbed into the blood. "If a drug's active ingredients don't get into the blood," Kuntzman says, "it won't work." Scientists may add other chemicals to the drug to help the body absorb it or,

the other side, to prevent it from being broken down and excreted too soon. Such changes in the drug's structure mean even more testing.

Absorption rates can cause a host of problems. For example, for a certain drug to be effective, 75 percent of it may need to reach the bloodstream. But absorption rates can vary among individuals from, say, 10 percent to 80 percent. So, the drug must be able to produce the desired effects in those who absorb only 10 percent, but not cause intolerable side effects in people who absorb 80 percent.

"If we can improve the absorption rate we can reduce the variation in what real dosages people would be subject to," Kuntzman says. A more standard absorption rate for all individuals, say around 75 percent to 80 percent, would mean that the dose could be reduced and still have the desired effects.

---

### THE WRONG ROAD

---

By this time in the testing process, many drugs that had seemed promising have fallen by the wayside. More often than many scientists care to admit, researchers have to just give up when a drug is poorly absorbed, is unsafe, or simply doesn't work. "In research you have to know when to cut your losses if you are going down a wrong road," says Merck's Clement Stone. And, he adds, there are many more wrong roads than right ones.

Nevertheless, progress may yet be made. Occasionally, Stone says, a stubborn scientist keeps looking and finds a usable compound after others had given up. In other cases, compounds may be put aside because they failed to work on one disease, only to be taken off the shelf years later and found to work on another.

Such was the case with zidovudine (formerly known as azidothymidine, or AZT), the first drug approved for treatment of AIDS (acquired immune deficiency syndrome). The drug was first studied in 1964 as an anti-cancer drug, but it showed little promise. It was not until the 1980s, when desperate searches began for a way to treat victims of the deadly AIDS virus, that scientists at Burroughs Wellcome Co., of Research Triangle Park, N.C., took another look at zidovudine. After it showed very positive results in human testing, it was quickly approved by FDA in March 1987.

Even so, "a minuscule number of drugs we test ever reach testing in man," says Richard Salvador, a Hoffmann-La Roche vice president and director of preclinical development. The Upjohn Company of Kalamazoo, Mich., estimates that of every 2,000 chemicals studied, only 200 show any potential in early tests. Only 20 of those may be tested in people, and only one may be safe and effective enough to reach pharmacy shelves. Other estimates are gloomier—PMA puts it at one in 10,000.

One of the most important new products to gain FDA approval for testing in people is a vaccine to protect against AIDS. In August 1987, FDA approved human studies of such a vaccine developed by MicroGeneSys, Inc., of West Haven, Conn.

---

### THE ROLE OF FDA

---

The role of FDA in the early stages of drug research is small. The Food, Drug, and Cosmetic Act requires FDA to ensure that the new drugs developed by pharmaceutical companies are

safe and effective. It does not give the agency responsibility to develop new drugs itself. So, FDA physicians, scientists and other staff review test results submitted by drug developers. The purpose: to determine whether the drug is safe enough to test in humans and, if so—after all human testing is completed—to decide whether the drug can be sold to the public and what its label should say about directions for use, side effects, warnings, and the like.

FDA first becomes involved when a drug company has completed its testing in animals and is ready to test a drug on humans. (Actually, some animal testing continues after human tests begin to learn whether long-term use of the drug may cause cancer or birth defects. Also, more animal data may be needed if human tests turn up unexpected effects. And new therapeutic uses may be found by continued animal studies.)

Although FDA usually does not tell drug companies what specific laboratory or animal tests to run, the agency does have regulations and guidelines on the kinds of results FDA expects to see in any request to conduct human testing. "We certainly send signals to the drug companies on what they need to do," says Elaine Esber, director of FDA's Office of Biologics Research and Review.

And the drug companies listen to those signals. Both Hoffmann-La Roche's Kuntzman and Merck's Stone say their companies follow and sometimes exceed FDA's guidelines. "We want to optimize our chances of taking a compound from animal to human testing," Stone says.

So drug research is a long, difficult and costly road, certainly. But sometimes the hard work, the scientific sleuthing, and the time and dollars spent pay off. Such was the case in August 1987, when FDA approved—in nine-and-a-half months—the much studied and much anticipated cholesterol-lowering drug mentioned earlier—lovastatin. That approval holds the promise of longer and better lives for millions of Americans with heart disease and substantial sales for Merck, the drug's developer. FDA's evaluation of lovastatin was aided by the care with which Merck conducted its studies, presented the results, and responded to requests from agency scientists conducting the review, according to Commissioner Frank E. Young, M.D., Ph.D.

But to scientists like Hoffmann-La Roche's Kuntzman, drug research goes even beyond preventing or curing disease or making money. It is also a tool for finding out more about the human body and its basic life processes.

---

### PROGRESS, NOT PERFECTION

---

"Research is an evolutionary process," Kuntzman says. "You change studies and use experiments to lead to other experiments. As you go along you may not even see the connection between studies. In a sense, research has no end. The only end would be when we understand everything there is to know about the human body. I expect that we will never know enough about the body."

Merck's Eve Slater agrees. "We can make progress," she says, "but we are unlikely to achieve perfection." In the end, that is what researching and developing new drugs is all about—understanding and progress. ■

Jeffrey P. Cohn is a free-lance writer in Washington, D.C., who often writes on health issues.

# Section 5

## Testing Drugs in Humans

---

# Testing in Real People'

by Ken Flieger

No part of the drug development process is more critical than clinical trials—testing a new drug in humans to find out whether it is really useful in fighting disease. Usually the answer is no. One major U.S. drug company says that of every 20 compounds it submits to clinical trial, only one may be sufficiently safe and effective to merit FDA approval for marketing. In drug development, unfortunately, failure is the norm.

According to an industry official involved in planning and evaluating clinical research, "Most compounds that look interesting in animal and other laboratory studies never even make it to clinical trial. They're either ineffective, too toxic, too difficult to produce in quantities sufficient for human testing (let alone marketing), or of such limited usefulness that the cost of development can't be recovered." Those that do show genuine promise in preclinical research and development face the most rigorous, costly, and time-consuming stage of drug development, evaluation first in healthy human volunteers and later—maybe—in patients who actually have the condition the drug is intended to remedy.

There's a common misconception that FDA is responsible for testing drugs before they're approved for sale. While the agency does a great deal of testing to check on the purity and potency of drugs, it's the drug sponsor—a pharmaceutical company, a research organization, a public or private agency, even an individual—that is required to initiate studies to assess drug safety and effectiveness. FDA's role is to examine the design and conduct of those studies, and, of course, the results, as part of the process of deciding whether a new drug can be approved for marketing.

Basically, FDA wants to be sure that the welfare of participants in clinical studies will be protected and that the studies will be planned and carried out by qualified experts. The method used to study the drug and the way the results are interpreted have to be scientifically valid and free of subjective bias. The investigators have to identify and analyze all their results, including those they didn't expect, and they must follow up any problems, especially those involving people who, for whatever reason, dropped out of the study.

But before an investigational drug can be given to the first patient, the sponsor has to provide FDA with the results of laboratory and animal research, plus information, if there is any, about previous use of the drug in humans in this country and abroad. The sponsor must describe in detail how the clinical

trials will be conducted—how many people will be involved, how they will be selected, where the studies will be done and by whom, how the drug's safety and effectiveness will be evaluated, and what findings would require the study to be changed or halted. This material is sent to FDA in the form of an investigational new drug application, or IND. Clinical trials can begin 30 days after FDA receives an IND unless the agency approves an earlier start or orders a "clinical hold" because of questions about the request.

Normally, clinical trials are carried out in three phases involving progressively larger numbers of people. Drug sponsors arrange with physicians and hospitals to actually conduct the studies.

Clinical trials are normally done in three phases. Phase 1 trials are concerned primarily with learning more about the safety of the drug, though they may also provide some information about effectiveness. Phase 1 testing is normally done on healthy volunteers. The volunteers are usually paid for their services, which consist chiefly of submitting to a variety of tests to learn what happens to the drug in the human body—how it's absorbed, metabolized (broken down), and excreted; what effects it has on various organs and tissues; and what side effects occur as the dose is increased. Evidence of toxicity at doses too small to produce any beneficial effect is one of the chief causes of failure in phase 1 drug testing.

These initial studies are critical to the design of later clinical trials. They provide essential information about how much of the drug a patient should receive, how often it should be used, and what precautions need to be taken to make sure the drug is being used safely. Phase 1 studies usually involve fewer than 100 subjects—sometimes as few as 20—who receive the drug for a month or so. To complete this phase normally takes from six months to over a year.

If the results of phase 1 testing present no unacceptable safety problems, phase 2 trials can begin. (Actually, in some cases, phase 2 studies may begin before all the phase 1 trials are completely evaluated.) This stage of clinical testing may take somewhat longer than phase 1 studies. It normally involves a few hundred patients and is designed to show whether the drug is effective in treating the disease or condition for which it's intended. Phase 2 studies also attempt to disclose short-term side effects and risks in people whose health is impaired.

## *How Experimental Drugs Are Tested in Humans*

|         | Number of Patients                  | Length                    | Purpose  | Percent of Drugs Successfully Completing* |
|---------|-------------------------------------|---------------------------|--|---|
| Phase 1 | 20 - 100                            | Several months            | Mainly safety                                    | 70 percent                                |
| Phase 2 | Up to several hundred               | Several months to 2 years | Some short-term safety, but mainly effectiveness | 33 percent                                |
| Phase 3 | Several hundred to several thousand | 1-4                       | Safety, effectiveness, dosage                    | 25-30 percent                             |

\*For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 will successfully complete phase 1 trials and go on to phase 2; about 33 will complete phase 2 and go to phase 3; 25 to 30 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

*(Continued from page 11)*

Most phase 2 studies are randomized controlled trials. A group of patients receiving the drug, a "treatment" group, is matched with a group that is similar in important respects, such as age, sex, disease state, and other factors that could affect the course of their illness and the effect of the investigational drug. This latter "control" group receives a standard treatment or a placebo (an inactive substance). Comparison of the two groups tells both the investigators and FDA a great deal about the drug. Often these phase 2 studies are "blinded"—designed and carried out so that neither the patients nor the researchers know who is getting the experimental drug. Blinded studies help avoid errors in interpreting results caused by over-enthusiasm or other kinds of bias among patients and investigators.

There is some controversy over whether it is ethical to give a placebo to some patients in certain drug studies, especially when their condition is a serious or even life-threatening one, such as AIDS (acquired immune deficiency syndrome). Some people think that in such cases *all* patients should be given the experimental drug, since it offers at least *some* hope, where the placebo offers none.

But to do so would defeat the purpose of the clinical trial, making it impossible to learn whether the experimental drug does, in fact, have any more effect than no treatment at all. And that knowledge is crucial in the battle against diseases such as AIDS, allowing more lives to be saved in the long run. It is generally agreed, for example, that the clinical trials of the

anti-AIDS drug zidovudine (formerly known as azidothymidine, or AZT) were actually shortened by testing it against a placebo. The studies showed dramatically better results for zidovudine, compared to a placebo, and FDA was able to approve the drug for marketing in March 1987, only four months after receiving an application from the drug's manufacturer, Burroughs Wellcome Co., of Research Triangle Park, N.C.

By the time the drug is ready for phase 3 studies, both the sponsor and FDA, which has been receiving reports on the progress and results of the clinical trials, know quite a bit about the drug's safety and effectiveness. They know by now from the results of the carefully controlled studies that the drug does have a therapeutic effect. They have a fairly good picture of its short-term side effects and adverse reactions. And they also know that the sponsor is very likely to apply to FDA for approval to put the drug on the market.

There is, however, much yet to be learned about how to use the drug properly. For example, phase 1 and phase 2 testing usually aren't designed to provide information about optimum dose rates and schedules. And, of course, scientists aren't likely to have data on long-term safety in humans. The comparatively small number of patients involved in phase 1 and 2 trials and their short duration generally mean that only the most common, frequent side effects and adverse reactions will have been seen. A more complete understanding of the drug's

---

## ***A Skeptic's Guide To Medical 'Breakthroughs'***

Everyone is gratified by news of a major drug breakthrough, especially if it promises help for people who are desperately or terminally ill or severely disabled. And if you or a loved one has been praying for such a drug, the news may seem like a miracle.

But can you accept the good news at face value? All too often you can't, because many such reports are either exaggerated or seriously inaccurate interpretations of scientific findings. Really significant advances in drugs and drug therapy are all too rare. They don't happen nearly as often as the tabloids and magazines at the supermarket checkout might lead you to believe. Sober skepticism is a good attitude to have when evaluating news about drug "breakthroughs." Here are a few other guidelines:

- Where did the news report appear? Is it in a newspaper, magazine, or broadcast news service that regularly covers health and medical affairs and assigns specialized reporters to the subject? Or is it part of a publication or broadcast that emphasizes sensational stories that seem, and probably are, too good to be true? Is the reporter someone whose coverage of health and medicine you believe to be accurate and cautious? If you are doubtful about the news medium in which the report appears, it's probably best to take the story with a grain of salt.
- News stories about drugs producing complete cures, especially in patients with cancer, AIDS, severe arthritis, or other grave illness, are likely to be cruelly wrong. Aside from antibiotics for a few infections, drugs that make a disease disappear totally and permanently are almost unknown.
- What's being reported? The results of one study in a small number of patients are seldom, if ever, conclusive.

This kind of preliminary information is presented at scientific meetings or published in scientific journals whose editors and readers know how to interpret such findings. News stories may place undue importance on these reports and jump to conclusions that the researchers themselves know are unjustified.

- Ask your doctor what he or she knows about the story. While physicians can't know everything, there's a good possibility that they would know about a truly important medical advance. A negative answer should make you even more than usually skeptical.

Most medical science writers and reporters try diligently to provide accurate and authoritative information. They avoid unfounded speculation, and they strive to put exciting discoveries in perspective. Their stories don't often grab front page headlines or lead off the evening news, but they can be trusted to give you solid information. And that's a great deal better than false hope. ■

---

## ***How to Enroll In a Drug Study***

There are several ways in which patients and their physicians can learn of clinical trials in which they may want to take part. Research subjects are frequently recruited through newspaper ads placed by participating hospitals. Such ads explain what kind of patients are wanted and how they can get further information about the study. Specialists are likely to be aware of new experimental drugs in their field of practice and know which of their colleagues are carrying out clinical trials.

Patients who are thinking about participating in drug testing should talk to their physicians, who may in turn contact a drug company or teaching hospital for information. (FDA is not permitted to release information about ongoing clinical studies unless the drug sponsor agrees or the information is already public knowledge.)

Protecting the right and safety of people who participate in drug testing is a major concern shared by drug sponsors, clinical investigators, and FDA. Each design, or protocol, for a clinical trial has to ensure that no participant will be subjected to unneces-

sary risk or be deprived of needed care merely to find out if a new drug is effective. Once an investigational drug has been shown to save patients' lives or prevent their disease from causing irreversible damage, patients in clinical trials cannot be denied that therapy by being given a placebo. On the other hand, once they're properly informed, patients may agree to take part in placebo-controlled studies when their only risk would be discomfort. (For more information about protecting research subjects, see "Protecting 'Human Guinea Pigs'" on page 18.)

Those contemplating enrolling in a drug study should beware of quackery disguised as legitimate clinical research. How can a person tell whether he or she is volunteering for bona fide medical research or is about to be victimized by medical fraud? A prudent first step would be to ask your doctor about the investigator, the institution, and the drug. If you decide to get in touch with the researchers, ask to see the informed consent form. Insist on meeting with someone in authority to explain the project to you in terms you can understand. Ask questions, and, if you are not completely satisfied with the answers, don't agree to participate. Don't sign anything that waives your rights if you are harmed

in the course of the study. No legitimate drug sponsor or investigator requires that.

Be very suspicious if you are asked to pay for an investigational drug. FDA can allow drug sponsors to recover research and development costs by selling investigational drugs, but only in the later stages of clinical trials and only when it's understood that the sponsor intends to bring the drug to market. This is not the usual pattern. Ask to see evidence that FDA has both approved the study and given approval of the investigational drug to be sold.

See if the drug used in the "clinical trial" is being advertised as effective treatment for people who have the disease. Such advertising violates FDA regulations. If you become aware of what appears to be health fraud masquerading as clinical research, call the nearest FDA office; it's listed in the phone book under U.S. Government.

Not everyone may be willing to become a clinical research subject. But, as an industry scientist pointed out, "participants in phase 2 and 3 clinical trials are very likely to get excellent care at the hands of people who really know their business. And they just might be involved in an important advance in treatment for their disease." ■

## *Drug Development Timelines*

### ZIDOVUDINE

|                |  |
|----------------|--|
| 1964           | Azidothymidine (AZT, now known as zidovudine) developed as potential cancer treatment. Shelved because of ineffectiveness. |
| October 1984   | Preclinical tests begin for use as antiviral to treat acquired immune deficiency syndrome (AIDS).                          |
| May 1985       | Investigational new drug exemption (IND) submitted.  |
| July 1985      | Phase I tests begin.   |
| February 1986  | Phase II tests begin.  |
| September 1986 | Trials terminated; phase III not conducted.*   |
| October 1986   | Treatment IND approved.**  |
| December 1986  | New drug application (NDA) submitted.  |
| March 1987     | NDA approved.  |

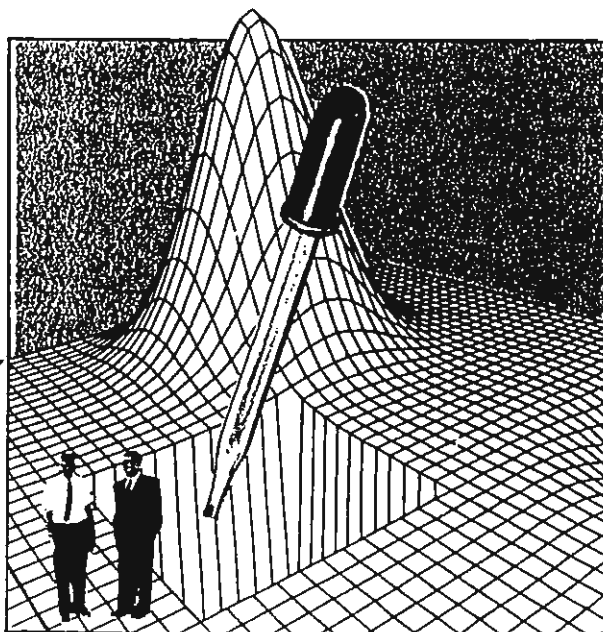
*\*The study was stopped because patients on the drug clearly were living longer than those given a placebo. It was deemed unethical to continue to withhold treatment from the control group.*

*\*\*Treatment protocol that allows access to the new drug before approval for marketing for patients who meet the medical criteria of the study protocol.*

### LOVASTATIN

|               |   |
|---------------|---|
| Late 1978     | Lovastatin isolated from microorganism <i>Aspergillus terreus</i> . |
| 1979          | Preclinical studies begin.  |
| March 1984    | Investigational new drug exemption (IND) submitted to FDA.          |
| May 1984      | Phase II clinical studies begin in United States.*                  |
| April 1985    | Phase III studies begin.  |
| November 1986 | New drug application (NDA) submitted.                               |
| August 1987   | NDA approved.   |

*\*Phase I clinical studies had begun abroad in April 1980.*



---

***There's a common misconception that FDA is responsible for testing drugs before they're approved for sale.***

*(Continued from page 12)*

safety, along with verification of its usefulness in treating disease, has to await the far more extensive testing that constitutes phase 3 clinical trials.

At the end of phase 2, representatives of the drug sponsor may meet with FDA staff to discuss their plans for phase 3 studies. At that meeting, FDA might suggest changes in the design of studies or indicate additional information the sponsor should develop to clarify the drug's safety and effectiveness. FDA might ask the sponsor to arrange studies in special groups—elderly patients, people with impaired kidney function, or patients receiving other drugs that may interact with the investigational drug, for example. The object of phase 3 testing and of the joint FDA-drug sponsor meetings is to develop information that will allow the drug to be marketed and used safely.

Phase 3 clinical trials can involve as many as several thousand patients who have the condition against which the drug is effective. It's not unusual for these studies to continue for three or four years or longer. Although they are often controlled studies, phase 3 trials tend to approximate more closely the conditions of ordinary medical practice. They expand on the research carried out in phase 2 in order to clarify the drug's benefit-risk relationship, discover less common and even rare side effects and adverse reactions, and generate information that will be incorporated into the drug's professional labeling, the FDA-approved guidance to physicians and others about how to use the drug.

Occasionally, the evidence of safety and effectiveness coming out of phase 2 studies is so strong that phase 3 trials are not needed. Such was the case with the anti-AIDS drug zidovudine: During the same four- to six-month period of phase 2 testing, only one AIDS patient died while being treated with zidovudine, while 19 died while being given a placebo.

The kind of patients who participate in phase 2 and 3 clinical trials depends on the drug under investigation and how it is thought to be useful. They may or may not be hospitalized. They may already be under treatment or have a newly diagnosed condition for which treatment has not yet begun. And, of course, some of the people who take part in phase 2 and 3 drug testing, the control patients, will not receive the investigational drug at all.

Of the 100,000 or more pages of information FDA may be

called on to review in order to decide if a drug can be approved for marketing, at least 80 percent or more is information generated by clinical testing. Some industry officials think FDA's requirements for clinical testing could be reduced and the process shortened. Most recognize, however, that it takes exhaustive clinical studies to discover relatively uncommon adverse effects—the kind that may occur in only one of several hundred patients receiving the drug—and to develop the detailed information health-care practitioners need in order to prescribe a drug safely and effectively.

The clinical trial phase of drug development can, and frequently does, take a very long time. FDA estimates a range of two to 10 years with an average of five years. The length of clinical trials depends largely on the kind of drug being studied. A drug to treat relatively common infections that is meant to be used only for a few days or weeks may get through all three clinical trial phases in two to four years. On the other hand, a drug for high blood pressure that patients may take for decades could be in the clinical trial phase for seven to eight years or more to thoroughly assess its long-term effects.

FDA has taken steps to simplify and expedite the clinical trial stage of drug development. The agency has reduced regulatory requirements and issued guidelines that help sponsors plan clinical research. Agency officials meet with drug sponsors who want to discuss the planning and conduct of clinical research. It is doubtful, however, that the extent of clinical trials could be substantially reduced without lowering U.S. standards of safety and effectiveness, standards that are respected throughout the world. However, drug companies could avoid redundant studies and prevent other problems by consulting with FDA along the way, urges Commissioner Frank E. Young, M.D., Ph.D.

The system is not perfect. Drugs that undergo rigorous, carefully designed and conducted clinical trials and are approved for sale sometimes cause unexpected problems when they come on the market. But we learn from failures as well as successes, and the system gets better. To make new drugs available to those who need them, studies in a few thousand willing participants help pave the way for safe and effective treatment in hundreds of thousands or millions of patients. ■

*Ken Flieger is a free-lance writer. He was formerly a member of FDA's Office of Health Affairs.*



# Testing Drugs In People

by Ken Flieger

**M**ost of us understand that drugs intended to treat people have to be tested in people. These tests, called clinical trials, determine if a drug is safe and effective, at what doses it works best, and what side effects it causes—information that guides health professionals and, for nonprescription drugs, consumers in the proper use of medicines.

Clinical testing isn't the only way to discover what effects drugs have on people. Unplanned but alert observation and careful scrutiny of experience can often suggest drug effects and lead to more formal study. But such observations are usually not reliable enough to serve as the basis for important, scientifically valid conclusions. Controlled clinical trials, in which results observed in patients getting the drug are compared to the results in similar patients receiving a different treatment, are the best way science has come up with to determine what a new drug really does. That's why controlled clinical trials are the only legal basis for FDA to conclude that a new drug has shown "substantial evidence of effectiveness."

The key components of FDA's review of marketing applications include:

- detailed and properly analyzed results of clinical trials
- information about how the trials were planned, designed, conducted, and assessed
- data on studies in animals
- information about how the drug is made.

(See the *FDA Consumer* special report *New Drug Development in the United States*, issued in January 1988.)

## Does It Work?

It's important to test drugs in the kind of people they're meant to help. It's also important to design clinical studies that ask, and answer, the right questions about in-

vestigational drugs. And that's no easy task.

The process starts with a drug sponsor, usually a pharmaceutical company, seeking to develop a new drug it hopes will find a useful and profitable place in the market. Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals. If the laboratory and animal study results show promise, the sponsor can apply to FDA to begin testing in people.

Once FDA and a local institutional review board—one of the panels of scientists, ethicists, clergy, and laypersons that oversee clinical research at medical centers throughout the country—approve the sponsor's plans for clinical trials, experienced clinical investigators give the drug to a small number of healthy volunteers or patients. These phase 1 studies assess the most common acute adverse effects and examine the size of doses that patients can take safely without a high incidence of side effects. Initial clinical studies also begin to clarify what happens to a drug in the human body—whether it's changed (metabolized), how much of it (or a metabolite) gets into the blood and various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If phase 1 studies don't reveal major problems, such as unacceptable toxicity, the next step is to conduct a clinical study in which the drug is given to patients who have the condition it's intended to treat. Researchers then assess whether the drug has a favorable effect on the condition.

## Usually, No Miracles

Again, the process appears straightforward—simply recruit groups of patients to participate in a clinical trial, administer the drug to those who agree to take part, and see if it helps them. Sounds easy enough,

and sometimes it is. In what may be medicine's most celebrated clinical trial, Louis Pasteur treated patients exposed to rabies with an experimental anti-rabies vaccine. All the treated patients survived. Since scientists knew that untreated rabies was 100 percent fatal, it wasn't hard to conclude that Pasteur's treatment was effective.

But that was a highly unusual case. Drugs do not usually miraculously reverse fatal illness. More often they reduce the risk of death, but don't entirely eliminate it. They usually accomplish this by relieving the symptoms of the illness, such as pain, anxiety, heart failure, or angina. Or a drug may alter a clinical measurement—reduce blood pressure or lower the cholesterol level, for example—in a way that physicians hope will be valuable. Drug effects like these can be a good deal harder to detect and evaluate than a result as dramatic as Pasteur's rabies cure.

This is mainly because diseases don't follow a predictable path. Many acute illnesses or conditions—viral ailments like colds or the flu, minor injuries, insomnia—can usually be counted on to go away spontaneously without treatment. Some chronic conditions like arthritis, multiple sclerosis, depression, or asthma often follow a varying course—better for a time, then worse, then better again, usually for no apparent reason. And heart attacks and strokes, for example, have widely variable death rates depending on treatment, age, and other factors, so that the "expected" mortality for an individual patient can be hard to predict.

A further difficulty in gauging the effectiveness of an investigational drug is that in some cases measurements of disease are subjective, relying in part on what is essentially a matter of interpretation by the physician or patient. Such measurements can be imprecise, influenced by a patient's or physician's expectations or hopes. In those circumstances, it's difficult to tell whether treatment is having a favorable effect, no effect, or even an adverse effect. The way to answer this critical question about an investigational drug is to subject it to a controlled clinical trial.

### Understanding Controls

In a controlled trial, patients in one group receive the investigational drug. Those in a comparable group—the con-

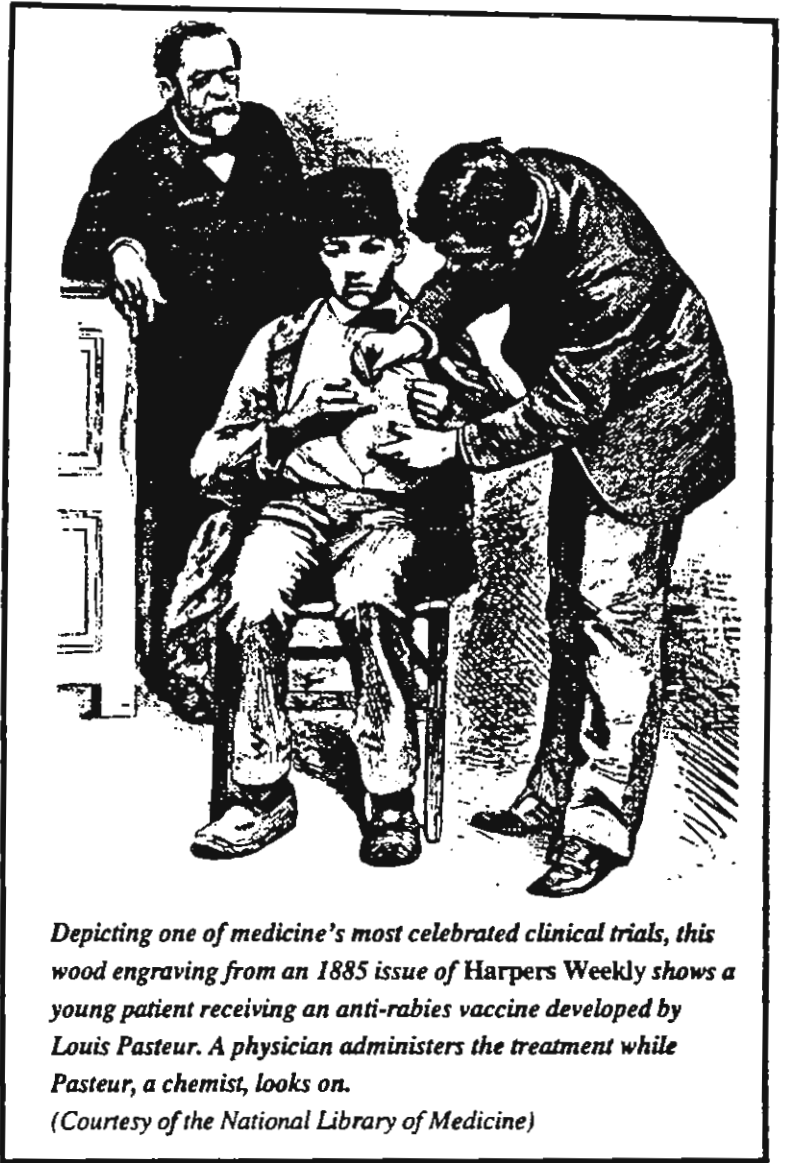
trols—get either no treatment at all, a placebo (an inactive substance that looks like the investigational drug), a drug known to be effective, or a different dose of the drug under study.

Usually the test and control groups are studied at the same time. In fact, usually the same group of patients is divided in two with each subgroup getting a different treatment. That is the best way to be sure the groups are similar.

In some special cases, a study uses a "historical control," in which patients given the investigational drug are compared with similar patients treated with the control drug at a different time and place. "Historical control" can also refer to a comparison of groups of patients treated at about the same time but at different institutions.

Sometimes patients are followed for a time after treatment with an investigational drug, and investigators compare their status before and after treatment. Here, too, the comparison is historical. It is based on an estimate of what would have happened without treatment. The historical control design is particularly useful when the disease being treated has high and predictable death or illness rates. Then investigators can be reasonably sure what would have happened without treatment.

It's important that treatment and control groups be as similar as possible in characteristics that can affect treatment outcome. For instance, all patients in specific groups must have the disease the drug is



*Depicting one of medicine's most celebrated clinical trials, this wood engraving from an 1885 issue of Harpers Weekly shows a young patient receiving an anti-rabies vaccine developed by Louis Pasteur. A physician administers the treatment while Pasteur, a chemist, looks on.*

*(Courtesy of the National Library of Medicine)*

meant to treat or same stage of the disease. In a clinical trial of a drug to treat angina (chest pain associated with cardiovascular disease), for example, if one group of patients being studied actually had sore ribs rather than angina, their differing response to the drug could not be assumed to be due to its effectiveness or lack thereof.

Treatment and control groups should also be of similar age, weight, and general health status, and be similar in other characteristics that could affect the outcome of the study, such as other treatment being received at the same time.

Two principal methods have been used to achieve this all-important comparability. One is to carefully pair each person in the treatment group with a control patient who has closely matching characteristics. This method is rarely used today because even in the best of circumstances, it's dif-

*Douglas Rosing, M.D., discusses heart disease treatment with a patient enrolled in a clinical trial at the National Institutes of Health.*

*(Photo courtesy of the National Institutes of Health)*



difficult to match pairs of patients for the myriad factors that could have a bearing on results.

In the more common approach, called randomization, patients are randomly assigned to either the treatment or control group, rather than deliberately selected for one group or the other. When the study population is large enough and the criteria for participation are carefully defined, randomization yields treatment and control groups that are similar in important characteristics. Because assignment to one group or another is not under the control of the investigator, randomization also eliminates the possibility of "selection bias," the tendency to pick healthier patients to get the new treatment.

#### **When It Helps to Be 'Blind'**

In clinical trials, bias (a "tilt" in favor of a treatment) can operate like a self-fulfilling prophecy. The hope for a good outcome can skew patient selection so that the treatment group includes a disproportionate number of patients likely to do well whatever their treatment. The same kind of inadvertent bias can lead both patients and investigators to overrate posi-

tive results in the treatment group and negative findings among controls, and cause data analysts to make choices that favor treatment. Clinical trials that include such biases are likely to be incapable of assessing drug effect.

In conjunction with randomization, a design feature known as "blinding" helps ensure that bias doesn't distort the conduct of a study or the interpretation of its results. Single-blinding consists of keeping patients from knowing whether they are receiving the investigational drug or a placebo. In a double-blind study, neither the patients, the investigators, nor the data analysts know which patients got the investigational drug. Only when the closely guarded assignment code is broken to identify treatment and control patients do the people involved in the study know which is which.

#### **Ethical Questions**

Testing experimental drugs in people inevitably presents ethical questions. For example, is it ethical to give patients a placebo when effective treatment is available? Not all authorities agree on the answer. But the generally accepted prac-

tice in the United States—and one increasingly being adopted abroad—is that well and fully informed patients can consent to take part in a controlled-randomized-blinded clinical trial, even when effective therapy exists, so long as they are not denied therapy that could alter survival or prevent irreversible injury. They can voluntarily agree to accept temporary discomfort in order to help evaluate a new treatment.

In any trial in which a possible effect on survival is being assessed, it's important to monitor results as they emerge. That way, if a major effect is seen—positive or negative—the trial can be stopped. This happened in the first clinical study of the AIDS drug zidovudine (AZT), when a clear survival advantage for patients receiving zidovudine was seen well before the trial was scheduled to end. The trial was then ended early, and within a week FDA authorized a protocol allowing more than 4,000 patients to receive zidovudine before it was approved for marketing under the brand name Retrovir. This is an example of the ethical principle that if a lifesaving or life-extending treatment for a disease does exist, patients cannot be denied it.

In some cases, a new treatment can be

## Personal Participation

Anyone interested in participating in a clinical trial should discuss the idea with his or her physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. They can obtain detailed information from a variety of sources, including drug sponsors.

Clinical trials are carried out at major medical research centers such as teaching hospitals, at specialized clinics for people with AIDS, Alzheimer's disease or other conditions, and even in doctors' offices. Although they often involve hospitalized patients, many clinical trials are conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper ads recruiting potential participants for clinical studies that tell readers where to call or write for further information.

Although investigational drug studies vary widely, some things should be expected by participants in virtually any clinical trial. For example, participants might have to give blood samples more often than during ordinary care. Tests to assess disease status might be more frequent. Participants are often required to keep detailed records of their symptoms and follow strict schedules.

It's also important to understand that volunteering for a clinical trial does not guarantee that an individual patient will receive the drug under investigation. Control patients may get a placebo, a drug already approved for their condition, or perhaps no treatment at all.

These and other aspects and implications of taking part in a clinical trial must be fully explained in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug—or the desire to take part in research that might one day benefit millions—is what makes people volunteer for clinical trials. But it shouldn't prevent them from finding out all they can about being a part of the process. ■

—K.F.

compared with established treatment, so long as the effectiveness of the latter can readily be distinguished from placebo and the study is large enough to detect any important difference.

It is also possible to evaluate new drugs in this situation in "add-on" studies. In this kind of trial, all participants receive standard therapy approved for treating the disease, but those in the treatment group also get the investigational drug. The control group gets either no added treatment or placebo. Any difference in results between the treatment and control groups can be attributed to the investigational drug. It is common to study new anti-seizure drugs in this way, as well as new

agents intended to reduce mortality after a heart attack.

### Testing in Women and Children

In recent years there has been growing interest at FDA and by the public in drug testing in patient populations that have been relatively neglected in clinical trials, especially women and children. Children are generally not included in trials at all until the drug has been fully evaluated in adults, unless the drug is intended for a pediatric disease, such as acute lymphocytic leukemia. When children are not likely to use drugs frequently (for example, drugs to treat high blood pressure), they often have not been included in clinical trials at

all. (See "Why FDA Is Encouraging Drug Testing in Children" in the July-August 1991 issue of *FDA Consumer*.)

Without pediatric studies or other sources of scientific information, labeling cannot include guidance about dosage, side effects, and when a drug should or should not be used in children. In October 1992, FDA proposed changes in its regulations governing drug labeling for "pediatric use." The proposal is aimed at encouraging drug sponsors to develop pediatric information—through clinical trials in children or by extrapolation of findings in adults—that can be included in drug labeling.

Although both sexes now are generally represented in clinical trials in proportions that reflect gender patterns of disease, FDA and women's health advocates agree that less care has been taken to develop information about significant differences in the ways men and women respond to drugs.

A new FDA guideline on the study and evaluation of gender differences in clinical drug trials, issued in July 1993, encourages drug companies to include appropriate numbers of women in drug development programs and to pay particular attention to factors that can affect drug behavior, such as phases of the menstrual cycle, menopause, and the use of oral contraceptives or estrogens. Another focus is discovering gender-related differences in how a drug is absorbed, metabolized or excreted, and how it works.

The guideline also does away with an FDA policy dating from 1977 that excluded women of childbearing potential from participation in early clinical studies. The agency believes that institutional review boards, as well as clinical investigators and women themselves, can gauge whether women's participation in clinical trials is appropriate and make sure that fetuses are not unduly exposed to potentially toxic agents. Studying drugs in people will probably never be an exact science. But steady progress in the methodology and, in a way, the philosophy of clinical trials is making the process more productive, more reliable, and more beneficial for us all. ■

Ken Flieger is a writer in Washington, D.C.

# Drug Testing, Through A Patient's Eyes

by Dori Stehlin

Eugene Novikoff usually spends the summer fishing in the Catskills. So why would he spend the month of August inside a hospital? He doesn't look sick, though possibly a little pale from missing days in the summer sun.

But Novikoff isn't healthy. He has a heart condition that makes crossing the street an exhausting endeavor. On bad days, the fatigue, shortness of breath, and angina (chest pain) he experiences prevent him from doing anything more strenuous than watching television.

There may be a drug that can alleviate his symptoms, but it is not yet approved by FDA. The only way to get it is to participate in a clinical trial—a test of the drug's safety and effectiveness—at the Clinical Center at the National Institutes of Health in Bethesda, Md.

A clinical trial—that is, an experiment done with people—is the final research step for a drug. These trials are performed at hospitals and research centers around the country. FDA studies the results from clinical trials along with other research in deciding whether to approve a New Drug Application.

For Novikoff, a clinical trial was the answer to his prayers. "It's almost a miracle that I got into this program," he said. "Getting this far is a comfort—knowing that you've got something that these people have worked with for many, many years."

This clinical trial is the end of a long search for Novikoff, 62. He first noticed his symptoms 17 years ago. For the past 14 years he's traveled to doctors all over the country, but until recently no one could



Eugene Novikoff

tell him why he would "suddenly run out of steam" with the slightest exertion.

The fatigue and chest pains were "the kind of things that make the average doctor go looking for blocked arteries," Novikoff said. "To their horror, I have no blocked arteries or any of the normal things they're looking for." Some doctors even suggested that the symptoms were all in his mind. "At the early stages of it you sort of half believe them. . . . But you finally get to a point where you say, there's no way this could be in my mind. There's no way."

Finally, in May 1986, a cardiologist in Massachusetts correctly diagnosed his condition as hypertrophic cardiomyopathy. In this form of heart disease, the heart muscle becomes excessively thick-

ened for no obvious reason. This thickening, which narrows the opening where the blood leaves the heart, forces the heart to increase the pressure necessary to pump blood. But even with the increased pressure, less and less blood is pumped. It is an uncommon condition and, often, as in Novikoff's case, very difficult to diagnose.

Because many of the other doctors he'd seen had realized that Novikoff had some kind of heart problem, he had already received the usual, approved drug treatments for his condition—beta blockers and calcium channel blockers. Neither worked. But the Massachusetts cardiologist was familiar with a surgical technique doctors at NIH were performing, and he recommended it to Novikoff. "I originally came here [to NIH] to confirm that I needed surgery. But they said they had a new drug here. . . . It sounded great to me."

The new drug, lidoflazine, is a calcium entry blocker. According to Dr. Richard Cannon, who is in charge of the clinical trial, the hypothesis behind the drug is that excessive calcium causes the thickening of the heart muscle. Like calcium channel blockers, lidoflazine doesn't allow calcium to enter certain muscle cells, especially in the heart. But lidoflazine blocks the uptake of calcium sooner and to a greater degree than the channel blockers. Although the drug won't thin out the thickened heart, NIH researchers believe it will get the heart to function more normally with less pressure.

Novikoff was ready and willing to participate in the clinical trial of lidoflazine. His doctor handled the paperwork, includ-

***"I originally came here [to NIH] to confirm that I needed surgery. But they said they had a new drug here. . . . It sounded great to me."***

ing a consent form Novikoff had to sign. This form, required by law, informed him that the treatment he would receive is experimental. It also explained all the known possible side effects of the drug. Novikoff said that between the form and the NIH staff he was told everything about the study and the drug. He added that he has been kept well-informed throughout his hospital stay. "Sometimes it's more than you want to know," he said.

The minor, or what Dr. Cannon calls "nuisance," side effects are nausea and the jitters. The major side effect, a change in the rhythm of the heartbeat, is potentially fatal. "The major side effect is pretty horrifying," Novikoff said. "It's a funny drug. If you tolerate it, you're probably OK; if you don't tolerate it, you're in serious trouble."

Cannon said the chances of getting serious side effects from the drug are small compared to the 4 percent to 5 percent fatality rate from the surgery. "We think we are administering it in a very careful way so that we can prevent even this very tiny risk," he added.

Novikoff said the side effects of the drug definitely sounded less frightening than the surgery. His wife, Vivian, agrees that the benefits outweigh the risks. "I'll just be very grateful if they can find something that will work," she said.

He was admitted to the Clinical Center two months after agreeing to participate in the study.

The first week involved a round of tests. Some were necessary to confirm his doctor's diagnosis. Others were part of the research for lidoflazine. At the end of the

first week, Novikoff started receiving the drug.

To reduce the incidence of both major and minor side effects, the drug is given in stages. The first doses he received were very low. Although he didn't experience any side effects, there was no improvement in his condition, either. The second week on the drug, his daily dose was increased. If no problems occur, Cannon said, Novikoff will receive "the ultimate dose . . . the one we want the patient to continue."

Once Novikoff takes that "ultimate dose" without problem for a week, he can go home. He'll have to return to the Clinical Center for checkups every few weeks. Because the drug only helps alleviate his symptoms, but doesn't "cure" him, he'll be on the drug indefinitely.

Because of the risk of irregular heartbeat, a portable electrocardiograph (EKG) constantly monitors Novikoff's heart. The unit fits into his shirt pocket, but since the nurses can't read it unless he is near his room, the EKG is still pretty confining. And being confined to one floor at the Clinical Center can be very dull.

"It's sheer boredom," he said. "They warned me beforehand. . . . Weekends are the worst time. Nothing goes on. Fortunately I'm a great reader or I'd be in real trouble." He is allowed to leave the floor to go to the library or cafeteria, but not for more than an hour at a time.

His wife spends the day with him. The Novikoff's home is in Florida, but luckily their daughter lives in Columbia, Md., about 20 miles from NIH.

He also has a television in the room, and he passes some of the time talking to the

other patients. "Unfortunately, most of them are a lot younger than me," he said, shaking his head. He lowered his voice and explained: "I've sort of lived my life. But there's an 18-year-old and a 21-year-old. It's very hard to take."

Of the seven other patients in the trial for lidoflazine, two have had to stop because of irregular heart rhythm.

Although he says he's lived his life, he isn't giving up what's left without a fight. "The risk is infinitely worth it," he said. "Originally it [his heart condition] would only bother me once a month. But as the years go by it is getting worse and worse and worse and really starting to impact my life."

Novikoff is an avid sport fisherman and he can't imagine living without his favorite pastime. "I don't want to have my life go down to looking at a TV set. It's just not worth it to me." ■

*Dori Stehlin is a member of FDA's public affairs staff.*

*Editor's Note: This interview was conducted in August 1986 at the start of Novikoff's second week on lidoflazine. During that week, his heartbeat became irregular. He immediately stopped taking the drug, and his heartbeat returned to normal. A few weeks later, doctors at NIH resectioned (removed) some of the thickened muscle. Ten days later, Novikoff went home.*

*Novikoff returned to NIH in June 1987 for a routine check-up. According to Dr. Cannon, Novikoff had less shortness of breath and was "generally much improved."*

# Section 6

## Protection of Human Research Subjects

# Protecting 'Human Guinea Pigs'

by Richard C. Thompson

In 1963, a New York hospital allowed some elderly ill and feeble patients to be injected under the skin with cancer cells to study immune response. Patients were not told what the injections were—just that their “resistance” was being measured. Nothing came from this ill-conceived effort, which was intercepted and stopped soon after it began, with none of the patients getting cancer.

That same year, in the classic thalidomide case, officials learned that some U.S. physicians had obtained and were using thalidomide for what they believed was a therapeutic use. Thalidomide was not approved in the United States then, and the physicians' actions amounted to uncontrolled testing of the drug in pregnant women. Only a few infants with birth defects resulting from exposure to the drug were born in this country, compared to several thousand in Europe, because an alert FDA medical officer, Frances O. Kelsey, Ph.D., M.D., prevented the drug from being made widely available here.

In early 1994, the federal government released documents detailing hundreds of radiation experiments performed on thousands of civilians and military personnel decades ago, apparently in some cases without adequate knowledge or consent. Experiments included giving food mixed with tracer doses of radioactive substances to subjects and injecting infants with radioactive iodine. Energy Department Secretary Hazel O'Leary has spearheaded

efforts to make the details of these experiments public.

These are worst-case examples of failure to inform and protect human subjects used without their knowledge in drug testing and medical experimentation. They are not remote historical events. The cancer injections were stopped just over 30 years ago. The radiation experiments occurred in the 1940s and 1950s.

Such disregard for the rights and welfare of patients is far less likely today. Review boards at hospitals and research institutions throughout the country make sure participants are fully informed and willing before studies ever get under way. Known as institutional review boards, or IRBs, these committees of experts and lay persons also review the research as it goes along. Watching these watchers are FDA and other federal agencies such as the National Institutes of Health, whose rules now protect those taking part in medical research.

In 1976, FDA issued regulations requiring IRB review of all studies using institutionalized subjects. Regulations amended in 1981 require all studies needing an FDA research permit to be reviewed and approved by an IRB before tests on humans can begin, whether or not subjects are in an institution.

Edmund Pellegrino, M.D., professor of medicine at Georgetown University in Washington, D.C., and an internationally recognized expert on medical ethics, says

that using human subjects to advance scientific knowledge is acceptable “as long as there is informed consent and the rights of the subjects are respected.”

In an instructional videotape prepared by FDA, Pellegrino says persons entering a study must be told they are “willing volunteers” who can stop or even leave the study at any time if they become stressed or apprehensive, or suffer too great discomfort, or simply wish to go no further.

The first responsibility of the physician is to “do no harm,” and there are few who set out to violate that principle. But at the extreme of those who did were scientists convicted at the 1946 Nuremberg trials of conducting experiments on concentration camp inmates. From those trials came the Nuremberg Code, a 1948 formal statement on medical ethics that led to present standards in the United States and elsewhere which protect human research subjects.

Informed consent was a requirement of the 1962 Kefauver-Harris Amendments to the federal Food, Drug, and Cosmetic Act. A signed consent document was not required, only a notation in the chart that verbal consent had been obtained. A 1967 FDA policy statement outlined the consent process and required consent to be obtained in writing for early stages of research.

The U.S. Public Health Service in 1966 defined the right of subjects to be told about the benefits, risks and purpose of the research for which they are volunteering.



It made this "informed consent" a condition of PHS funding for research grants.

A decade later, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research developed principles governing research involving people and made recommendations concerning IRBs. In 1981, FDA revised regulations, expanding the requirement for written informed consent to all studies of products FDA regulates.

Before it will approve a new drug or device for marketing, FDA requires evidence of the product's safety and effectiveness from the manufacturer. The evidence comes first from tests with rabbits, rats and other laboratory animals, then from "clinical trials" in human volunteers. The process from the first tests to final approval can take a number of years.

Persons taking part in clinical trials are not necessarily patients in hospitals and institutions. Many are patients of private practitioners involved in clinical research. Many are not patients at all, but are healthy individuals who have been recruited for a study through a newspaper ad, poster, or other source. FDA's IRB and informed-consent regulations ensure that research subjects are informed and willing participants and that their health and safety are not unnecessarily endangered.

An IRB is composed of at least five people with varying backgrounds who are generally knowledgeable through training or experience in the research areas likely to be considered. Racial, ethnic and other interests must be represented, and at least one member must come from a non-scientific discipline, such as law or the clergy, and at least one must not be affiliated with the research institution. Maintaining a diverse membership helps an IRB stay objective.

The IRB meets to review the protocol, or research plan, for the proposed project and may approve or disapprove it or—as

happens most frequently—make changes before granting approval. It also must review and approve or modify and approve the informed consent form to receive research subjects. The IRB also conducts continuing review at least annually while research is under way.

IRB review ensures that:

- Risks to subjects are minimized. Procedures must be used that are consistent with good research design and do not expose subjects to unnecessary risk. If the subject is a patient, the study must be designed and conducted in a way that does not adversely affect the patient's progress.
- Informed consent is obtained and documented from each subject or the subject's legal representative.
- Selection of subjects is fair and equitable, and there are safeguards to protect subjects, such as the mentally retarded, who may not be able to look out for their own interests.
- Risks to subjects are reasonable in relation to expected benefit to those subjects and the importance of the knowledge that may be gained.
- Provisions exist to protect the privacy of subjects and to maintain data confidentiality.

IRBs also ensure that appropriate additional safeguards are in place to protect the rights and welfare of vulnerable populations, such as women, children, prisoners, those with mental disabilities, and persons who are economically or educationally disadvantaged.

Periodically, FDA inspects IRB records and operations to certify that approvals, human subject safeguards (including informed consent), membership, and conduct of business are what they should be. Sometimes these inspections yield evidence of problems, such as in 1993 when FDA imposed penalties on a large California university IRB for infractions that included failure to report deaths.

Informed consent—the key element in

protecting the rights and welfare of study subjects—is not simply a matter of having the subject sign a piece of paper. It requires that the researcher:

- give the subject adequate information about the study
- respond fully to the subject's questions and be certain that the subject understands all the risks and responsibilities that participation entails
- ensure that the subject (if a patient is receiving treatment, for example) is aware of other options, along with their advantages and disadvantages
- obtain the subject's voluntary consent to take part.

Researcher and subject should discuss the study and the subject's role in it until both are satisfied that the subject can make an informed decision about whether to participate.

In July 1993, FDA released new guidelines for including women and minorities in clinical research. The guidelines promote recruitment of women and minority participants and foster understanding of cultural nuances. In March 1994, the National Institutes of Health published guidelines implementing a new statutory requirement that women and minorities be adequately represented in federally funded research. IRBs, together with investigators and institutional officials, will play important roles in ensuring compliance with these guidelines.

How an IRB fulfills its role can be seen in a Georgetown University study into the effects of strenuous exercise on blood clotting. The study involved healthy young female runners recruited through the campus newspaper. Runners had blood drawn before and after treadmill exercise, with the fibrin (blood-clotting) time recorded. Blood pressure, heart rate, and respiration also were recorded.

Participants knew that findings might help determine whether exercise is desirable for persons recovering from heart

attacks. The study also benefited participants by allowing them to better understand their own physiology when running, an aid when deciding whether to stay in competition. Also, participants and their doctors were informed of any health problems that showed up in the study.

Before approving the study, the IRB at Georgetown asked that participants be told that the study followed earlier successful research of male athletes; that the total blood drawn would be one-quarter that of a routine blood donation; and that, although it was a low-risk study, emergency equipment would be on standby. The IRB found it a big plus that the physician doing the research had gone through the blood and treadmill test herself when the study was designed.

Pellegrino stresses that study subjects must not be coerced or misled by researchers, who often do not realize how little the subjects understand. He says that patients receiving treatment who are asked to join a study "can easily confuse the experiment with their treatment." He also acknowledges that some scientists feel IRB review "somehow interferes with that research."

FDA does not require that subjects be compensated if there is injury or other unfavorable result. But in any study that involves more than minimal risk, subjects must be told before they enter the study whether compensation and medical treatment will be provided and what that compensation will be or how to obtain information about it. The institution or IRB must establish a compensation policy before a study is begun. (Congress is currently considering legislation that would mandate compensation or require it of health insurers.)

An additional layer of review sometimes used is an independent Data and Safety Monitoring Board. At periodic

intervals during clinical research, this board reviews accumulated data and makes recommendations on continuation or modification of the study.

Present FDA policy requires that only under certain circumstances may sponsors charge clinical investigators or research subjects for investigational drugs. A firm intending to charge for experimental drugs must first justify the charges to FDA. Companies sponsoring research with investigational medical devices, however, may generally charge the investigator for the cost of the device. The investigator in turn can pass that charge along to the patient, but no profit is to be made from the experimental drug or device. Patients must be told before they enter a study if they will be charged for services or products as a result of taking part in the study, and the IRB must be aware of and approve such proposed charges. The consent document must list all charges attributable to the study.

Taking part in a research project does not waive any of the subject's legal rights, including privacy rights, since study records are confidential. However, FDA can inspect and copy medical records as part of its approval process for drugs and devices. Usually, the agency doesn't need the names of individual subjects—only study results.

FDA regulations permit emergency use of a test article (drug or device) without prior IRB review, provided such use is reported to the IRB within five working days. Any subsequent use, however, must have prior review and approval. This means that an investigator may, in a life-threatening emergency, use a device or administer a course of treatment to a patient without prior IRB review, but a second use must be reviewed by the IRB at the hospital or other institution. This was done in the 1980s at the University of Arizona

Medical Center, when a Copeland artificial heart not yet approved by FDA was used in a patient for three days as a "bridge" until a human replacement heart could be found.

If a project carries little or no risk, FDA regulations permit an IRB to use an "expedited review." This means that the research can be reviewed and approved by the chairman or senior members without convening the full IRB. Minor changes in an existing project also can be approved through an expedited review.

Institutions engaged in research involving humans will generally have their own IRBs that review work done on the premises or elsewhere by the staff of the institution. However, the IRB need not be "on site" at the institution as long as it is available to review that institution's research. An IRB in a hospital, for example, is not required to review studies done outside the hospital's jurisdiction, but the IRB may do so if the hospital is willing.

IRB members usually are not paid for their services, but there is nothing in the regulations to prevent it. Any payment should be a fixed amount and not contingent upon a favorable review. Travel and other expenses may be reimbursed.

FDA relies upon the careful review of the responsible IRB to ensure that research studies are not unnecessarily risky and are valid endeavors. Human subjects are informed about the research and agree to participate voluntarily in an approved consent process. Together, these two activities serve to protect the rights and welfare of research participants. ■

*Richard C. Thompson is a former member of FDA's public affairs staff. John Henkel, staff writer for FDA Consumer, also contributed to this article.*

Food and Drug Administration  
Protection of Human Subjects  
(Informed Consent regulations)  
21 CFR Part 50

and

Institutional Review Board  
Requirements  
21 CFR Part 56

**PART 50—PROTECTION OF HUMAN  
SUBJECTS**

**Subpart A—General Provisions**

Sec.

50.1 Scope.

50.3 Definitions.

**Subpart B—Informed Consent of Human  
Subjects**

50.20 General requirements for informed consent.

50.21 Effective date.

50.23 Exception from general requirements.

50.25 Elements of informed consent.

50.27 Documentation of informed consent.

**Subpart C—Protections Pertaining to Clinical  
Investigations Involving Prisoners as Sub-  
jects**

50.40 Applicability.

50.42 Purpose.

50.44 Restrictions on clinical investigations involving prisoners.

50.46 Composition of institutional review boards where prisoners are involved.

50.48 Additional duties of the institutional review boards where prisoners are involved.

**AUTHORITY:** Secs. 201, 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

**SOURCE:** 45 FR 36390, May 30, 1980, unless otherwise noted.

**Subpart A—General Provisions**

§ 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sec-

tions 505(i), 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 706, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981]

### § 50.3 Definitions.

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 *et seq.* as amended (21 U.S.C. 321-392)).

(b) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis

pending additional study, described in § 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) Data and information about an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for these drugs, described in § 314.300 of this chapter.

(12) An application for a biological product license, described in part 601.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an *in vitro* diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An *Application for an Investigational Device Exemption*, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) *Sponsor* means a person who initiates a clinical investigation, but who

does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The word *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(i) *Institutional review board* (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

(j) *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(k) *Test article* means any drug (including a biological product for human use), medical device for human use,

human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(l) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(m) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991]

### Subpart B—Informed Consent of Human Subjects

SOURCE: 46 FR 8951, Jan. 27, 1981, unless otherwise noted.

#### § 50.20 General requirements for informed consent.

Except as provided in § 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the insti-

tution, or its agents from liability for negligence.

#### § 50.21 Effective date.

The requirements for informed consent set out in this part apply to all human subjects entering a clinical investigation that commences on or after July 27, 1981.

#### § 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) The Commissioner may also determine that obtaining informed consent is not feasible when the Assistant Secretary of Defense (Health

Affairs) requests such a determination in connection with the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD). DOD's request for a determination that obtaining informed consent from military personnel is not feasible must be limited to a specific military operation involving combat or the immediate threat of combat. The request must also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment. The written request must also include a statement that a duly constituted institutional review board has reviewed and approved the use of the investigational drug without informed consent. The Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.

(2) In reaching a determination under paragraph (d)(1) of this section that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel, the Commissioner will review the request submitted under paragraph (d)(1) of this section and take into account all pertinent factors, including, but not limited to:

(i) The extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use;

(ii) The context in which the drug will be administered, e.g., whether it is intended for use in a battlefield or hospital setting or whether it will be self-administered or will be administered by a health professional;

(iii) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(iv) The nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug.

(3) The Commissioner may request a recommendation from appropriate experts before reaching a determination on a request submitted under paragraph (d)(1) of this section.

(4) A determination by the Commissioner that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel will expire at the end of 1 year, unless renewed at DOD's request, or when DOD informs the Commissioner that the specific military operation creating the need for the use of the investigational drug has ended, whichever is earlier. The Commissioner may also revoke this determination based on changed circumstances.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990]

#### § 50.25 Elements of informed consent.

(a) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treat-

ment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue

participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in § 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A *short form* written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the



representative in addition to a copy of the short form.

**Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects**

**EFFECTIVE DATE NOTE:** At 46 FR 35085, July 7, 1981, the effective date of subpart C was stayed until further notice.

**§ 50.40 Applicability.**

(a) The regulations in this subpart apply to all clinical investigations involving prisoners as subjects that are regulated by the Food and Drug Administration under sections 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations involving prisoners that support applications for research or marketing permits for products regulated by the Food and Drug Administration.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects to the extent such research is limited or barred by applicable State or local law.

**§ 50.42 Purpose.**

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

**§ 50.44 Restrictions on clinical investigations involving prisoners.**

(a) Except as provided in § 50.44(b), clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 505(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration may not involve prisoners as subjects.

(b) Clinical investigations that are regulated by the Food and Drug Administration under sections 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, may involve prisoners as subjects only if the institution responsible for the conduct of the clinical investigation has certified to the Food and Drug Administration that the institutional review board has approved the clinical investigation under § 50.48; and

(1)(i) In the judgment of the Food and Drug Administration, the proposed clinical investigation involves solely research on practices both innovative and accepted, which have the intent and reasonable probability of improving, the health and well-being of the subjects;

(ii) In cases in which these studies require the assignment of prisoners in a manner consistent with protocols approved by the institutional review board to control groups that may not benefit from the research, the study may proceed only after the Food and Drug Administration has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the **FEDERAL REGISTER** of its intent to approve such research; or

(2) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis, which is much more prevalent in prisons than elsewhere) provided that the Food and Drug Administration has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the **FEDERAL REGISTER** of its intent to approve such research; subject to the approval of the Food and Drug Administration, prisoners may participate in the research even though they are assigned, in a manner consistent with protocols approved by the institutional review board, to control groups that may not benefit from the research.

**§ 50.46 Composition of institutional review boards where prisoners are involved.**

In addition to satisfying any other requirements governing institutional review boards set forth in this chapter, an institutional review board, in carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the institutional review board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the institutional review board.

(b) At least one member of the institutional review board shall be a prisoner, or a prisoner advocate with appropriate background and experience to serve in that capacity, except that if a particular research project is reviewed by more than one institutional review board, only one institutional review board need satisfy this requirement.

**§ 50.48 Additional duties of the institutional review boards where prisoners are involved.**

(a) In addition to all other responsibilities prescribed for institutional review boards under this chapter, the institutional review board shall review clinical investigations covered by this subpart and approve such clinical investigations only if it finds that:

(1) The research under review represents one of the categories of research permitted under § 50.44(b) (1) and (2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the clinical investigation, when compared to the general living conditions, medical care, quality of food, amenities, and opportunity for earnings in prison, are not of such a magnitude that his or her ability to weigh the risks of the clinical investigation against the value of such advantages in the limited-choice environment of the prison is impaired;

(3) The risks involved in the clinical investigation are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to

all prisoners and immune from arbitrary intervention by prison authorities or prisoners; unless the principal investigator provides to the institutional review board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that research project;

(5) Any information given to subjects is presented in language which is appropriate for the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the clinical investigation in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the clinical investigation will have no effect on his or her parole; and

(7) Where the institutional review board finds there may be need for followup examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The institutional review board shall carry out such other duties as may be assigned by the Food and Drug Administration.

(c) The institution shall certify to the Food and Drug Administration, in such form and manner as the Food and Drug Administration may require, that the duties of the institutional review board under this section have been fulfilled.

**PART 56—INSTITUTIONAL REVIEW BOARDS**

**Subpart A—General Provisions**

- Sec.
- 56.101 Scope.
- 56.102 Definitions.
- 56.103 Circumstances in which IRB review is required.
- 56.104 Exemptions from IRB requirement.
- 56.105 Waiver of IRB requirement.

**Subpart B—Organization and Personnel**

Sec.

56.107 IRB membership.

**Subpart C—IRB Functions and Operations**

- 56.108 IRB functions and operations.
- 56.109 IRB review of research.
- 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 56.111 Criteria for IRB approval of research.
- 56.112 Review by institution.
- 56.113 Suspension or termination of IRB approval of research.
- 56.114 Cooperative research.

**Subpart D—Records and Reports**

56.115 IRB records.

**Subpart E—Administrative Action for Noncompliance**

- 56.120 Lesser administrative actions.
- 56.121 Disqualification of an IRB or an institution.
- 56.122 Public disclosure of information regarding revocation.
- 56.123 Reinstatement of an IRB or an institution.
- 56.124 Actions alternative or additional to disqualification.

**AUTHORITY:** Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

**SOURCE:** 46 FR 8975, Jan. 27, 1981, unless otherwise noted.

**Subpart A—General Provisions**

§ 56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, bi-

ological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

**§ 56.102 Definitions.**

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 321-392)).

(b) *Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 170.35.

(3) A food additive petition, described in part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the proce-

dures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in § 314.300 of this chapter.

(11) An application for a biological product license, described in part 601.

(12) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601.

(13) An *Application for an Investigational Device Exemption*, described in parts 812 and 813.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(15) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(16) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(17) A product development protocol for a medical device for human use, described in section 515 of the act.

(18) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(20) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(21) Data and information regarding an electronic product submitted as

part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous for purposes of this part.

(d) *Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The term *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(g) *Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *institu-*

*tional review committee* as used in section 520(g) of the act.

(h) *Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) *Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) *Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

(m) *IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution

within the constraints set forth by the IRB and by other institutional and Federal requirements.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991]

#### § 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

#### § 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investiga-

tion remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

**§ 56.105 Waiver of IRB requirement.**

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

**Subpart B—Organization and Personnel**

**§ 56.107 IRB membership.**

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as com-

munity attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991]

### Subpart C—IRB Functions and Operations

#### § 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130)

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

#### § 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the FEDERAL REGISTER.

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in § 56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§ 56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:  
(i) By using procedures which are con-

sistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or



undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

#### § 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

#### § 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

#### § 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

### Subpart D—Records and Reports

#### § 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show at-

tendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by § 56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by § 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130)

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

**Subpart E—Administrative Actions  
for Noncompliance**

**§ 56.120 Lesser administrative actions.**

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the

parent institution determined to be responsible for formal designation of the IRB.

**§ 56.121 Disqualification of an IRB or an institution.**

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under § 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the **FEDERAL REGISTER**.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institu-

tion is reinstated as provided in § 56.123.

**§ 56.122 Public disclosure of information regarding revocation.**

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

**§ 56.123 Reinstatement of an IRB or an institution.**

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under § 56.121(c).

**§ 56.124 Actions alternative or additional to disqualification.**

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

# Section 7

## Inclusion of Women in Clinical Trials

**WOMEN IN CLINICAL TRIALS OF NEW DRUGS**  
**A Change in Food and Drug Administration Policy**

**T**HE Food and Drug Administration (FDA) is taking two important steps to ensure that new drugs are properly evaluated in women. First, it is providing formal guidance to drug developers to emphasize its expectations that women will be appropriately represented in clinical studies and that new drug applications will include analyses capable of identifying potential differences in drug actions or efficacy between the sexes. Second, the agency is altering a 16-year-old policy that has excluded most women with "childbearing potential" from the earliest phases of clinical trials.

Attention to sex differences is part of a larger effort

Address reprint requests to Dr. Ruth B. Merkatz at the Food and Drug Administration, HS-1, 5600 Fishers La., Rockville, MD 20857.

by the FDA to ensure that the safety and efficacy of drugs are adequately studied in the full range of patients who will receive therapy and that information is obtained that will allow physicians to individualize therapy. These actions are also being taken in response to questions about whether this country's drug-development process produces adequate information about the effects of drugs in women,<sup>1-4</sup> as well as more general issues concerning women's health.<sup>5-11</sup>

**SEX-SPECIFIC ISSUES IN DRUG RESPONSE**

Responses to drugs are influenced by many factors, including age, sex, ethnic background, metabolic phenotype, body-fat content and distribution, and body size.<sup>12,13</sup> The presence of diseases other than the one for which a study drug is being tested and the use of concomitant therapies are also relevant. Such factors, either singly or in combination, can influence a drug's pharmacokinetics (the concentration of the drug in the blood or other tissues over time) or its pharmaco-

dynamics (the body's response to a given concentration of a drug). When such differences are recognized, adjustments in the dose or dose interval, choice of drug, monitoring procedures, or other aspects of drug administration can improve outcomes for patients.

Sex-related differences in pharmacokinetics or response have been identified for a number of drugs.<sup>14,15</sup> Propranolol, for example, is metabolized more slowly in women than in men; it has been suggested that sex hormones regulate some of the enzymes that metabolize this drug.<sup>16</sup> The half-life of theophylline is significantly shorter in female nonsmokers and smokers than in male nonsmokers and smokers, presumably because of differences in hepatic metabolism.<sup>17</sup> Lower rates of clearance of acetaminophen,<sup>18</sup> several benzodiazepines,<sup>19,20</sup> lidocaine,<sup>21</sup> aspirin,<sup>22</sup> ondansetron,<sup>23</sup> and mephobarbital<sup>24</sup> have also been described.

The most likely causes of differences in pharmacokinetics between women and men and among women are variations in body size and composition and the effects of hormones. The usually smaller body size of women and their higher body-fat content may influence the pharmacokinetics of drugs even if there are no differences in metabolism. For example, a smaller body size results in relatively higher blood concentrations after a given dose of ethanol.<sup>25</sup> In addition, the higher body-fat content of women and their lower body-water volume contribute to higher blood alcohol concentrations. These distributional aspects of pharmacokinetics are magnified by metabolic differences. Recently, it has been demonstrated that the gastric mucosa of women elaborates less alcohol dehydrogenase than that of men.<sup>26</sup>

The hormonal environment could affect both the pharmacokinetics of drugs and their pharmacodynamic effects. Four factors appear to be relevant to women: (1) the effects of levels of gonadotropins and circulating steroidal hormones, notably estradiol and progesterone, during the menstrual cycle; (2) the differences between premenopausal and postmenopausal women, including the effects of hormone-replacement therapy after menopause; (3) the effects of drastically different hormone levels during pregnancy and the metabolic consequences of pregnancy itself; and (4) the effects of steroidal contraceptives on the metabolism of drugs taken concomitantly and, conversely, the effects of other drugs on the efficacy of contraceptives.

An example of the influences of the varying levels of sex hormones during the menstrual cycle is insulin binding. In one study, insulin binding to monocytes and erythrocytes was higher in the follicular phase than in the luteal phase.<sup>27</sup> There is an inverse relation between the binding of insulin to monocytes and levels of estradiol and progesterone. This correlation may result in an exacerbation of hyperglycemia during the luteal phase in some women with insulin-dependent diabetes mellitus.<sup>28</sup>

The differences in hormonal patterns between premenopausal and postmenopausal women and the use of exogenous hormones may affect pharmacokinetics. For example, the half-life of prednisolone is significantly longer in young women taking oral contraceptives than in women of the same age who are not taking such agents. A similar increase also occurs in postmenopausal women who are receiving conjugated estrogens, as compared with women not taking hormones.<sup>29</sup>

Approximately 10 million women in the United States are currently taking steroidal contraceptives, and the possibility that concomitant drug therapy could decrease the effectiveness of these contraceptives is of serious concern. Griseofulvin increases the hepatic metabolism of contraceptive steroids, thus lowering blood levels.<sup>30</sup> Plasma contraceptive-hormone concentrations may also be lowered by broad-spectrum antibiotics such as tetracycline,<sup>30</sup> the anti-tubercular agent rifampin,<sup>31</sup> and some anticonvulsant agents, including carbamazepine and phenytoin.<sup>30,32</sup> Susceptible women may experience breakthrough bleeding or even become pregnant when given these agents in conjunction with oral contraceptives, especially the low-estrogen oral contraceptives commonly used today.

#### IDENTIFYING SEX-RELATED EFFECTS IN CLINICAL TRIALS

As specified in the FDA's 1977 "General Considerations for the Clinical Evaluation of Drugs," drugs are tested in three phases before a sponsor submits the new drug application required for marketing approval.<sup>33,34</sup> Phase 1 studies are the initial studies in humans and generally involve small numbers of healthy volunteers or patients treated over a short period of time. These studies assess individual tolerance of the drug and examine its metabolism and short-term pharmacokinetics. They may also provide preliminary pharmacologic information related to clinical effectiveness.

Phase 2 studies, which normally involve a few hundred patients, are the earliest controlled trials designed to demonstrate effectiveness and relative safety. During phase 3, the final testing phase before a marketing application is submitted to the FDA for review, as many as several thousand patients are studied. These studies provide additional evidence regarding safety and effectiveness, including data on long-term exposure; refine information on dose-response and concentration-response relations; and identify relatively rare adverse effects. The inclusion of a broad sample of the population in phase 3 trials and the examination of the data for differences in response make it possible to identify demographic, pathophysiologic, and other characteristics that affect patients' responses to the drug.

The 1977 guidelines stated that drugs should be studied in the population that would receive them and specifically stated that all age groups should be in-

cluded. The guidelines were not explicit, however, about the need to study both sexes. Nevertheless, FDA surveys conducted in 1983 and 1988 found that, in general, both sexes had substantial representation in clinical trials conducted before FDA approval of drugs, in proportions that usually reflected the prevalence of the disease in the sex and age groups included in the trials<sup>35</sup> (and Temple R, FDA: personal communication). Women tended to predominate in studies of nonsteroidal antiinflammatory drugs, whereas men predominated in studies of coronary artery disease. Roughly equal numbers of men and women were included in trials of most antibiotics, antihistamines, and hypnotics. Despite adequate participation by both women and men, however, few analyses of the data were being conducted to detect possible differences in effectiveness or safety between men and women.

In an effort to stimulate the use of the collected data to learn about individual characteristics that affect the behavior of drugs, the FDA in 1988 specifically called for studies of whether safety and effectiveness were similar within population subgroups defined by such characteristics as sex, age, and race.<sup>36</sup> Recent evaluations have shown that the requested analyses were not being carried out regularly. In consultation with the FDA, the General Accounting Office (GAO) reviewed the participation of women in phase II and III clinical trials of new drugs approved from 1988 through 1991.<sup>37</sup> The GAO found that the recommended analyses were being carried out in only about 50 percent of the trials. Because the GAO survey included many applications submitted to the FDA before the 1988 guidelines were published, the FDA surveyed new drug applications submitted from June 1991 to July 1992. It found that safety data had been analyzed according to sex just 64 percent of the time and that data on effectiveness had been analyzed in this way just 54 percent of the time.

In the light of these findings, the FDA will review all new drug applications shortly after submission to ensure that they include appropriate analyses by sex. If such analyses are lacking, the FDA will call for their submission and may consider refusing to initiate review of the application if sex-specific analyses are not provided within a reasonable period (Temple R, FDA: personal communication).

#### **GUIDELINES FOR THE EVALUATION OF SEX DIFFERENCES IN THE CLINICAL EVALUATION OF DRUGS**

In addition to reviewing new drug applications to see that analysis according to sex is included, the FDA is issuing new guidelines on the participation of women in drug evaluations.<sup>38</sup> This document is similar in approach to one published in 1989 to ensure that elderly patients would be included in studies and evaluations.<sup>39</sup> The guidelines urge that reasonable numbers of women be included in studies of new drugs. "Reasonable numbers" are not defined precisely; rather, the agency expects enough representation of both

sexes so that significant differences can be detected. The guidelines stress the importance of assessing possible pharmacokinetic differences between women and men, either by formal studies or with use of pharmacokinetic screening.

Pharmacokinetic screening is an approach to assessing the full range of factors, such as demographic characteristics, underlying disease, and concomitant therapy, that can alter a drug's pharmacokinetics.<sup>40</sup> It consists of obtaining a small number of steady-state blood-concentration measurements in most subjects in phase 2 and phase 3 trials and then analyzing them to detect relations between pharmacokinetics and particular characteristics of the subgroup, such as sex, age, renal or hepatic function, body size, muscle mass, and concomitant therapy. If the results suggest important differences, more formal pharmacokinetic studies can then be undertaken.

Few clinically important sex-related pharmacodynamic differences in clinical response have been documented up to now, and the guidelines do not call for separate clinical or pharmacodynamic studies in women in most cases. Instead, substantial representation of both sexes is expected in studies of safety and effectiveness, and the data should be examined for sex differences in the effectiveness, adverse-event rates, and dose response of drugs. If these analyses suggest differences between the sexes, or if the presence of such differences could be especially important, as in the case of drugs with a low therapeutic index, additional formal studies may be needed.

The FDA guidelines emphasize three pharmacokinetic issues: (1) the effects of the menstrual cycle and menopausal status on a drug's pharmacokinetics; (2) the effects of concomitant estrogen supplementation or use of systemic contraceptive agents, including both estrogen-progestin combinations and long-acting progestones, on a drug's pharmacokinetics; and (3) the influence of a drug on the effectiveness of oral contraceptives.

Finally, the new guidelines recognize that although clinical or pharmacokinetic data collected from late phase 2 and phase 3 studies may provide evidence of differences between the sexes, these data may become available too late to affect the design and dose selection of the pivotal controlled trials. The FDA therefore encourages the inclusion of women in all age groups early in drug development. Thus, the agency no longer prohibits women with childbearing potential from participating in the earliest phases of most clinical trials.

#### **THE INCLUSION OF WOMEN IN EARLY PHASES OF CLINICAL TRIALS**

The guidelines published in 1977<sup>33</sup> specifically stated that women with childbearing potential should be excluded from phase 1 and early phase 2 studies. Once some information about relative safety and effectiveness had been amassed in early phase 2 trials, and once preclinical data on teratogenicity and female fertility in animals had been obtained, women with child-

bearing potential (broadly defined as the "capacity" to become pregnant) could participate in later phase 2 and phase 3 studies.

In addition to premenopausal women who were sexually active and using no contraception, the exclusion applied to women who were unlikely to become pregnant, such as women using oral, injectable, or mechanical contraception, women whose partners had had vasectomies, women who were sexually inactive, and lesbians. The restriction arose, in part, from earlier discoveries of birth defects that followed exposure to specific drugs.<sup>41-43</sup> It reflected the view that risk to the fetus was unacceptable in studies that were not intended to have important medical benefits for the subjects. It did not apply to women with life-threatening diseases. Thus, women with conditions such as cancer and, more recently, AIDS have been included in the earliest phases of drug trials, before the completion of animal-reproduction studies. In these situations, the potential risk to the fetus was balanced by the compelling possibility of prolonging the life of the mother.

In 1993, protecting the fetus from unanticipated exposure to potentially harmful drugs remains critically important, but the ban on women's participation in early clinical trials no longer seems reasonable for several reasons. First, there are notable scientific benefits to including women with childbearing potential in the early phases of trials. If important sex differences can be identified during phase 1 and early phase 2 studies, later phase 2 and phase 3 trials can be designed more suitably to further clinical understanding of the appropriate use of drugs in women.

Second, from an ethical perspective, the restriction on women with childbearing potential implies a lack of respect for their autonomy and decision-making capacity. The ethical principles articulated in the Belmont Report<sup>44</sup> — respect for persons, beneficence, and justice — as well as recent actions of the Congress and decisions of the Supreme Court suggest that women should have the right to make their own risk-benefit choices about their pregnancies. For example, the Pregnancy Discrimination Act, as interpreted by the Supreme Court in the landmark case of *United Automobile Workers v. Johnson Controls*, prohibits the blanket exclusion of pregnant women from jobs they are qualified to perform solely because working conditions pose potential risks to exposed fetuses.<sup>45,46</sup> Although the purposes of clinical trials are manifestly different from the purposes of employment, the Court's emphasis on a woman's right to participate in decisions about fetal risk underscores the principles of autonomy and informed consent. Consistent with regulations issued in their present form by the FDA in 1981, subjects in clinical trials are expected to be fully informed in an unbiased manner about findings from animal-reproduction studies, to the extent that they have been completed, and to be reminded of the uncertainties inherent in experimental therapies.<sup>47</sup>

Third, it is possible to reduce the risk of fetal expo-

sure through protocol design. Since early clinical studies are typically of very short duration, often involving a single dose of medication, one approach is to administer a drug during or immediately following a woman's menstrual period, after a negative result from a pregnancy test that detects the beta subunit of the human chorionic gonadotropin molecule. For longer studies, trial subjects are expected to be counseled about the need to use reliable forms of contraception. Local institutional review boards will be expected to undertake careful reviews of investigational protocols that involve potential risks to the fetus from known or probable teratogens, in order to determine whether the trials should proceed. The FDA also reviews the risks and benefits of such protocols.

Whether removal of the impediments to their participation will increase the number of women in early trials depends partly on drug companies' concerns about liability. A review of case law suggests that manufacturers have not faced substantial litigation by clinical-trial participants.<sup>48</sup> Liability litigation occurs mostly when an approved drug has been used in a population in whom it has not first been systematically studied.<sup>49</sup> The future legal climate cannot be fully anticipated, however, and many states have ruled that once children reach the age of majority, those adversely affected by the medical decisions of a parent have the necessary cause of action to allow a lawsuit to proceed. If we are to achieve broader participation of women in all phases of clinical trials, legitimate issues such as liability will have to be addressed as part of ongoing dialogue among drug developers, scientists, policy makers, health advocates, and women's groups.

#### TESTING DRUGS IN PREGNANT WOMEN

The FDA and the scientific community are concerned about the difficulty of testing drugs and biologic agents in pregnant women and the lack of systematic procedures for assessing postmarketing exposure. Maximizing protection of fetuses from potentially toxic therapies is prudent, and fear of liability is understandable, but the result is that many drugs are ultimately used during pregnancy without reliable data on their maternal and fetal effects. The potential risk of current practice was highlighted by the recent discovery, after the product was marketed, of sometimes fatal neonatal renal problems associated with pregnant women's use of angiotensin-converting-enzyme inhibitors during the second and third trimesters for the treatment of hypertension.<sup>50</sup> This finding, which emerged from scattered clinical reports and the experience of a particular physician, underscores the need for a more formal mechanism for the pre-approval study of drugs that are likely to be used in pregnancy and for the systematic collection of postmarketing exposure data.

When a clinical trial represents the only source of a promising experimental therapy for a life-threatening condition, it is more obviously essential to include pregnant women. Thus, the agency has advocated



that pregnant women who are infected with the human immunodeficiency virus be included in the early testing of new therapies for AIDS. Even in less urgent cases, the participation of women in formal studies may be appropriate when the drugs' use in pregnancy is likely. The FDA intends to explore further the complex issues of including pregnant women in clinical trials of new drugs and biologic agents and of improving the collection of postmarketing data in a series of public workshops and conferences similar to those that led to the policy changes highlighted in this article.

RUTH B. MERKATZ, Ph.D., R.N.,  
ROBERT TEMPLE, M.D.,  
SOLOMON SOBEL, M.D., KARYN FEIDEN,  
DAVID A. KESSLER, M.D.,  
AND THE WORKING GROUP  
ON WOMEN IN CLINICAL TRIALS

The members of the Working Group on Women in Clinical Trials are as follows: Grant Bagley, M.D., Ilisa Bernstein, Pharm.D., James Bilstad, M.D., Bruce Burlington, M.D., Linda Carter, Mary Ann Danello, Ph.D., Mary Gross, Jane Henney, M.D., Patricia M. Kuntze, Eileen Leonard, M.D., Catherine Lorraine, J.D., Thomas Ludden, Ph.D., Diane Murphy, M.D., Carl Peck, M.D., Mary Pendergast, J.D., Margaret Porter, J.D., Carol Scheman, Elyse Summers, J.D., Michael Taylor, J.D., Theresa Toigo, R.Ph., Gloria Troendle, M.D., Suzanne White, Janet Woodcock, M.D., and Nancy Yeates.

#### REFERENCES

- Pinn VW. Women's health research: prescribing change and addressing the issues. *JAMA* 1992;268:1921-2.
- Ray BA, Braude MC, eds. Women and drugs: a new era for research. National Institute on Drug Abuse research monograph 65. Rockville, Md.: National Institute on Drug Abuse, 1986.
- Forging a women's health research agenda. Washington, D.C.: National Women's Health Resource Center, 1991.
- Kirschstein RL. Research on women's health. *Am J Public Health* 1991; 81:291-3.
- Report of the Public Health Service Task Force on Women's Health Issues. Vol. 2. Washington, D.C.: Department of Health and Human Services, 1985. (DHHS publication no. (PHS) 85-50206.)
- H.R. 1161, Women's Health Equity Act of 1991, Second session, 102nd Congress, 1992.
- Opportunities for research on women's health. Washington, D.C.: National Institutes of Health, 1992. (NIH publication no. 92-3457A.)
- Research to improve women's health: an agenda for equity. Washington, D.C.: National Women's Health Network, 1991.
- Johnson TL. A women's health research agenda. *J Womens Health* 1993;2:95-8.
- Forum on drug development: women and drug development: report of a workshop. Washington, D.C.: National Academy of Sciences, Institute of Medicine, 1993.
- Seminar on women in clinical trials of FDA-regulated products. *Food Drug Law J* (in press).
- Benet LZ, Massoud N, Gambertoglio JG, eds. Pharmacokinetic basis for drug treatment. New York: Raven Press, 1984.
- Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: principles of therapeutic drug monitoring. 2nd ed. Spokane, Wash.: Applied Therapeutics, 1986.
- Hamilton JA. An overview of the clinical rationale for advancing gender-related psychopharmacology and drug abuse research. In: Ray BA, Braude MC, eds. Women and drugs: a new era for research. National Institute on Drug Abuse research monograph 65. Rockville, Md.: National Institute on Drug Abuse, 1986:14-20.
- Hamilton JA, Parry B. Sex-related differences in clinical drug response: implications for women's health. *J Am Med Assoc* 1983;38:126-32.
- Walle T, Walle UK, Cowart TD, Conradi EC. Pathway-selective sex differences in the metabolic clearance of propranolol in human subjects. *Clin Pharmacol Ther* 1989;46:257-63.
- Nafziger AN, Bertino JS Jr. Sex-related differences in theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1989;37:97-100.
- Abernethy DR, Divoll M, Greenblatt DJ, Amecr B. Obesity, sex, and acetaminophen disposition. *Clin Pharmacol Ther* 1982;31:783-90.
- Divoll M, Greenblatt DJ, Harmatz JS, Shader RI. Effect of age and gender on disposition of temazepam. *J Pharm Sci* 1981;70:1104-7.
- Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Oxazepam kinetics: effects of age and sex. *J Pharmacol Exp Ther* 1980;251:86-91.
- Wing LMH, Miners JO, Birkett DJ, Foenander T, Lillywhite K, Wanwimolruk S. Lidocaine disposition — sex differences and effects of cimetidine. *Clin Pharmacol Ther* 1984;35:695-701.
- Miners JO, Grgurinovich N, Whitehead AG, Robson RA, Birkett DJ. Influence of gender and oral contraceptive steroids on the metabolism of salicylic acid and acetylsalicylic acid. *Br J Clin Pharmacol* 1986;22:135-42.
- Pritchard JF, Bryson JC, Kermode AE, Benedetti TL, Powell JR. Age and gender effects on ondansetron pharmacokinetics: evaluation of healthy aged volunteers. *Clin Pharmacol Ther* 1992;51:51-5.
- Hooper WD, Qing MS. The influence of age and gender on the stereoselective metabolism and pharmacokinetics of mephobarbital in humans. *Clin Pharmacol Ther* 1990;48:633-40.
- Arthur MJP, Lee A, Wright R. Sex differences in the metabolism of ethanol and acetaldehyde in normal subjects. *Clin Sci* 1984;67:397-401.
- Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med* 1990;322:95-9.
- Bertoli A, De Pirro R, Fusco A, Greco AV, Magnatta R, Lauro R. Differences in insulin receptors between men and menstruating women and influence of sex hormones on insulin binding during the menstrual cycle. *J Clin Endocrinol Metab* 1980;50:246-50.
- Widom B, Diamond MP, Simonson DC. Alterations in glucose metabolism during menstrual cycle in women with IDDM. *Diabetes Care* 1992;15:213-20.
- Gustavson LE, Legler UF, Benet LZ. Impairment of prednisolone disposition in women taking oral contraceptives or conjugated estrogens. *J Clin Endocrinol Metab* 1986;62:234-7.
- Shenfield GM, Griffin JM. Clinical pharmacokinetics of contraceptive steroids: an update. *Clin Pharmacokinet* 1991;20:15-37.
- Orme ML, Back DJ, Breckenridge AM. Clinical pharmacokinetics of oral contraceptive steroids. *Clin Pharmacokinet* 1983;8:95-136.
- Back DJ, Breckenridge AM, Crawford FE, MacIver M, Orme ML, Rowe PH. Interindividual variation and drug interactions with hormonal steroid contraceptives. *Drugs* 1981;21:46-61.
- Food and Drug Administration. General considerations for the clinical evaluation of drugs. Washington, D.C.: Government Printing Office, 1977. (Publication no. HEW (FDA) 77-3040.)
- Kessler DA. The regulation of investigational drugs. *N Engl J Med* 1989; 320:281-8.
- Office for Legislative Affairs. Letter to Senator John Heinz. Survey of recent new drug applications. Washington, D.C.: Food and Drug Administration, September 27, 1983.
- Center for Drug Evaluation and Research. Guideline for the format and content of the clinical and statistical sections of new drug applications. Washington, D.C.: Food and Drug Administration, 1988.
- General Accounting Office. Women's health: FDA needs to ensure more study of gender differences in prescription drug testing. Washington, D.C.: Government Printing Office, 1992. (Publication no. GAO/HRD-93-17.)
- Center for Drug Evaluation and Research. Guideline for the study of and evaluation of gender differences in the clinical evaluation of drugs. Washington, D.C.: Food and Drug Administration (in press).
- Idem. Guideline for the study of drugs likely to be used in the elderly. Washington, D.C.: Food and Drug Administration, 1989.
- Temple R. The clinical investigation of drugs for use by the elderly: Food and Drug Administration guidelines. *Clin Pharmacol Ther* 1987;42:681-5.
- Christie GA. Thalidomide and congenital abnormalities. *Lancet* 1962; 2:249.
- Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 1971;284:878-81.
- Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer* 1970;25:745-57.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Belmont report: ethical principles and guidelines for the protection of human subjects of research. Washington, D.C.: Government Printing Office, 1979. (DHEW publication no. (OS) 78-0012.)
- International Union, United Automobile, Aerospace and Agricultural Implement Workers of America, UAW, et al. v. Johnson Controls, Inc. 111 S. Ct. 1196 (1991).
- Pregnancy Discrimination Act of 1978, 92 Stat. 2076, 42 USC 2000e(k).
- 21 CFR Secs. 50 and 50.25 (b) (1) 1990.
- Reisman EK. Products liability — what is the current situation and will it change (and how) when more women are included in studies? Presented at the Women in Clinical Trials of FDA-Regulated Products Workshop, Food and Drug Law Institute, Washington, D.C., October 5, 1992.
- Levine C. Women as research subjects: new priorities, new questions. In: Blank RH, Bonnicksen AL, eds. Emerging issues in biomedical policy: an annual review. Vol. 2. New York: Columbia University Press, 1993:169-88.
- Piper JM, Ray WA, Rosa FW. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol* 1992;80:429-32.

# Federal Register

---

Thursday  
July 22, 1993

---

## Part VI

### Department of Health and Human Services

---

Food and Drug Administration

---

Guideline for the Study and Evaluation of  
Gender Differences in the Clinical  
Evaluation of Drugs; Notice

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 93D-0236]

**Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is publishing a guideline entitled "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." This guideline provides new guidance on FDA's expectations regarding inclusion of both genders in drug development and revises the section "Women of Childbearing Potential" in the 1977 guideline entitled, "General Considerations for the Clinical Evaluation of Drugs" (HEW Publication No. (FDA) 77-3040).

**DATES:** Written comments by November 19, 1993.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of this notice, which includes the text of the new guideline, and of the other guidelines mentioned in this document, are available from the Center for Drug Evaluation and Research (HFD-8), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send two self-addressed adhesive labels to assist that office in processing your requests.

**FOR FURTHER INFORMATION CONTACT:** Patrick J. Savino, CDER Executive Secretariat Staff (HFD-8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8012.

**SUPPLEMENTARY INFORMATION:**

**I. Introduction**

In this document, FDA is publishing a new guideline on FDA's expectations regarding inclusion of patients of both genders in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and conduct of specific additional studies in women, where indicated. This guideline revises the section of the 1977 guideline, entitled "General Considerations for the Clinical Evaluation of Drugs," that excluded women of childbearing potential from participation in early

studies of drugs. For the purpose of this document, the agency will refer to the "General Considerations for the Clinical Evaluation of Drugs" as the "1977 guideline."

Although the new guideline outlines in some detail the specific considerations related to the evaluation of gender differences during evaluation of drug products, the agency views the principles of inclusion of women in product development programs and analysis of subgroup differences as being broader standards which apply equally to the clinical development of biological products and medical devices.

The new guideline reflects good drug development practice implicit in the law and regulations. Certain requirements, such as inclusion of adequate numbers of women and by-gender analyses, have been emphasized in the past. However, as with any new guideline, where sponsors have developed drugs in good faith relying on existing guidelines, they will have an opportunity to satisfy newly appreciated data needs after approval where this is compatible with the public health and the law. This new guideline does not change FDA's commitment to safe development of drugs but gives more flexibility to institutional review boards (IRB's), investigators, and patients in determining how best to ensure safety.

**II. Background**

**A. Participation of Women in Clinical Studies**

Over the past decade there has been growing concern that the drug development process does not produce adequate information about the effects of drugs in women. This concern arises from a number of sources.

Analyses of published clinical trials in certain therapeutic areas (notably cardiovascular disease) have indicated that there had been little or no participation of women in many of the studies. Certain major studies of the role of aspirin in cardiovascular and cerebrovascular disease, for example, did not include women, and this omission left the scientific community with doubts about whether aspirin was, in fact, effective in women for these indications. Similarly, published studies of anti-anginal drugs often had few or no women in them. It has been suggested that a similar situation might exist for the studies intended to support marketing approval of new drugs.

In addition, FDA notes that there has been little study of the effects of such aspects of female physiology as the menstrual cycle and menopause, or of

the effects of drugs widely used in women such as oral contraceptives and systemic progestins and estrogens, on drug action and pharmacokinetics.

Concern has also been expressed that the 1977 policy excluding women of childbearing potential from early drug studies may have led to a more general lack of participation of women in drug development studies, and thus to a paucity of information about the effects of drugs in women. In addition to concerns about whether the policy interfered with development of adequate data on drug therapy in women, the 1977 guideline, seen from the viewpoint of the 1990's, has appeared rigid and paternalistic, leaving virtually no room for the exercise of judgment by responsible female research subjects, physician investigators, and IRB's.

Concerns about the adequacy of data on the effects of drugs in women have arisen at a time when FDA, drug developers, and the scientific community have focused increasingly on the need to individualize treatment in the face of the wide variety of demographic, disease-related, and individual patient-related factors that can lead to different responses to drugs in subsets of the population. Optimal use of drugs requires identification of these factors so that appropriate adjustments in dose, concomitant therapy, or monitoring can be made.

Subgroup-specific differences in response can arise because of variation in a drug's pharmacokinetics (i.e., the drug's concentration in plasma or elsewhere as a function of time) or pharmacodynamics (the body's response to a given concentration of the drug).

**B. Pharmacokinetic and Pharmacodynamic Differences Among Patients**

Important variations in pharmacokinetics can arise from many factors:

1. A number of demographic characteristics may affect pharmacokinetics: Older people are more likely to have decreased renal function, which may cause drugs excreted by the kidney to accumulate; younger people metabolize theophylline more rapidly; ethnic groups differ in the prevalence of metabolic abnormalities such as slow acetylation and G6PD deficiency; women metabolize certain substances at rates different from men (for example, they metabolize alcohol and ondansetron more slowly).

2. Diseases other than the one being studied may alter the pharmacokinetics of many drugs: Kidney disease may decrease the ability to excrete drugs in

the urine; liver disease can interfere with the metabolism of drugs or with their excretion into the bile.

3. The presence of other drugs may lead to pharmacokinetic interactions: Quinidine and fluoxetine inhibit the metabolism of imipramine and desipramine, as well as that of many other drugs metabolized by cytochrome P450 2D6 (debrisoquin hydroxylase); ketoconazole and erythromycin inhibit the metabolism of terfenadine. In such cases, toxic blood concentrations of the drug whose metabolism is inhibited can occur even while a constant dose of the drug is maintained.

4. In addition, other differences between individual subjects may affect pharmacokinetics. For example, small body size or muscle mass may lead to higher blood concentrations after a given dose.

Documented subgroup pharmacodynamic differences are fewer, but have been observed, including increased sensitivity to beta-blockers in Asians, decreased sensitivity to beta-blockers in the elderly, decreased responsiveness to the blood pressure-lowering effects of adrenocortical extract (ACE) inhibitors and beta-blockers in African-Americans, and increased sensitivity to the central nervous system effects of midazolam in older people.

Despite the many examples of documented pharmacokinetic and pharmacodynamic differences in population subsets, there has often been insufficient attention in the course of drug development to looking for such differences among individuals in responses to drugs, including differences related to gender. In the case of gender, some have suggested the lack of information may have resulted from the exclusion of women from clinical trials. A number of studies have evaluated this possibility.

In 1983 and 1989, FDA examined the relative numbers of individuals from two important demographic groups, women and the elderly, in the data bases of new drug applications (NDA's). FDA found, in general, that the proportions of women and men included in the clinical trials were similar to the respective proportions of women and men who had the diseases for which the drugs were being studied, taking into account the age range of the population studied. The General Accounting Office (GAO) conducted a larger study of drugs approved during the period 1988 through 1991, with generally similar findings. Thus, women typically represent a majority of patients in NDA data bases of drugs used to treat conditions more common (or more

commonly treated) in women (e.g., arthritis and depression) and a minority, although usually a sizable one of about 30 percent or more, in conditions that occur predominantly in males in the age ranges usually included in clinical trials (e.g., angina pectoris). Appendix I of the guideline includes additional details of these surveys.

Although women have been included in the later phases of clinical trials, inclusion alone is not sufficient for adequate assessment of potential gender differences. There must be an effort to use the data to discover such differences. An FDA guideline issued in 1988 ("Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications") called for analyses of gender-related differences in response. FDA and GAO examined NDA's to see whether analyses of this kind were being conducted and submitted. Both examinations found that in many cases (about half) the data bases were not being analyzed to determine whether there were gender, age, or race differences in response to drugs.

A further reason for the lack of information about potential gender differences in drug response is the lack of specific studies of pharmacokinetics in women, even where gender-related differences in pharmacokinetics might be expected or important. There are a variety of potential differences of this type, including differences due to menopause or the menstrual cycle, or to concomitant oral contraceptive or estrogen use, as well as differences based on different body fat proportion, and differences in weight or muscle mass.

#### C. FDA Guidance on Individualization of Treatment

Since 1988, FDA has taken several major steps to encourage development of data that support informed individualization of treatment:

1. The agency's 1988 guideline entitled, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," calls for analyses of NDA data to identify variations among population subsets in favorable responses (effectiveness) and unfavorable responses (adverse reactions) to drugs. The population subsets that should be evaluated routinely include demographic subsets, such as different genders, age groups and races, people receiving other drug therapy, and people with concomitant illness.
2. The agency has addressed specifically the need to develop information on a particular

demographic subset, the elderly, in the 1989 guideline entitled, "Guideline for the Study of Drugs Likely to be Used in the Elderly."

3. In the Federal Register of November 1, 1990 (55 FR 46134), the agency proposed to amend the labeling regulation (21 CFR 201.57) to require a "Geriatric Use" section that would contain available information on experience with the drug in the elderly and describe any needed modifications in the use of the drug in that population. In the Federal Register of October 16, 1992 (57 FR 47423), the agency proposed to amend the same regulation to facilitate inclusion of information on the use of drugs in children.

#### D. Changes in the Guideline

The new guideline discusses FDA's expectations regarding inclusion of patients of both genders in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and, where appropriate, assessment of pharmacodynamic differences and the conduct of specific additional studies in women. The policy applies to all drug or disease specific clinical guidelines based on the 1977 guideline, that exclude women of childbearing potential from participation in early studies of drugs.

### III. Revised Policy on Inclusion of Women of Childbearing Potential in Clinical Trials

#### A. The 1977 Guideline—"General Considerations for the Clinical Evaluation of Drugs"

The 1977 guideline set forth a policy on, among other things, the inclusion of women of childbearing potential in clinical trials. The policy stated that, in general, women of childbearing potential should be excluded from the earliest studies of a new drug, that is, phase 1 and early phase 2 studies. Phase 1 refers to the first introduction of a new drug into humans, who are often, but not always, healthy volunteers, to study the basic tolerability of the drug, its metabolism, and its short-term pharmacokinetics. With the exception of some early studies in life-threatening diseases, phase 1 studies usually do not have therapeutic intent. Phase 2 refers to the initial controlled trials of a drug to study its effectiveness. Before the first such study, there is generally no evidence that the drug is of therapeutic value in humans.

If adequate information on effectiveness and relative safety were amassed during phase 1 and early phase 2, the guideline stated that women of

childbearing potential could be included in subsequent studies of effectiveness, that is, later phase 2 and phase 3 studies, so long as animal teratogenicity and the female part of animal fertility studies had been completed. The policy did not specifically address the manner in which the early human evidence of safety and effectiveness and the results of animal reproduction studies should be used to make decisions about participation of women in later trials, leaving these considerations to the usual risk-benefit assessment made by the patient, physician, and IRB, with subsequent FDA review.

In the 1977 guideline, the term "women of childbearing potential" was defined very strictly, essentially referring to all premenopausal women physiologically capable of becoming pregnant, including women on oral, injectable, or mechanical contraceptives, single women, celibate women, and women whose partners had been sterilized by vasectomy. There was no provision for the use of pregnancy testing to identify women who could participate in studies without a risk of fetal exposure. The 1977 guideline also noted, however, that women of childbearing potential could receive investigational drugs in the earliest phases of testing, even in the absence of adequate reproduction studies in animals, when the drugs were intended for life-saving or life-prolonging treatment.

The effect of the 1977 guideline has been that women generally have not been included in phase 1 nontherapeutic studies or in the earliest controlled effectiveness studies (i.e., early phase 2), except for studies of life-threatening illnesses, such as acquired immune deficiency syndrome (AIDS) and cancer.

#### *B. Reasons for Revising the 1977 Policy*

The policy set forth in the 1977 guideline has been under discussion for several years within and outside the agency, and there has been increasing sentiment that it should be revised. For example, in October 1992, FDA and the Food and Drug Law Institute cosponsored a meeting on women in clinical trials of FDA-regulated products at which many speakers described the current restrictions as paternalistic and overprotective, denying young women the opportunity available to men and older women to participate in early drug development research.

Although the 1977 guideline has not resulted in a failure to include adequate numbers of women in the later phases of clinical trials, it has restricted the

early accumulation of information about response to drugs in women that could be utilized in designing phase 2 and 3 trials, and has perhaps delayed appreciation of gender-related variation in drug effects. The early exclusion also may have perpetuated, in a subtle way, a view of the male as the primary focus of medicine and drug development, with women considered secondarily. There is reason to believe that earlier participation of women in studies would increase the likelihood that gender-specific data might be used to make appropriate adjustments in larger clinical studies (e.g., different doses in women or weight adjusted (milligram per kilogram) dosing instead of fixed doses).

The agency believes that removal of the prohibition on participation of women of childbearing potential in phase 1 and early phase 2 trials is consistent with congressional efforts to prevent unwarranted discrimination against such women. For example, in the employment context, the Pregnancy Discrimination Act, as interpreted by the U.S. Supreme Court in the landmark case of *International Union, United Automobile, Aerospace and Agricultural Implement Workers, UAW v. Johnson Controls, Inc.*, 111 S.Ct. 1196 (1991), prohibits the blanket exclusion of pregnant women from jobs they are qualified to perform solely because the working conditions of those jobs pose potential risks to exposed fetuses. The Court emphasized that "decisions about the welfare of future children must be left to the parents who conceive, bear, support, and raise them, rather than to the employers who hire those parents." While the purposes of clinical trials to develop safe and effective drugs are manifestly different from the purposes of private employment, FDA takes serious note of the Court's position on a woman's right to participate in decisions about fetal risk and believes it is appropriate to consider the Court's opinion in developing policy on the inclusion of women in clinical trials.

#### *C. Current FDA Position on Participation of Women of Childbearing Potential in Early Clinical Studies*

The agency has reconsidered the 1977 guideline and has concluded that it should be revised. This does not reflect a lack of concern for potential fetal exposure or indifference to potential fetal damage, but rather the agency's opinion that (1) exclusion of women from early trials is not medically necessary because the risk of fetal exposure can be minimized by patient behavior and laboratory testing, and (2) initial determinations about whether

that risk is adequately addressed are properly left to patients, physicians, local IRB's, and sponsors, with appropriate review and guidance by FDA, as are all other aspects of the safety of proposed investigations.

The agency is, therefore, withdrawing the restriction on the participation of women of childbearing potential in early clinical trials, including clinical pharmacology studies (e.g., dose tolerance, bioavailability, and mechanism of action studies), and early therapeutic studies. It is expected that, in accordance with good medical practice, appropriate precautions against becoming pregnant and exposing a fetus to a potentially dangerous agent during the course of study will be taken by women participating in clinical trials. It is also expected that women will receive adequate counseling about the importance of such precautions, that efforts will be made to be sure that a woman entering a trial is not pregnant at the time the trial begins (i.e., a pregnancy test detecting the beta subunit of the hCG molecule is negative), and that the woman participant is fully informed about the current state of the animal reproduction studies and any other information about the teratogenic potential of the drug. As is the case for all studies carried out under an investigational new drug application (IND), the adequacy of the precautions taken will be considered by FDA in its review of protocols. In situations where enrollment continues over a prolonged period (unlikely for early clinical studies) and significant new information about teratogenicity becomes available, the sponsor has the responsibility to transmit this information quickly to the investigator and to current as well as potential study participants in the informed consent process.

The agency recognizes that this change in FDA's policy will not, by itself, cause drug companies or IRB's to alter restrictions they might impose on the participation of women of childbearing potential. We do not at this time perceive a regulatory basis for requiring routinely that women in general or women of childbearing potential be included in particular trials, such as phase 1 studies. However, as this guideline delineates, careful characterization of drug effects by gender is expected by the agency, and FDA is determined to remove the unnecessary Federal impediment to inclusion of women in the earliest stages of drug development. The agency is confident that the interplay of ethical, social, medical, legal and political forces will allow greater participation of

women in the early stages of clinical trials.

In some cases, there may be a basis for requiring participation of women in early studies. When the disease under study is serious and affects women, and especially when a promising drug for the disease is being developed and made available rapidly under FDA's accelerated approval or early access procedures, a case can be made for requiring that women participate in clinical studies at an early stage. When such a drug becomes available under expanded access mechanisms (for example, treatment IND or parallel track) or is marketed rapidly under subpart E procedures (because an effect on survival or irreversible morbidity has been shown in the earliest controlled trials), it is medically important that a representative sample of the entire population likely to receive the drug has been studied, including representatives of both genders. Under these circumstances, clinical protocols should not place unwarranted restrictions on the participation of women.

The agency advises that this guideline represents its current position on the clinical evaluation of drugs in humans. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

#### IV. Comments

Interested persons may, on or before November 19, 1993, submit to the Dockets Management Branch (address above) written comments regarding this guideline. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. These comments will be considered in determining whether further amendments to, or revisions of, the guideline are warranted.

The new guideline replaces that portion of the 1977 guideline that dealt with women of childbearing potential. The text of the new guideline on gender differences follows:

#### Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs

##### I. Introduction

The Food and Drug Administration (FDA) advises that this guideline represents its current position on the clinical evaluation of drugs in humans.

This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

The principles of inclusion of women in product development programs and analysis of subgroup differences outlined in this guideline also apply to the clinical development of biological products and medical devices.

##### A. Abstract

In general, drugs should be studied prior to approval in subjects representing the full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave qualitatively similarly in demographic (age, gender, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many quantitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse effect. Recognition of these differences can allow safer and more effective use of drugs. Rarely, there may be qualitative differences as well. It is very difficult to evaluate subsets of the overall population as thoroughly as the entire population, but sponsors are expected to include a full range of patients in their studies, carry out appropriate analyses to evaluate potential subset differences in the patients they have studied, study possible pharmacokinetic differences in patient subsets, and carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, are suggested by existing data, or that would be particularly important if present: Study protocols are also expected to provide appropriate precautions against exposure of fetuses to potentially dangerous agents. Where animal data suggest possible effects on fertility, such as decreased sperm production, special studies in humans may be needed to evaluate this potential toxicity.

##### B. Underlying Observations

The following general observations and conclusions underlie the recommendations set forth in this guideline:

1. Variations in response to drugs, including gender-related differences, can arise from pharmacokinetic differences (that is, differences in the way a drug is absorbed, excreted, metabolized, or distributed) or pharmacodynamic differences (i.e., differences in the pharmacologic or clinical response to a given concentration of the drug in blood or other tissue).

2. Gender-related variations in drug effects may arise from a variety of sources. Some of these are specifically associated with gender, e.g., effects of endogenous and exogenous hormones. Gender-related differences could also arise, however, not because of gender itself, but because the frequency of a particular characteristic (for example, small size, concomitant hepatic disease or concomitant drug treatment, or habits such as smoking or alcohol use) is different in one gender, even if the characteristic could occur in either gender. Proper management of patients of both genders thus requires that physicians know all the factors that can influence the pharmacokinetics of a drug. An approach is needed that will identify, better than is done at present, all such factors. Understanding how various factors may influence pharmacokinetics will greatly enhance our ability to treat people of both genders appropriately.

3. For a number of practical and theoretical reasons, the evaluation of possible gender-related differences in response should focus initially on the evaluation of potential pharmacokinetic differences. Such differences are known to occur and have, at least to date, been documented much more commonly than documented pharmacodynamic differences. Moreover, pharmacokinetic differences are relatively easy to discover. Once reliable assays are developed for a drug and its metabolites (such assays are now almost always available early in the development of the drug), techniques exist for readily assessing gender-related or other subgroup-related pharmacokinetic differences.

Formal pharmacokinetic studies are one means of answering questions about specific subgroups. Another approach is use of a screening procedure, a "pharmacokinetic screen" (see "Guideline for the Study of Drugs Likely To Be Used in the Elderly"). Carried out in phase 2 and 3 study populations, the pharmacokinetic screen can greatly increase the ability to detect pharmacokinetic differences in subpopulations and individuals, even when these differences are not anticipated. By obtaining a small number of blood concentration determinations in most or all phase 2 and 3 patients, it is possible to detect markedly atypical pharmacokinetic behavior in individuals, such as that seen in slow metabolizers of debrisoquin, and pharmacokinetic differences in population subsets, such as patient populations of different gender, age, or race, or patients with particular underlying diseases or

concomitant therapy. The screen may also detect interactions of two factors, e.g., gender and age. The relative ease with which pharmacokinetic differences among population subsets can be assessed contrasts with the difficulty of developing precise relationships of most clinical responses to drug dose or to the drug concentration in blood, which usually would be necessary when attempting to observe pharmacodynamic differences between two subgroups.

A final reason to emphasize pharmacokinetic evaluation is that it must be carried out to allow relevant assessment of pharmacodynamic differences or relationships. Assessing pharmacodynamic differences between groups or establishing blood concentration-response relationships is possible only when groups are reasonably well matched for blood concentrations. Enough pharmacokinetic data must therefore be available to permit the investigator to administer doses that will produce comparable blood concentrations in the subsets to be compared or, alternatively, to compare subsets that have been titrated to similar blood concentrations.

4. The number of documented gender-related pharmacodynamic differences of clinical consequence is at this time small, and conducting formal pharmacodynamic/effectiveness studies to detect them may be difficult, depending on the clinical endpoint. Such studies are therefore not routinely necessary. The by-gender analyses of clinical trials that include both men and women, however, which are specified in the 1988 guideline entitled "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" are not difficult to carry out. Particularly if these analyses are accompanied by blood concentration data for each patient, they can detect important pharmacodynamic/effectiveness differences related to gender.

#### C. Inclusion of Both Genders in Clinical Studies

The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response. Although it may be reasonable to exclude certain patients at early stages because of characteristics that might make evaluation of therapy more difficult (e.g., patients on concomitant

therapy), such exclusions should usually be abandoned as soon as possible in later development so that possible drug-drug and drug-disease interactions can be detected. Thus, for example, there is ordinarily no good reason to exclude women using oral contraceptives or estrogen replacement from trials. Rather, they should be included and differences in responses between them and patients not on such therapy examined. Pharmacokinetic interaction studies (or screening approaches) to look at the interactions resulting from concomitant treatment are also useful.

Ordinarily, patients of both genders should be included in the same trials. This permits direct comparisons of genders within the studies. In some cases, however, it may be appropriate to conduct studies in a single gender, e.g., to evaluate the effects of phases of the menstrual cycle on drug response.

Although clinical or pharmacokinetic data collected during phase 3 may provide evidence of gender-related differences, these data may become available too late to affect the design and dose-selection of the pivotal controlled trials. Inclusion of women in the earliest phases of clinical development, particularly in early pharmacokinetic studies, is, therefore, encouraged so that information on gender differences may be used to refine the design of later trials. Note that the strict limitation on the participation of women of childbearing potential in phase 1 and early phase 2 trials that was imposed by the 1977 guideline entitled, "General Considerations for the Clinical Evaluation of Drugs," has been eliminated.

There is no regulatory or scientific basis for routine exclusion of women from bioequivalence trials. For certain drugs, however, it is possible that changes during the menstrual cycle may lead to increases in intra-subject variability. Such variability could be related to hormonally-mediated differences in metabolism or changes in fluid balance. Sponsors of bioequivalence trials are encouraged to examine available information on the pharmacokinetics and metabolism of the test drugs and related drugs to determine whether there is a basis for concern about variability in pharmacokinetics during the menstrual cycle. Where the available information does raise such concern, measures could be taken to reduce or adjust for variability, e.g., administration of each drug at the same phase of the menstrual cycle, or inclusion of larger numbers of subjects. Sponsors are encouraged to collect data that will contribute to the

understanding of the relationship between hormonal variations and pharmacokinetics.

#### D. Analysis of Effectiveness and Adverse Effects by Gender

FDA's guideline on the clinical and statistical sections of NDA's calls for analyses of effectiveness, adverse effects, dose-response, and, if available, blood concentration-response, to look for the influence of: (1) Demographic features, such as age, gender, and race; and (2) other patient characteristics, such as body size (body weight, lean body mass, fat mass), renal, cardiac, and hepatic status, the presence of concomitant illness, and concomitant use of drugs, including ethanol and nicotine. Analyses to detect the influence of gender should be carried out both for individual studies and in the overall integrated analyses of effectiveness and safety. Such analyses of subsets with particular characteristics can be expected to detect only relatively large gender-related differences, but in general, small differences are not likely to be clinically important. The results of these analyses may suggest the need for more formal dose-response or blood concentration-response studies in men or women or in other patient subsets. Depending on the magnitude of the findings, or their potential importance (e.g., they would be more important for drugs with low therapeutic indices), these additional studies might be carried out before or after marketing.

#### E. Defining the Pharmacokinetics of the Drug in Both Genders

The factors most commonly having a major influence on pharmacokinetics are renal function, for drugs excreted by the kidney, and hepatic function, for drugs that are metabolized or excreted by the liver; these should be assessed directly as part of the ordinary development of drugs. The pharmacokinetic effects of other subgroup characteristics such as gender can be assessed either by a pharmacokinetic screening approach, described in the 1989 guideline entitled, "Guideline for the Study of Drugs Likely to Be Used in the Elderly," or by formal pharmacokinetic studies in specific gender or age groups.

Using either a specific pharmacokinetic study or a pharmacokinetic screen, the pharmacokinetics of a drug should be defined for both genders. In general, it is prudent to at least carry out pilot studies to look for major pharmacokinetic differences before conducting definitive controlled trials, so that differences that might lead to the

need for different dosing regimens can be detected. Such studies are particularly important for drugs with low therapeutic indices, where the smaller average size of women alone might be sufficient to require modified dosing, and for drugs with nonlinear kinetics, where the somewhat higher milligram per kilogram dose caused by a woman's smaller size could lead to much larger differences in blood concentrations of drug. Gender may interact with other factors, such as age. The potential for such interactions should be explored.

Three pharmacokinetic issues related specifically to women that should be considered during drug development are: (1) The influence of menstrual status on the drug's pharmacokinetics, including both comparisons of premenopausal and postmenopausal patients and examination of within-cycle changes; (2) the influence of concomitant supplementary estrogen treatment or systemic contraceptives (oral contraceptives, long-acting progesterone) on the drug's pharmacokinetics; and (3) the influence of the drug on the pharmacokinetics of oral contraceptives. Which of these influences should be studied in a given case would depend on the drug's excretion, metabolism, and other pharmacokinetic properties, and on the steepness of the dose-response curve.

Hormonal status during the menstrual cycle may affect plasma volume and the volume of distribution (and thus clearance) of drugs. The activity of certain cytochrome P450 enzymes may be influenced by estrogen levels and, in addition, microsomal oxidation by these enzymes may decline in the elderly more in men than women. Oral contraceptives can cause decreased clearance of drugs (e.g., imipramine, diazepam, chlordiazepoxide, phenytoin, caffeine, and cyclosporine), apparently by inhibiting hepatic metabolism. They can also increase clearance by inducing drug metabolism (e.g., of acetaminophen, salicylic acid, morphine, lorazepam, temazepam, oxazepam, and clofibrate). Certain anticonvulsants (carbamazepine, phenytoin) and antibiotics (rifampin) can reduce the effectiveness of oral contraceptives. Many of the potential interactions of gender and gender-related characteristics (e.g., use of oral contraceptives) can be evaluated with the pharmacokinetic screen. In some cases, specific studies will be needed.

#### F. Gender-Specific Pharmacodynamic Studies

Because documented demographic differences in pharmacodynamics

appear to be relatively uncommon, it is not necessary to carry out separate pharmacodynamic/effectiveness studies in each gender routinely. Evidence of such differences should be sought, however, in the data from clinical trials by carrying out the by-gender analyses suggested in the guideline on the clinical and statistical sections of NDA's. These analyses of controlled trials involving both genders are probably more likely to detect differences than studies carried out entirely in one gender. Experience has shown that gender differences can be detected with such approaches.

If the by-gender analyses suggest gender-related differences, or if such differences would be particularly important, e.g., because of a low therapeutic index, additional formal studies to seek such differences between the blood level-response curves of men and women should be conducted. Even in the absence of a particular concern based on the by-gender analyses, if there is a readily measured pharmacodynamic endpoint, such as blood pressure or rate of ventricular premature beats, and if there are good dose-response data for the overall population, it should be feasible to develop dose response data from population subsets (e.g., both genders) in the critical clinical trials.

#### G. Precautions in Clinical Trials Including Women of Childbearing Potential

Appropriate precautions should be taken in clinical studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and patients of potential risk and the need for precautions. In all cases, the informed consent document and investigator's brochure should include all available information regarding the potential risk of fetal toxicity. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their significance in humans. If these studies have not been completed, other pertinent information should be provided, such as a general assessment of fetal toxicity in drugs with related structures or pharmacologic effects. If no relevant information is available, the informed consent should explicitly note the potential for fetal risk.

In general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of childbearing potential, i.e., usually by the end of phase 2 and before any expanded access program is implemented.

Except in the case of trials intended for the study of drug effects during

pregnancy, clinical protocols should also include measures that will minimize the possibility of fetal exposure to the investigational drug. These would ordinarily include providing for the use of a reliable method of contraception (or abstinence) for the duration of drug exposure (which may exceed the length of the study), use of pregnancy testing (beta HCG) to detect unsuspected pregnancy prior to initiation of study treatment, and timing of studies (easier with studies of short duration) to coincide with, or immediately follow, menstruation. Female subjects should be referred to a study physician or other counselor knowledgeable in the selection and use of contraceptive approaches.

#### H. Potential Effects on Fertility

Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative treatment, and the duration of therapy. Where patients of reproductive potential are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate monitoring and/or laboratory studies to allow detection of these effects. Long-term followup will usually be needed to evaluate the effects of such drugs in humans.

#### Appendix I

##### *I. Surveys of Participation of Women in Clinical Trials in New Drug Applications (NDA's)*

The extent of participation of women in the data bases of NDA's has been examined several times in recent years, by FDA in 1983 and 1989, and by the General Accounting Office (GAO) in 1992. In general, the genders were represented to approximately the extent one would predict from the gender prevalence of the condition treated by the drug in the age group studied. The relative disease prevalence in men and women can vary with age. Consider, for example, the participation of women in studies of anti-anginal drugs. Almost all patients in angina studies, which require vigorous treadmill exercise tests, are under 75 years old and the large



majority are under 65. Although eventually women develop symptomatic coronary artery disease in their 60's, 70's, and 80's, and become similar to men in the prevalence of this condition, they are much less likely than men to be affected in their 40's, 50's, and early 60's. The overall NDA data base for an anti-anginal drug, made up primarily of people 50 to 65, will therefore include a significantly greater proportion of men than women. Efforts to include more very old patients in trials, i.e., patients in their 70's and 80's, should lead to a greater proportion of women in trials of anti-anginal drugs.

Results of the FDA and GAO surveys are described below. Also included is an analysis of gender distribution in recently approved or submitted NDA's for antidepressant drugs. This analysis was conducted to evaluate the frequently heard claim that this class of drugs is studied predominantly (or even exclusively) in males despite the wide use of antidepressants in women.

#### A. The 1983 Survey

Primarily carried out to assess the inclusion of the elderly in NDA's, the 1983 survey looked at the age and gender prevalence of patients included in 11 pending NDA's. The NDA's were chosen because they were readily available and did not need to be retrieved from storage; figures were taken by FDA staff from the pending applications. In one case (ranitidine), the values represent only domestic patients for only one claim, leading to a small number of patients; many more patients (those included in foreign studies, or in studies of other claims) were available for safety evaluation.

Table 1 shows the results of the survey. As expected, the non-steroidal anti-inflammatory drugs (NSAID's) were studied predominantly in women, because arthritis, especially rheumatoid arthritis, is more common in women. This predominance was slightly less prominent in the case of zomepirac, which was studied extensively for pain (gender-neutral), in addition to arthritis. The hypnotic drug (triazolam) and the antibiotics (cefoperazone and netilmycin) were studied in approximately equal proportions of men and women. The patient populations included in the NDA's for verapamil, for angina, and bumetanide, for heart failure, were about two-thirds male, and about two-thirds of the patients were less than 60 years old, an age group in which angina and heart failure are more prevalent in men than in women. In the patients over age 70, representing 10 percent of the bumetanide patients and 7 percent of verapamil patients, the

gender distribution was about equal (49 percent women in the verapamil studies and 45 percent women in the bumetanide studies). Studies of ranitidine for duodenal ulcer, a predominantly male disease, included about 75 percent males. Other indications for this drug, such as gastric ulcer, would be expected to have a different gender distribution. The two anti-cancer drugs in this survey were studied principally for exclusively male conditions, cancer of the prostate and testis.

#### B. The 1989 Survey

In an effort to avoid possible selection bias, all drugs approved in 1988 were surveyed; this time the sponsors provided the data. FDA asked them to provide data reflecting "the principal data base used for safety review" in the latest safety update and asked that phase 1 subjects/patients be excluded. Sponsors gave either data on all patients or only patients given the test drug; the estimates of gender exposure should not be greatly affected by this difference.

Table 2 shows the results of the 1989 survey for 12 of the 20 drugs approved in 1988. Because sponsors had little control over gender distributions in the small populations available for study, four orphan drugs were omitted from the survey (tiopronin for prevention of cystine stones; ethanolamine oleate for esophageal varices; ifosfamide, third-line therapy for testicular cancer; and mesna, a prophylactic agent for ifosfamide-induced hemorrhagic cystitis). Also omitted were three contrast agents for single dose uses (but these agents are in the 1992 GAO survey), and a topical product (oxiconazole cream) for which gender distribution was not available.

Again, the anti-inflammatory drug (diclofenac) was studied predominantly in women (more than two-thirds of the patients), as was nimodipine, for prevention of vascular spasm after subarachnoid hemorrhage, also a female-predominant condition. Pergolide, an anti-Parkinson's disease drug; astemizole, an antihistamine; and octreotide, a drug for symptoms of carcinoid tumor, were studied in about equal numbers of men and women. The studies of the cardiovascular drugs nicardipine (angina and hypertension) and carteolol (hypertension) included 59 and 67 percent men, respectively, reflecting the male gender predominance of angina, and perhaps hypertension, in the relatively young (two-thirds of the patients were under the age of 60) populations studied. Nizatidine and misoprostol were studied extensively in duodenal ulcer, a

predominantly male disease, with about 70 percent of patients being male, although approval of misoprostol was for a different claim. Cefotiam, an intravenous antibiotic, was studied mainly in elderly patients (65 percent over 60; 36 percent over 70); about two-thirds were male, for unclear reasons. The topicals were studied in a predominantly young population (about 90 percent under the age of 60), more often in males. Certain tinea infections (tinea cruris and tinea pedis) are more common in males, accounting for the high proportion (72 percent) of males in studies of naftifine. Why photoplex was studied somewhat more in males (63 percent) is not clear.

#### C. The GAO Survey

In 1992, the GAO analyzed the gender, age, and race distribution of all NDA's approved from January 1988 through June 1991. Data were collected by means of a questionnaire sent to the sponsor of each drug. The number of patients receiving the test drug during drug development, domestic studies only, was requested, and patients were broken down by gender, age (<15, 15 to 49, 50 to 64, >65), and race. The age distribution data allow a separate analysis of women of childbearing potential (taken here as women age 15 to 49). Data are available for 53 drugs (of 63 drugs approved during the 3 1/2-year period, 4 drugs intended for single gender use and 6 whose sponsors provided no, or no usable, questionnaire were omitted).

The results of the GAO survey are given in Tables 3A and 3B for phase 2 and 3 patients. The tables show gender distribution overall for the whole data base and for the 15 to 49 age group as well. For anti-inflammatory, anti-infective, central nervous system/anesthetic, topical, antihistamine, and cancer drugs, women constituted 40 percent or more of the patients studied, with occasional exceptions. The most striking exception is mefloquine, where only 11 percent of patients were women. This occurred because the primary studies of mefloquine for treatment of malaria were conducted in Thai military personnel. Women fairly consistently represented less than 40 percent of the patients for anti-ulcer drugs (duodenal ulcer, a male-predominant condition, was a principal disease studied for nizatidine, omeprazole, and misoprostol) but accounted for 55 percent of the patients in studies of dipentum, a drug for ulcerative colitis (ulcerative colitis is more common in women). Women consistently made up less than 40 percent of the populations studied for

cardiovascular disease, including populations used to evaluate agents used to diagnose or evaluate coronary artery disease, except for nimodipine (for spasm after subarachnoid bleed) and adenosine (for supraventricular tachycardia). For drugs to treat ventricular arrhythmias and angina, both commonly the result of coronary disease, the fraction of women ranged from 15 percent (bepridil, for unresponsive angina) to 20 to 30 percent (propafenone, moricizine, and indecainide), reflecting the lower rate of coronary artery disease in younger women and the fact that most patients in studies are under 60 years old. Studies of drugs for hypertension (carteolol, doxazosin, nicardipine,

isradipine, ramapril, pinacidil) included 27 to 42 percent women. In some cases, these drugs were being evaluated for other claims, such as angina or heart failure, which are male predominant in the age groups studied. For all of the antihypertensives, there were at least 290 women in the domestic data base, enough to detect significant gender differences in response.

Of interest is the observation that there was no tendency for women to represent a lower percentage of patients in the 15 to 49 age group than in the overall population. There is thus no suggestion in these data that the restriction on participation of women of childbearing potential in early trials carries over to later phase 2 or 3 trials.

#### D. Antidepressants

By chance, none of the surveys included any antidepressant drugs, a class of drug frequently cited as needing study in women, both because women are frequently given antidepressants and because of suspected interactions of the drugs with the menstrual cycle.

Table 4 shows gender participation for sertraline and paroxetine, the two most recently approved antidepressants, as well as two agents likely to be approved within the next year. Women, as expected based on past experience, represented 58 to 65 percent of the patients.

#### II. Tables

TABLE 1

| Drug                                   | n     | Percent of total |      |
|--|-------|------------------|------|
|  |       | Female           | Male |
| <b>Anti-inflammatory:</b>              |       |                  |      |
| Benoxaprofen (Oralflex) .....          | 3,446 | 64               | 36   |
| Ketoprofen (Orudis) .....              | 1,579 | 68               | 32   |
| Zomepirac (Zomax) .....                | 3,479 | 60               | 40   |
| <b>Cardiovascular:</b>                 |       |                  |      |
| Verapamil (Isoptin) .....              | 1,810 | 36               | 64   |
| Bumetanide (Bumex) .....               | 838   | 27               | 72   |
| <b>Hypnotic:</b>                       |       |                  |      |
| Triazolam (Halcion) .....              | 4,254 | 49               | 51   |
| <b>Antibiotic:</b>                     |       |                  |      |
| Cefoperazone (Cefobid) .....           | 1,958 | 52               | 48   |
| Netilmicin (Netromycin) .....          | 3,376 | 43               | 57   |
| <b>Anti-ulcer:</b>                     |       |                  |      |
| Ranitidine (Zantac) .....              | 193   | 23               | 77   |
| <b>Anti-cancer (prostate, testes):</b> |       |                  |      |
| Leuprolide (Lupron) .....              | 387   | 17               | 83   |
| Etoposide (Vepesid) .....              | 259   | 16               | 84   |

TABLE 2

| Drug                                   | n     | Percent of total |      |
|--|-------|------------------|------|
|  |       | Female           | Male |
| <b>Anti-inflammatory:</b>              |       |                  |      |
| Diclofenac (Voltaren) .....            | 8,175 | 69               | 31   |
| <b>Cardiovascular/cerebrovascular:</b> |       |                  |      |
| Nicardipine (Cardene) .....            | 2,962 | 41               | 59   |
| Carteolol (Cartrol) .....              | 1,536 | 33               | 67   |
| Nimodipine (Nimotop) .....             | 1,301 | 64               | 36   |
| <b>Anti-ulcer:</b>                     |       |                  |      |
| Nizatidine (Axx) .....                 | 2,063 | 31               | 69   |
| Misoprostol (Cytotec) .....            | 8,687 | 28               | 72   |
| <b>Antibiotic:</b>                     |       |                  |      |
| Cefotiam (Ceradon) .....               | 844   | 33               | 67   |
| <b>Anti-Parkinson:</b>                 |       |                  |      |
| Pergolide (Permax) .....               | 1,836 | 45               | 55   |
| <b>Antihistamine:</b>                  |       |                  |      |
| Astemizole (Hismanal) .....            | 1,356 | 48               | 52   |
| <b>Anti-carcinoid symptoms:</b>        |       |                  |      |
| Octreotide (Sandostatin) .....         | 455   | 49               | 51   |
| <b>Topical (tinea, sunscreen):</b>     |       |                  |      |
| Naftifine (Naftin) .....               | 452   | 28               | 72   |
| Photoplex .....                        | 227   | 37               | 63   |

TABLE 3A.— ALL AGES

| Drug                                      | n     | Percent of total |      |
|---|-------|------------------|------|
|   |       | Female           | Male |
| <b>Anti-inflammatory/Analgesic:</b>       |       |                  |      |
| Dezocine (Dalgan) .....                   | 1,417 | 60               | 40   |
| Diclofenac (Voltaren) .....               | 1,714 | 64               | 36   |
| Etidolac (Lodine) .....                   | 5,395 | 65               | 35   |
| Ketorolac (Toradol) .....                 | 1,248 | 64               | 36   |
| <b>Anti-infectives:</b>                   |       |                  |      |
| Ofloxacin (Floxin) .....                  | 3,585 | 56               | 44   |
| Cefmetazole (Zefazone) .....              | 2,769 | 67               | 33   |
| Cefixime (Suprax) .....                   | 1,859 | 60               | 40   |
| Fluconazole (Diflucan) .....              | 983   | 36               | 64   |
| Naftifine (Naftin) .....                  | 222   | 38               | 62   |
| Cefpiramide .....                         | 1,325 | 39               | 61   |
| Mefloquine (Lariam) .....                 | 1,319 | 11               | 89   |
| Oxiconazole (Oxistat) .....               | 886   | 35               | 65   |
| <b>Central Nervous System/Anesthetic:</b> |       |                  |      |
| Clomipramine (Anafranil) .....            | 3,826 | 54               | 46   |
| Propofol (Diprivan) .....                 | 696   | 48               | 52   |
| Clozapine (Clozaril) .....                | 581   | 37               | 63   |
| Estazolam (Prosan) .....                  | 1,243 | 50               | 50   |
| Pipecuronium (Arduan) .....               | 580   | 52               | 48   |
| Doxacurium (Nuromax) .....                | 987   | 39               | 61   |
| Pergolide (Permax) .....                  | 1,667 | 43               | 57   |
| <b>Cardiovascular:</b>                    |       |                  |      |
| Nimodipine (Nimotop) .....                | 343   | 69               | 31   |
| Adenosine (Adenocard) .....               | 109   | 48               | 52   |
| Doxazosin (Cardura) .....                 | 698   | 42               | 58   |
| Pinacidil (Pindac) .....                  | 1,774 | 36               | 64   |
| Nicardipine (Cardene) .....               | 1,915 | 37               | 63   |
| Benazepril (Lotensin) .....               | 2,130 | 32               | 68   |
| Isradipine (Dynacirc) .....               | 1,842 | 27               | 73   |
| Propafenone (Rhythmol) .....              | 3,328 | 30               | 70   |
| Ramapril (Altace) .....                   | 1,723 | 33               | 67   |
| Carteolol (Cartrol) .....                 | 1,253 | 28               | 72   |
| Moricizine (Ethmozine) .....              | 1,017 | 21               | 79   |
| Indecainide (Decabid) .....               | 761   | 23               | 77   |
| Bepiridil (Vascor) .....                  | 884   | 15               | 85   |
| <b>Cancer:</b>                            |       |                  |      |
| Octreotide (Sandostatin) .....            | 569   | 38               | 62   |
| Carboplatin (Paraplatin) .....            | 2,214 | 77               | 23   |
| Lavamisole (Ergamisol) .....              | 1,038 | 48               | 52   |
| Ondansetron (Zofran) .....                | 939   | 29               | 71   |
| <b>Diagnostics:</b>                       |       |                  |      |
| Technescan Mag 3 .....                    | 160   | 43               | 57   |
| Ioversol (Optiray) .....                  | 1,101 | 45               | 55   |
| Gadopentetate (Magnevist) .....           | 410   | 41               | 59   |
| TC-99M Sestamibi (Cardolyte) .....        | 1,102 | 29               | 71   |
| TC-99M Exametazime (Ceretek) .....        | 202   | 28               | 72   |
| Iotalan (Osmovist) .....                  | 545   | 31               | 69   |
| <b>Topicals:</b>                          |       |                  |      |
| Photoplex .....                           | 371   | 40               | 60   |
| Fluticasone (Cutivate) .....              | 730   | 42               | 58   |
| Halobetasol (Ultravate) .....             | 662   | 46               | 54   |
| Metipranolol (Optipranolol) .....         | 465   | 53               | 47   |
| Cefotiam (Ceredon) .....                  | 715   | 34               | 66   |
| Rev-Eyes .....                            | 646   | 47               | 53   |
| <b>Gastrointestinal 1:</b>                |       |                  |      |
| Olsalazine (Dipentum) .....               | 98    | 55               | 45   |
| Nizatidine (Axid) .....                   | 3,854 | 35               | 65   |
| Misoprostol (Cytotec) .....               | 1,917 | 37               | 63   |
| Omeprazole (Losec) .....                  | 2,189 | 26               | 74   |
| <b>Antihistamine:</b>                     |       |                  |      |
| Astemizole (Hismanal) .....               | 979   | 41               | 59   |

TABLE 3B.—AGES 15 TO 49

| Drug                                      | n     | Percent of total |      |
|---|-------|------------------|------|
|   |       | Female           | Male |
| <b>Anti-inflammatory/Analgesic:</b>       |       |                  |      |
| Dezocine (Dalgan) .....                   | 1,142 | 61               | 39   |
| Diclofenac (Voltaren) .....               | 577   | 55               | 45   |
| Etodolac (Lodine) .....                   | 3,155 | 65               | 35   |
| Ketorolac (Toradol) .....                 | NA    | NA               | NA   |
| <b>Anti-infectives:</b>                   |       |                  |      |
| Ofloxacin (Floxin) .....                  | 2,890 | 60               | 40   |
| Cefmetazole (Zefazone) .....              | 1,621 | 72               | 28   |
| Cefdinir (Suprax) .....                   | 879   | 70               | 30   |
| Fluconazole (Diflucan) .....              | 759   | 64               | 36   |
| Naftifine (Nafin) .....                   | 151   | 36               | 64   |
| Cefpiramide .....                         | 362   | 44               | 56   |
| Mefloquine (Lariam) .....                 | 1,189 | 9                | 91   |
| Oxiconazole (Oxistat) .....               | NA    | NA               | NA   |
| <b>Central Nervous System/Anesthetic:</b> |       |                  |      |
| Clozapine (Clozaril) .....                | 3,277 | 55               | 45   |
| Propofol (Diprivan) .....                 | 514   | 58               | 42   |
| Clozapine (Clozaril) .....                | 510   | 35               | 65   |
| Estazolam (Prosan) .....                  | 784   | 42               | 58   |
| Pipecuronium (Arduan) .....               | 263   | 57               | 43   |
| Doxacurium (Nuromax) .....                | 623   | 37               | 63   |
| Pergolide (Permax) .....                  | 357   | 63               | 37   |
| <b>Cardiovascular:</b>                    |       |                  |      |
| Nimodipine (Nimotop) .....                | 195   | 63               | 37   |
| Adenosine (Adenocard) .....               | 62    | 43               | 57   |
| Doxazosin (Cardura) .....                 | 62    | 43               | 57   |
| Pinacidil (Pindac) .....                  | 682   | 37               | 63   |
| Nicardipine (Cardene) .....               | 596   | 39               | 61   |
| Benazepril (Lotensin) .....               | 602   | 27               | 73   |
| Isradipine (Dynacirc) .....               | 692   | 27               | 73   |
| Propafenone (Rhythmol) .....              | 604   | 46               | 54   |
| Ramapril (Altace) .....                   | 622   | 23               | 77   |
| Carteolol (Cartrol) .....                 | 410   | 24               | 76   |
| Moricizine (Ethmozine) .....              | 193   | 31               | 69   |
| Indecainide (Decabid) .....               | 94    | 44               | 56   |
| Bepidil (Vascor) .....                    | 93    | 13               | 8    |
| <b>Cancer:</b>                            |       |                  |      |
| Octreotide (Sandostatin) .....            | 391   | 34               | 66   |
| Carboplatin (Paraplatin) .....            | 563   | 70               | 30   |
| Levamisole (Ergamisol) .....              | 195   | 50               | 50   |
| Ondansetron (Zofran) .....                | 288   | 19               | 81   |
| <b>Diagnostics:</b>                       |       |                  |      |
| Technescan Mag 3 .....                    | 101   | 47               | 53   |
| Ioversol (Optiray) .....                  | 370   | 51               | 49   |
| Gadopentetate (Magnevist) .....           | 183   | 29               | 71   |
| TC-99m Sestamibi (Cardolyte) .....        | 402   | 34               | 66   |
| TC-99m Exametazine (Ceretek) .....        | 26    | 50               | 50   |
| Iotalan (Osmovist) .....                  | 327   | 34               | 66   |
| <b>Topicals:</b>                          |       |                  |      |
| Photoplex .....                           | 296   | 34               | 66   |
| Fluticasone (Cutivate) .....              | 405   | 45               | 55   |
| Halobetasol (Ultravate) .....             | 360   | 45               | 55   |
| Metipranolol (Optipranolol) .....         | 70    | 41               | 59   |
| Cefotiam (Ceradon) .....                  | NA    | NA               | NA   |
| Rev-Eyes .....                            | 531   | 47               | 53   |
| <b>Gastrointestinal:</b>                  |       |                  |      |
| Olsalazine (Dipentum) .....               | 72    | 60               | 40   |
| Nizatidine (Axid) .....                   | 2,302 | 32               | 68   |
| Misoprostol (Cytotec) .....               | 945   | 33               | 67   |
| Omeprazole (Loec) .....                   | NA    | NA               | NA   |
| <b>Antihistamine:</b>                     |       |                  |      |
| Astemizole (Hiemanal) .....               | NA    | NA               | NA   |

TABLE 4.—ALL AGES

| Drug                     | Date | n     | Percent of total |      |
|--------------------------|------|-------|------------------|------|
|                          |      |       | Female           | Male |
| Sertaline (Zoloft) ..... | 1991 | 2,979 | 58               | 42   |

TABLE 4.—ALL AGES—Continued

| Drug                    | Date | n     | Percent of total |      |
|-------------------------|------|-------|------------------|------|
|                         |      |       | Female           | Male |
| Paroxetine (Paxl) ..... | 1992 | 4,126 | 65               | 35   |
| Pending No. 1 .....     | NA   | 2,181 | 62               | 38   |
| Pending No. 2 .....     | NA   | 2,256 | 62               | 38   |

Dated: July 19, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 93-17411 Filed 7-21-93; 8:45 am]

BILLING CODE 4160-01-P

# Section 8

## FDA Review of New Drug Products

# Benefit Vs. Risk: How FDA Approves New Drugs

by Dixie Farley

Under current law, all new drugs need proof that they are effective, as well as safe, before they can be approved for marketing. But it's important to realize that no drug is absolutely safe. There is always some risk of an adverse reaction. It's when the benefits outweigh the risks that the Food and Drug Administration considers a drug safe enough to approve.

In fact, it was little more than 30 years ago that U.S. drug law first embraced the idea of risk vs. benefit that is now the key to new drug approval. Providing evidence of safety before marketing was first required by the Federal Food, Drug, and Cosmetic (FD&C) Act in 1938, but not until the Kefauver-Harris Drug Amendments of 1962 did firms also have to show a drug's effectiveness before marketing.

Before any drug gets on the market today, FDA decides—as quickly as a thorough evaluation allows—whether the studies submitted by the drug's sponsor (usually the manufacturer) show it to be safe *and effective* for its intended use. Here's what goes into those decisions.

"Take AZT, for example," says Robert Temple, M.D., director of the Office of Drug Evaluation I, in FDA's Center for Drug Evaluation and Research. (AZT stands for azidothymidine, the former generic name of the drug now known generally as zidovudine and marketed as Retrovir to treat AIDS.) "It has significant toxicity. If you weren't quite sure it had a benefit, it would be hard to describe it as 'safe.' But we know, from well-controlled studies, that it has a benefit. In the first large clinical study with the drug, there were 19 deaths in patients taking a



placebo [an inactive substance], but only one death in those on AZT."

Zidovudine was approved in March 1987 in a record 107 days. But no corners were cut. Indeed, FDA expended an estimated eight staff years at a cost of \$600,000 on zidovudine's evaluation. That the review was so rapid was due largely to the fact that FDA was involved with the drug every step along the way from the start of clinical studies in AIDS patients.

FDA has in a number of ways taken steps to make urgently needed drugs available sooner. These are drugs for treating serious or life-threatening diseases that have no good treatment.

Under the accelerated approval rule, the agency can rely as a basis for drug approval on a reasonable "surrogate" endpoint—that is, an effect of a drug on a marker of the disease, rather than an actual effect on survival or illness. (An example

of a marker would be CD4 cell counts, used to measure the strength of the immune system. Usually such a surrogate can be assessed much sooner than such an endpoint as survival.) In accelerated approval, FDA approves the drug on condition that the sponsor study the actual clinical benefit of the drug.

According to FDA Commissioner David A. Kessler, M.D., "We cannot wait for all the evidence when people are suffering and dying from a devastating disease. But, we must ensure that all the evidence we need eventually does get collected."

## Promising Experimental Drugs

Today's policies also allow broader use of some investigational drugs even before they are approved for marketing.

These new policies include the Treatment IND (IND stands for investigational new drug application) and the parallel track mechanism. (See "A Drug Review Glossary," page 28, and "FDA Finds New Ways to Speed Treatments to Patients," page 19.)

Both allow promising drugs, not yet approved for marketing, to be used in "expanded access" protocols—relatively unrestricted studies in which the intent is not only to learn more about the drug, especially about its safety, but also to provide treatment for people with no real alternative. But these expanded access protocols also require researchers to formally investigate the drug in well-controlled studies and to supply some evidence that the drug is likely to be helpful.

"This expanded access does not represent just 'giving the drug out,'" Temple

says. "The sponsor has the obligation to develop the drug properly, so we will know whether it really is useful."

FDA participates actively in the drug development process, seeking to provide clear standards and expectations. Sponsors are encouraged to meet with FDA, Temple says, at an "end of phase 2 conference" before carrying out the large-scale controlled clinical trials. (For information about the various phases of drug study, see "Testing Drugs in People," page 6.) At this conference, FDA gives advice about the design of the sponsor's study plan to ensure that the trials will be acceptable.

As Temple puts it: "We try to find and eliminate flaws in the individual studies and overall development plan that we know will give us trouble later on in the NDA review. We don't want people to carry out a large study that has no chance of being considered adequate and well-controlled."

FDA also provides advice, he says, in the form of guidelines on how to study particular classes of drugs and on how to submit and analyze data in a marketing application.

In addition, to ensure that institutional review boards meet FDA's rules for the protection of the rights and welfare of research subjects, the agency routinely inspects the boards every five years. "We may go more often, if there are problems," says Frances O. Kelsey, Ph.D., M.D., director of FDA's division of scientific investigations.

FDA routinely inspects animal laboratories every two years, or more often, Kelsey says, "if a review division has a question about a specific animal study."

### Reviewing NDAs

The documentation required in an NDA is supposed to tell the drug's whole story, including: what happened during the clinical tests; how the drug is constituted—its components and composition; results of the animal studies; how the drug behaves in the body; and how it's manufactured, processed and packaged, especially the quality controls. FDA also requires samples of the drug and its labels.

Full reports of a drug's studies must be

## The Review Team

The members of the FDA review team simultaneously apply their special technical expertise to the review of an NDA:

- Chemists focus on how the drug is made, and whether the manufacturing, controls and packaging are adequate to ensure the identity, strength, quality, and purity of the product.
- Pharmacologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies.
- Physicians evaluate the results of the clinical tests—including the drug's adverse as well as therapeutic effects—and whether the proposed labeling accurately reflects the effects of the drug.
- Pharmacokineticists 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.
- Statisticians evaluate the designs for each controlled study and the analyses and conclusions of safety and effectiveness based on the study data.
- Microbiologists, with others, evaluate the data on anti-infectives (antibiotics, antivirals and antifungals). These drugs differ from others in that they're intended to affect the workings of microbes instead of patients. Reviewers need to know how the drug acts on these microorganisms, which ones it affects, any resistance to the drug, and clinical laboratory methods needed to evaluate the drug's effectiveness. Microbiologists also are concerned with ensuring that injectable drugs are free of organisms. ■

submitted so that FDA can evaluate the data. The controlled clinical trials are especially important because they provide the only basis, under law, for demonstrating effectiveness. They answer the question, "Does this drug work for the proposed use?" The whole data bank is used to look for adverse effects. From analyses of the data, FDA reviewers assess the benefit-to-risk relationship. (See "The Review Team.")

The human studies also generate information that will be in the drug's professional labeling, the guidance approved by FDA on how to use the drug. This is the package insert that accompanies a drug in all shipments to physicians and pharmacies.

Whenever an NDA is submitted to FDA, the agency lists it in a computer database, and the division of scientific investigations learns of that NDA by routinely checking the database.

According to Alan Lisook, M.D., who works in the division with Kelsey, "After determining the important studies supporting approval, we send assignments to the field to make on-site inspections of the investigators who did the work, to verify that it was valid." The division may also participate in the inspections.

Since more and more foreign studies are being accepted as primary evidence for drug approval, the agency has been doing a larger number of foreign inspections, Lisook says, "the same as we do here. We compare the data submitted with those data available on site." The sponsor makes sure FDA has access to the research, he says.

If FDA's evaluation of studies reveals major deficiencies, substantially more work by the sponsor may be needed, ranging from further analyses to the conduct of new studies—in either case thereby extending the evaluation time and delaying approval.

"It's particularly important," Temple says, "that sponsors use the opportunities FDA offers during the IND to discuss the critical studies and overall plans, so that they know what we expect with respect to study design, conduct and analysis. This can greatly reduce the chance that the application will 'recycle.'"

FDA has undertaken various ways to re-



duce drug review time, which during the past several years has averaged (median) about two years, down from about two-and-one-half years.

For example, funds provided by the Prescription Drug User Fee Act of 1992 (see "User Fees to Fund Faster Reviews," page 50) allow the agency to hire several hundred additional reviewers and support staff and expedite its move to accepting computerized NDAs.

Writing to Congress in September 1992, Commissioner Kessler listed FDA's goals for using the additional resources, including the following five-year goals for review and approval time frames for new prescription drugs:

- Within six months of an NDA's submission date, review and act on complete applications for "priority" drugs (those appearing to represent an advance over available therapy).
- Within 12 months, review and act on NDAs for "standard" drugs (those appearing to have therapeutic qualities similar to those of an already marketed drug).  
(In both classifications, major amendments received within three months of the action due date extend a time frame three months.)
- Within six months, review and act on supplements not requiring clinical data review.
- Within 12 months, review and act on supplements requiring clinical data review.
- Within six months, review and act on complete applications resubmitted after receipt of a "not approvable" letter (which describes deficiencies that preclude approval unless corrected).

### Priorities

The order in which applications are looked at is determined with the aid of a classification system. (See "Review Priorities.") The idea is to give priority to drugs with the greatest potential benefit. For example, all AIDS drugs receive the highest priority, and all drugs that offer a significant medical advance over existing therapies for any disease are considered "priority drugs."

Which of FDA's review staffs gets an NDA depends on the drug. For example, cancer treatments go to the division of

## Review Priorities

FDA classifies investigational new drug applications (INDs) and new drug applications (NDAs) to assign review priority on the basis of the drug's chemical type and potential benefit:

### Chemical Type

- 1. New molecular entity, or NME:** An active ingredient that has never been marketed in this country.
- 2. New derivative:** A chemical derived from an active ingredient already marketed (a "parent" drug).
- 3. New formulation:** A new dosage form or new formulation of an active ingredient already on the market.
- 4. New combination:** A drug that contains two or more compounds, the combination of which has not been marketed together in a product.
- 5. Already marketed drug product, but a new manufacturer:** A product that duplicates another firm's already marketed drug product: same active ingredient, formulation, or combination.
- 6. Already marketed drug product, but a new use:** A new use for a drug product already marketed by a different firm.

### Treatment Potential

- P. Priority review drug:** A drug that

appears to represent an advance over available therapy.

**S. Standard review drug:** A drug that appears to have therapeutic qualities similar to those of an already marketed drug.

### Other Designations

(may apply simultaneously)

**AA. AIDS drug:** A drug indicated for treating AIDS or other HIV-related disease.

**E. Subpart E drug:** A drug developed or evaluated under special procedures for drugs to treat life-threatening or severely debilitating illnesses. (The name refers to Title 21 of the *Code of Federal Regulations*, Part 312, Subpart E, which governs this classification. Also see, "The Evolution of U.S. Drug Law," page 26.)

**V. Designated orphan drug:** A drug for which the sponsor received orphan designation under the Orphan Drug Act. Such a sponsor is eligible for tax credits and exclusive marketing rights for the drug. ■

oncology and pulmonary drug products, and contraceptive drugs go to the division of metabolism and endocrine drug products. Generic drugs go to a different office, the Office of Generic Drugs.

FDA frequently seeks advice from its 17 standing advisory committees on drugs. (See "Getting Outside Advice for 'Close Calls,'" page 30.) This is especially true when an approval decision is a "close call."

To be sure approval decisions reflect the most recent safety data, FDA requires safety updates four months after the NDA

is submitted, again after it sends the firm an "approvable letter," and at other times if necessary. Updates must report new adverse reactions and important changes in the frequency or severity of effects that are known.

After FDA primary reviewers finish their evaluation, additional review is given by supervisory personnel. "In general," says the agency's Leah Ripper, "office directors take final action on new molecular entities, switches from prescription to OTC status, and other impor-

## A Special System for OTC Drugs

FDA has always applied the same standards to nonprescription drugs as it does to prescription ones whenever proposed over-the-counter (OTC) products meet the criteria for "new drugs." (See "New Drug" in glossary.) In 1966, FDA contracted for a review of the effectiveness of all new drugs approved solely on the basis of their safety since passage of the 1938 Federal Food, Drug, and Cosmetic Act. Special attention soon became focused on OTC drugs: Of the 512 OTC drug products evaluated, 75 percent lacked substantial evidence of effectiveness.

That was when FDA decided it was time to tackle a broader review of OTC drugs—no small job, considering that more than 300,000 products were on the market. Those products, however, involved only about 700 active ingredients. It didn't take long for FDA planners to decide on a strategy: Classify the drugs by treatment category (antacids, laxatives, and so on) and evaluate the ingredients. So, rather than review thousands of, say, individual antacid products, FDA evaluated the far fewer active ingredients found in them—for example, aluminum hydroxide and magnesium carbonate.

That review, under FDA's Office of OTC Drug Evaluation, is actually a three-phase process of producing a final regulation (called a monograph) to establish standards for each product-treatment category.

- The first phase, conducted from 1972 to 1981, was a review by panels of outside advisors who determined whether ingredients could be generally recognized as safe and effective for self-use. FDA published the reports in the *Federal Register*.
- The second phase—still continuing—is FDA's review of the panel's findings on the ingredients. In these reviews, FDA takes into account public comments and any new data. The conclusions are published as a proposed rule (or tentative final monograph).
- After considering any new information and objections, FDA publishes the final regulation, or monograph.

An OTC drug product doesn't need specific approval before marketing so long as it meets its category's standards.

Sometimes an approved prescription drug is deemed safe enough for self-use and is switched to OTC status.

A number of ingredients were taken off the market as a result of the advisory panels' OTC drug review. Among them were:

- camphorated oil, a liniment often accidentally ingested with frequently toxic results
- hexachlorophene, once common in deodorant soaps, but now available only by prescription for special antimicrobial purposes because it may damage the central nervous system
- tribromsalan, removed from drugs and cosmetics because it was found to make skin extra sensitive to light
- zirconium, still safe in most forms of antiperspirants, but removed from aerosols because of concern it could cause lung nodules.

For lack of proof of effectiveness, FDA banned some 200 ingredients in November 1990, including products used to treat problems ranging from acne and dandruff to diarrhea and pain. In May 1993, the agency banned several hundred more, including products for such problems as pain, digestive upsets, menstrual symptoms, and skin rashes. ■

## The Evolution of U.S. Drug Law

FDA acts as public health protector by ensuring that all drugs on the market are safe and effective. *Authority to do this* comes from the 1938 Federal Food, Drug, and Cosmetic Act, a law that has undergone many changes over the years, just as it changed earlier drug regulation. Some major milestones in the evolution of U.S. drug law are:

- **Food and Drugs Act (1906):** This first drug law required only that drugs meet standards of strength and purity. The burden of proof was on FDA to show that a drug's labeling was false and fraudulent before it could be taken off the market.
- **Federal Food, Drug, and Cosmetic Act (1938):** A bill was introduced into the Senate in 1933 to completely revise the 1906 drug law—widely recognized then as being obsolete. But congressional action was stalled. It took a tragedy in which 107 people died from a poisonous ingredient in "Elixir Sulfanilamide" to prompt passage of revised legislation that, for the first time, required a manufacturer to prove the safety of a drug before it could be marketed. Among other provisions, the law also eliminated the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases, provided for tolerances for unavoidable poisonous substances, authorized factory inspections, and added the remedy of court injunction to previous remedies of seizure and prosecution.
- **Durham-Humphrey Amendment (1951):** Until this law, there was no requirement that any drug be labeled for sale by prescription only. The amendment defined prescription drugs as those unsafe for self-medication and which should therefore be used only under a doctor's supervision.
- **Kefauver-Harris Drug Amendments (1962):** News reports about the role of FDA medical officer Frances O. Kelsey, Ph.D., M.D., in keeping the drug thalidomide off the U.S. market aroused public interest in drug regulation. Thalidomide had been associated with the birth of thou-

sands of malformed babies in Western Europe. In October 1962, Congress passed these amendments to tighten control over drugs. Before marketing a drug, firms now had to prove not only safety, but also effectiveness for the product's intended use. The requirement was applied retroactively to 1938, when the FD&C Act was passed. (Pre-1938 drugs were "grandfathered"—allowed to be sold because they were generally recognized as safe and effective, provided no evidence to the contrary developed.) To help implement the amendments, FDA contracted with the National Academy of Sciences/National Research Council to review the efficacy of drugs approved solely on the basis of safety since 1938. Firms were required to send adverse reaction reports to FDA, and drug advertising in medical journals was required to provide complete information to doctors—the risks as well as the benefits. The amendments also required that informed consent be obtained from study subjects.

- **Orphan Drug Act (1983):** "Orphans" are drugs and other products for treating rare diseases. They may offer little or no profit to the manufacturer, but may benefit people with the rare diseases. To foster orphan product development, this law allows drug companies to take tax deductions for about three-quarters of the cost of their clinical studies. Firms also are given exclusive marketing rights for seven years for any orphan products that are approved.
- **Drug Price Competition and Patent Term Restoration Act (1984):** This law expands the number of drugs suitable for an abbreviated new drug application, or ANDA. ANDAs make it less costly and time-consuming for generics, which are often sold at lower prices than brand-name drugs, to reach the market. "Patent Term Restoration" refers to the 17 years of legal protection given a firm for each drug patent. Some of that time allowance is used while the drug goes through the approval process, so this law allows restoration of up to five years of lost patent time.
- **Generic Drug Enforcement Act (1992):** This law imposes debarment and other remedies for criminal convictions based on activities relating to the approval of ANDAs.
- **Prescription Drug User Fee Act (1992):** Manufacturers must now pay user

fees for certain new drug applications and supplements, an annual establishment fee, and annual product fees. Using these funds, FDA plans to hire some 700 new staff by the end of fiscal year 1997, when the act will expire unless renewed by Congress.

Though not involving changes in law, the following changes in drug regulations are noteworthy:

- **Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards (1981):** These standards clarify FDA requirements for informed consent and provide protection of the rights and welfare of human subjects involved in research within FDA's jurisdiction. They also establish standards governing the composition, operation and responsibility of institutional review boards that review clinical investigations. In 1991, other federal agencies adopted a revised version of these regulations, resulting in a "common federal rule."
- **Revision of New Drug Application Regulations (1985):** These changes provide for safety reports after an application for a new drug is submitted, more focused and better organized data, use of summaries and tables for easier review, earlier problem solving, and allowance of approval on the basis of foreign studies alone. It also strengthens the monitoring of adverse reactions from marketed drugs.
- **Revision of Investigational New Drug Application Regulations (1987):** The revision encourages problem-solving meetings with FDA, requires deadlines in safety reports, and increases sponsor control over initial human test design so long as subjects face no unreasonable, significant risks.
- **Treatment Use of Investigational New Drugs (1987):** (See "A Drug Review Glossary," page 28.)
- **Procedures for Subpart E Drugs (1988):** Intended to speed availability of new drugs to patients with life-threatening or severely debilitating illnesses, these procedures encourage sponsors to work with FDA early on to develop the most time-efficient, well-designed animal and human studies. FDA expects this cooperative effort will allow approval after phase 2 clinical trials. (For information about the



*The "Elixir Sulfanilamide" tragedy of 1937 ensured enactment the following year of the Federal Food, Drug, and Cosmetic Act. More than 100 people died from using the untested, poisonous new drug formulation, but FDA had legal authority to bring only a trivial charge of misbranding against the manufacturer. The product was labeled an "elixir," which implied it was an alcohol solution; actually, it was a diethylene glycol solution. If the term "solution" had been used instead, no charge of breaking the law could have been made.*

various phases of drug study, see "Testing Drugs in People," page 6.) "Subpart E" refers to the section of the *Code of Federal Regulations* governing this new drug classification.

- **Accelerated Approval (1992):** See "A Drug Review Glossary," page 28.
- **Parallel-Track Mechanism (1992):** See "A Drug Review Glossary," page 28. ■

# A Drug Review Glossary

**Abbreviated New Drug Application, or ANDA:** A simplified submission permitted for a duplicate of an already approved drug. ANDAs are for products with the same or very closely related active ingredients, dosage form, strength, administration route, use, and labeling as a product that has already been shown to be safe and effective. An ANDA includes all the information on chemistry and manufacturing controls found in a new drug application (NDA), but does not have to include data from studies in animals and humans. It must, however, contain evidence that the duplicate drug is bioequivalent (see "Bioequivalence") to the previously approved drug.

**Accelerated Approval:** A highly specialized mechanism intended to speed approval of drugs promising significant benefit over existing therapy for serious or life-threatening illnesses. It incorporates elements aimed at making sure that rapid review and approval is balanced by safeguards to protect both the public health and the integrity of the regulatory process. This mechanism may be used when approval can be reliably based on evidence of a drug's effect on a "surrogate endpoint" (see "Surrogate Endpoint"), or when FDA determines an effective drug can be used safely only under restricted distribution or use. Usually, such a surrogate can be assessed much sooner than such an endpoint as survival. In accelerated approval, FDA approves the drug on condition that the sponsor study the actual clinical benefit of the drug.

**Action Letter:** An official communication from FDA to an NDA sponsor that informs of a decision by the agency. An approval letter allows commercial mar-

keting of the product. An *approvable* letter lists minor issues to be resolved before approval can be given. A *not approvable letter* describes important deficiencies that preclude approval unless corrected.

**Advisory Committee:** A panel of outside experts convened periodically to advise FDA on safety and efficacy issues about drugs and other FDA-regulated products. FDA isn't bound to take committee recommendations, but usually does.

**Amendment to an NDA:** A submission to change or add information to an NDA or supplement not yet approved.

**Bioavailability:** Rate and extent to which a drug is absorbed or is otherwise available to the treatment site in the body.

**Bioequivalence:** Scientific basis on which generic and brand-name drugs are compared. To be considered bioequivalent, the bioavailability of two products must not differ significantly when the two products are given in studies at the same dosage under similar conditions. Some drugs, however, are intended to have a different absorption rate. FDA may consider a product bioequivalent to a second product with a different rate of absorption if the difference is noted in the labeling and doesn't affect the drug's safety or effectiveness or change the drug's effects in any medically significant way.

**Clinical Studies:** Human studies designed to distinguish a drug's effect from other influences—for example, a spontaneous change in disease progression or in the effect of a placebo (an inactive substance that looks like the test drug). Such studies conducted in this country must be under an approved IND (see "Investigational New Drug Application"), under the guidance of an institutional review board, and in accord with FDA rules on human studies and informed consent of participants.

**Drug Product:** The finished dosage form (tablet, capsule, etc.) that contains a drug substance—generally, but not necessarily,

in association with other active or inactive ingredients.

**Drug Substance:** The active ingredient intended to diagnose, treat, cure, or prevent disease or affect the structure or function of the body, excluding other inactive substances used in the drug product.

**Effectiveness:** The desired measure of a drug's influence on a disease condition. Effectiveness must be proven by substantial evidence consisting of adequate and well-controlled investigations, including human studies by qualified experts, that prove the drug will have the effect claimed in its labeling.

**Investigational New Drug Application, or IND:** An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

**New Drug:** A drug first investigated or proposed for marketing after 1938 (when the Federal Food, Drug, and Cosmetic Act was passed)—that is, the drug was *not* generally recognized as safe and effective before that date.

**New Drug Application, or NDA:** An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for FDA review—including chemistry, pharmacology, medical, biopharmaceutics, statistics, and, for anti-infectives, microbiology.

**Parallel Track Mechanism:** A U.S. Public Health Service policy that makes promising investigational drugs for AIDS and other HIV-related diseases more widely

available under "parallel track" protocols while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out. The system established by this policy is designed to make the drugs more widely available to patients with these illnesses who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.

**Pharmacology:** The science that deals with the effect of drugs on living organisms.

**Post-Marketing Surveillance:** FDA's ongoing safety monitoring of marketed drugs.

**Preclinical Studies:** Studies that test a drug on animals and other nonhuman test systems. They must comply with FDA's good laboratory practices. Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies). Also, because animals have a much shorter lifespan than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on offspring.

**Raw Data:** Researcher's records of patients, such as patient charts, hospital records, x-rays, and attending physician's notes. These records may or may not accompany an NDA, but must be kept in the researcher's file. FDA may request their submission or may audit them at the researcher's office.

**Safety:** No drug is completely safe or without the potential for side effects. Before a drug may be approved for marketing, the law requires the submission of results of tests adequate to show the drug is safe under the conditions of use in the proposed labeling. Thus, "safety" is determined case by case and reflects the drug's risk-vs.-benefit relationship.

**Safety Update Reports:** Reports that an NDA sponsor must submit to FDA about any new safety information that may affect the use for which the drug will be approved, or draft labeling statements about contraindications, warnings, precautions, and adverse reactions. Safety update reports are required four months after the application is submitted, after the applicant receives an approvable letter, and at other times upon FDA request.

**Supplement:** A marketing application submitted for changes in a product that already has an approved NDA. FDA must approve all important NDA changes (in packaging or ingredients, for instance) to ensure that the conditions originally set for the product are not adversely affected.

**Surrogate Endpoint:** A laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. An example would be CD4 cell counts, used to measure the strength of the immune system.

**Treatment IND:** A mechanism that allows promising investigational drugs to be used in "expanded access" protocols—relatively unrestricted studies in which the intent is both to learn more about the drugs, especially their safety, and to provide treatment for people with immediately life-threatening or otherwise serious diseases for which there is no real alternative. But these expanded access protocols also require researchers to formally investigate the drugs in well-controlled studies and to supply some evidence that the drugs are likely to be helpful. The drugs cannot expose patients to unreasonable risk.

**User Fees:** Charges to drug firms for certain NDAs, drug products, and manufacturing establishments. FDA uses these fees to hire more application reviewers and to accelerate reviews through the use of computer technology. ■

tant actions, such as a major new use of a drug. Other approval decisions are made at the division level." Ripper is special assistant to the director of the Office of Drug Evaluation II.

### Final Actions

In the final analysis, FDA's decision whether to approve a new drug for marketing boils down to two questions:

- Do the results of well-controlled studies provide substantial evidence of effectiveness?
- Do the results show the product is safe under the conditions of use in the proposed labeling? Safe, in this context, means that the benefits of the drug appear to outweigh its risks.

When the review is complete, FDA writes to the applicant to say the drug is either approved for marketing, is "approvable," provided minor changes are made, or is not approvable because of major problems. In the last case, the applicant can then amend or withdraw the NDA or ask for a hearing. Once its NDA is approved, a drug is on the market as soon as the firm gets its production and distribution systems going.

As reflected by the innovations of accelerated approval, the Treatment IND, and the parallel track mechanism, the need for effective treatments for serious illnesses has been so great that it has called for changing the drug approval process.

"The riskiest thing we can do when it comes to life-threatening diseases," says Commissioner Kessler, "is to be unwilling to take risks. But when we take risks, we have to follow through."

Thus, while change is inevitable and often desirable, there are some constants at FDA. Safety and effectiveness, risk vs. benefit, remain the pivotal issues in FDA drug review. ■

*Dixie Farley is a staff writer for FDA Consumer.*

# Section 9

## Speeding Availability and Approval of Promising Therapies

# *Experimental Drugs for the Desperately Ill*

by Frank E. Young, M.D., Ph.D.

When I was directing the medical center at the University of Rochester in New York, people occasionally would come to me who had a spouse or child suffering from some untreatable disease or who were themselves desperately ill. They'd ask my help in obtaining some promising but still experimental treatment. Sometimes they had heard that the treatment—usually a new drug—was being tested at the National Institutes of Health in Bethesda, Md. "But I don't have the money to move myself and my family there," they'd say. "If I can't get this treatment, there's no other hope. Dr. Young, is there anything you can do?"

I'd have to try to explain that the controlled clinical trials such as were being done at NIH were necessary, even though they took precious time. If they proved successful, in another year or two the drug could be approved by FDA and I could obtain it for my patients. "But Dr. Young," they'd reply, "my wife will be dead in six months."

The memory of such anguish and hopelessness still haunts me. But now, a regulation, issued May 22, 1987, by FDA holds the promise of hope for many of those desperately ill patients and their loved ones. This rule acknowledges that there are times when a new experimental drug shows such promise—especially when it is for a life-threatening condition for which there is no other hope—that it seems unethical and even cruel to withhold it from desperate patients.

It is a fine line that public health officials must walk to protect the public from unsafe or useless drugs while allowing them access to some as yet unproven treatment that may be their last hope. The terrible disease AIDS has brought this issue to public scrutiny as never before.

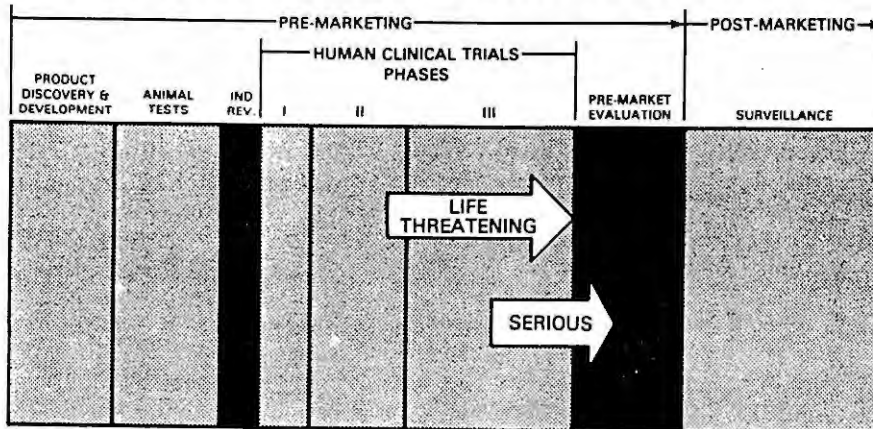
FDA does have the discretion to allow broader use of important experimental drugs when studies indicate some real promise, even though the final verdict is not yet in. In fact, for more than a decade, FDA has allowed thousands of patients access to promising new drugs that were still in the experimental stage of development. Most notably, experimental drugs called beta blockers, used to treat certain heart conditions, were made available in the mid-1970s to patients who couldn't tolerate other drugs. Many beta blockers are now approved as safe and effective treatments, due in part to information reported by the doctors who were using them experimentally to treat their patients.

More recently, after early studies showed very promising results, it took FDA only one week to approve broader use of an experimental drug for AIDS patients called zidovudine (formerly known as azidothymidine or AZT). This enabled more than 4,000 patients to receive the drug while it underwent final review at FDA. And on March 20, 1987, FDA approved the drug (marketed under the brand name Retrovir by Burroughs Wellcome Co.) as safe and effective for helping certain patients with AIDS and advanced AIDS-related complex. The agency's review and approval was accomplished in less than four months—one of the shortest approval actions on record.

The new FDA rules could bring such promising and important—but still experimental—drugs to desperately ill patients years earlier than was the case. These new procedures are proposed to apply to immediately life-threatening conditions, recognizing that in those cases patients are willing to accept a greater risk, since there may be no other hope. There are also criteria for diseases that are serious but not immediately life-threatening. The rules apply where no other satisfactory treatment exists.

FDA anticipates that approvals for expanded studies of drugs for immediately life-threatening diseases can be given near the end of the second phase of clinical testing; that is, after the drug's safety testing has been done and the proper dose determined, and after some evidence of therapeutic benefit is available. Approval for expanded uses of experimental drugs for serious but not immediately life-threatening diseases would ordinarily occur at the middle of the third and final phase of testing. That is the stage at which the preliminary evidence of safety and effectiveness is examined in

## NEW DRUG PROCESS: TREATMENT USE



*The arrows on this chart show when a promising experimental drug can be made available to additional desperately ill patients, under a rule issued in 1987 by FDA. With drugs for immediately life-threatening conditions, expanded availability can begin near the end of the second phase of human testing—that is, after the drug's initial safety testing has been done and the proper dose determined (phase I), and after some evidence of therapeutic benefit has been obtained (phase II). For serious but not immediately life-threatening illnesses, approval for expanded treatment availability can occur sometime during the third and final phase of testing. During phase III, early evidence of safety and effectiveness is being verified before marketing approval of the drug is finally sought from FDA. Once granted, FDA approval of an investigational drug for treatment use will normally continue until regular marketing of the drug begins. ("IND Rev." means FDA review of an investigational new drug application, approval of which is necessary before a drug can be tested in people.)*

earlier studies is being verified before marketing approval is finally sought from FDA. We trust that these procedures will allow clinical trials to continue unfettered while permitting physicians and patients—with their informed consent—to obtain access to breakthrough drugs earlier than usual. Recent FDA approvals of the expanded availability of protropin—a cloned form of human growth hormone—and zidovudine while both drugs were still experimental illustrate the new policy. In each case, the agency weighed the potential risks against the potential benefits when no alternative therapy existed.

The new rule allows for the sale of such experimental drugs to help ensure that drug companies have enough incentive to make them available. This should promote greater competition by allowing small companies to test products that are extremely expensive to produce, such as those made through biotechnology.

Nevertheless, it would not be appropriate to make drugs widely available too early in the development process. While dying patients may be willing to "try anything," it would be irresponsible—and far from compassionate—to raise false hopes. The risks of a drug, as well as its benefits, must be measured very carefully. There are very few conditions, not even AIDS, that can't be made worse. For example, in the clinical trials of the once-promising AIDS drugs HPA-23 and suramin, the chemicals turned out to be so toxic that the studies had to be ended. It's not easy to be patient amid reports of dramatic results with a new drug for AIDS or Alzheimer's disease, for instance. But it's not always easy, or even possible, to tell whether those early findings are real.

As FDA grapples with these decisions, each new drug will have different considerations that must be weighed on its own merits. Obviously, the seriousness of the illness and the lack of any other effective treatment play a large role in deciding whether to make a drug available. When a drug has been studied extensively and is in the final stage of testing, we would rarely say no to a doctor who wanted to give the drug to a patient. In fact, we must be sure that we're doing everything possible to get promising drugs—whether they're for AIDS or other serious conditions—to as many patients as possible, just as soon as we have the information to make a reasonable judgment.

We need to be flexible as we weigh risks against benefits in deciding whether to expand the use of experimental drugs. But we also need to recognize that there will never be a "no risk" decision. We have to recognize our limitations, while moving ahead with the information we have. Always we must let science provide the light and compassion guide the way. ■

*Dr. Young was commissioner of Food and Drugs from 1985 to 1989.*



## Fast-Tracking the First AIDS Drug

The drug zidovudine, brand name *Retrovir* (formerly called *azidothymidine* or *AZT*), was originally developed in 1964 as a potential cancer treatment, but it showed little promise for this use. Years later, a fresh look at the compound's anti-viral properties led to its becoming the first drug approved to treat AIDS—acquired immune deficiency syndrome.

Close cooperation between FDA and the drug's sponsors, *Burroughs Wellcome Co.* of Research Triangle Park, N.C., and the National Cancer Institute, helped to expedite the testing and review of zidovudine. FDA approved the drug to treat certain patients with AIDS on March 20, 1987—within just four months of receiving a new drug application from *Burroughs Wellcome*.

FDA press officer Brad Stone interviewed Dr. Ellen Cooper, group leader (anti-virals) of FDA's Division of Anti-Infective Drug Products, and Dr. James Bilstad, deputy director (medical affairs) of FDA's Office of Biologics Research and Review, to trace the development and approval of this important new drug.

**FDA CONSUMER:** *Zidovudine is categorized as an anti-viral drug. What is an anti-viral drug, and how does it work in treating AIDS?*

**COOPER:** An anti-viral drug interferes with viral replication. Zidovudine works in part by inhibiting reverse transcriptase, an enzyme necessary for the replication of HIV [human immunodeficiency virus], the retrovirus that causes AIDS. In addition, the virus is "tricked" into incorporating zidovudine into its DNA replication chain. This action effectively aborts the virus's ability to replicate itself.

**FDA CONSUMER:** *How does zidovudine trick the virus?*

**COOPER:** Zidovudine's chemical structure is in some ways very similar to thymidine—one of the key nucleosides, or links, that make up the DNA genetic chain that reproduces the AIDS virus. Evidently, the AIDS virus mistakes zidovudine for real thymidine and incor-

porates the drug as a link on the DNA chain. While zidovudine is similar enough to thymidine to link onto one end of the chain, it lacks features that would allow other nucleosides to link on and complete the chain. In this sense, zidovudine can be seen as a deliberately defective link that preempts the virus's reproductive chain.

**FDA CONSUMER:** *How did zidovudine receive FDA approval so quickly?*

**BILSTAD:** Because of the urgent need for effective AIDS therapies, experimental treatments for this disease receive top priority for review. NDAs [new drug applications] for drugs for diseases for which there is a satisfactory existing therapy sometimes have to wait in line for review. This is not the case with AIDS drugs—Commissioner [Frank E.] Young has determined that they are to get immediate review, and we are striving to meet that goal.

**COOPER:** In addition, the new drug ap-

plication for zidovudine was based largely on a placebo-controlled study with which FDA staff had been quite familiar from the beginning. FDA and *Burroughs Wellcome* had cooperated closely from the time clinical trials began in April 1985. This cooperation was mutually beneficial as it kept both parties abreast of the other's problems, advances and needs. Since many of the details of the study were already known to FDA reviewers, it took less time to review the results than might otherwise have been the case.

**FDA CONSUMER:** *Didn't FDA do some of the preliminary research on zidovudine as a treatment for AIDS?*

**COOPER:** Yes. Well before *Burroughs Wellcome* first applied for permission to begin clinical [human] testing, the company asked Dr. Gerald Quinnan's lab at FDA's Division of Virology to test the drug in vitro [in the test tube] against the AIDS virus, because earlier animal studies conducted by the company had indicated zidovudine's high level of activity against the virus. Dr. Samuel Broder's lab at the National Cancer Institute and Dr. Dani Bolognese's lab at Duke University [in Durham, N.C.] did additional testing.

**FDA CONSUMER:** *Is this type of extensive cooperation and ongoing consultation between FDA and AIDS researchers unusual, or is it the norm for AIDS drugs?*

**BILSTAD:** Definitely the norm. FDA is eager to work whenever possible with any companies or research or academic institutions pursuing promising treat-

*Zidovudine can be seen as a deliberately defective link on the DNA chain that interferes with the AIDS virus's ability to reproduce.*



ments for this disease. We encourage all companies working on AIDS therapies to communicate with us even before they apply for clinical testing, because this cooperation can be of tremendous value in expediting the review and approval processes.

**COOPER:** The urgency of the AIDS situation really requires close cooperation, and there has been a strong emphasis within the agency on working to streamline the process by eliminating any gaps in communication.

**FDA CONSUMER:** *What patients benefit from zidovudine, and how?*

**COOPER:** The AIDS patients who were shown to benefit from zidovudine in the placebo-controlled trial [which provided the definitive data on the drug's efficacy] had recovered from a recently diagnosed episode of *Pneumocystis carinii* pneumonia [the most common opportunistic infection in AIDS patients in the United States] and lacked any signs of other opportunistic infections or of Kaposi's sarcoma [a malignancy that produces lesions on the skin and other areas of the body].

In addition, certain patients with advanced AIDS-related complex [ARC] were shown to benefit from the drug in this trial. The benefits that can be expected from zidovudine in patients with advanced disease are prolonged survival and a decrease in the severity and incidence of opportunistic infections, at least during the first four to six months of treatment. These benefits are related because AIDS patients most often die of opportunistic infections.

AIDS patients with opportunistic infections other than *Pneumocystis carinii* pneumonia were not specifically studied in the controlled trials. Monitoring of

these patients in open trials, however, showed that they too benefited from the drug.

For AIDS patients without any opportunistic infections—such as patients with Kaposi's sarcoma alone, it is unclear whether the benefits of taking zidovudine outweigh the risks, and so the drug is not yet recommended for these patients. Studies are under way to determine if zidovudine would be helpful to them.

**FDA CONSUMER:** *What risks are associated with zidovudine?*

**BILSTAD:** The drug has some significant side effects. In some patients, it can seriously inhibit the production of essential white and red blood cells. A substantial percentage of the AIDS patients receiving the drug need repeated blood transfusions to overcome the depletion of their red blood cells.

Overall, however, zidovudine's potential benefits clearly outweigh its risks in the patients for whom it has been ap-

proved, because it can prolong their lives.

**FDA CONSUMER:** *Are there any studies to evaluate the long-term efficacy of zidovudine in AIDS and ARC patients?*

**COOPER:** FDA is working with Burroughs Wellcome to follow the progress of representative groups of patients on zidovudine to determine the drug's long-term effectiveness. The company is engaged in two major studies. The first will closely monitor patients who have received zidovudine since September 1986, when it was made more widely available on an experimental basis by FDA and Burroughs Wellcome. The second study will survey the progress of 1,500 patients, most of whom first received zidovudine following its approval by FDA last March. Nurses and epidemiologists will monitor and record the data from medical charts of these patients at about a dozen treatment centers throughout the country.

Although these two studies are just getting under way, empirical data from an ongoing study of patients who were switched from placebo to zidovudine when the initial trial was ended in September 1986 indicate that the drug continues to prolong survival in these patients.

**FDA CONSUMER:** *Are these extensive post-marketing studies usual?*

**COOPER:** No, their degree and intensity are certainly unusual. Important questions about zidovudine remain unanswered. If we were dealing with a less severe illness that did not require such urgent action, these questions might have been resolved before the drug was approved.

**BILSTAD:** We hope to obtain the answers

***"We have a long way to go, but a lot of good people are working on AIDS research."***

to many of these questions through studies such as those described by Dr. Cooper, and also, of course, from additional clinical studies like those being conducted at NIH-sponsored AIDS Treatment Evaluation Units.

**FDA CONSUMER:** *What extra burdens are placed on medical reviewers who must analyze potential treatments for a disease like AIDS?*

**COOPER:** Added pressures are brought to bear because of the urgency of a situation in which there is no known treatment for a deadly disease. It is also harder to assess the effect of a given treatment when the natural history of the disease it is designed to treat is still not fully known.

The carefully controlled design of the zidovudine trial was important for allowing rapid evaluation of the drug's effect. By examining two similar groups of patients—one treated with the drug and the other given a placebo—researchers and reviewers can more readily identify the source of differences, both good and bad, they may develop in the medical status of each group's participants.

**BILSTAD:** In the case of zidovudine's clinical trials, the fact that 19 patients on placebo, but only one patient on the drug, died in the same four- to six-month period gave us a strong early indication that the drug was effective.

**FDA CONSUMER:** *Does zidovudine's development and approval have any implications for development of other therapies?*

**COOPER:** While there is probably no absolute direct relationship between the development of zidovudine and other AIDS drugs that are being studied, this approval is definitely an encouraging step



for drug development everywhere. For one thing, regardless of the remaining questions about its long-term efficacy and unknown side effects, the zidovudine experience demonstrates that an anti-retroviral drug can significantly alter the clinical course of this disease, even in its advanced stages. Prior to the zidovudine trial, many people felt that patients with fully developed AIDS could not be helped by an anti-viral drug.

**BILSTAD:** Experience with zidovudine also shows that FDA, industry and other government agencies can work together quickly and effectively to develop, test and review drugs to combat AIDS.

**FDA CONSUMER:** *Are you surprised that an effective treatment for AIDS has been found so soon after the discovery of the disease?*

**COOPER:** Because of the tremendous amount of study and work that has gone

into researching, developing and testing AIDS drugs, there was reason to hope that progress would be made. But I think everyone was surprised that a drug with such a striking impact on mortality was found so early in the development process.

**FDA CONSUMER:** *Finally, what would you tell those who are suffering from AIDS about the outlook for the future?*

**COOPER:** In general, the longer term outlook is encouraging. I think zidovudine and drugs like it, which inhibit but do not destroy the AIDS virus, are the first generation of anti-retrovirals. Other, more advanced classes of anti-viral drugs are being explored, which we hope will undergo clinical study in the near future. These therapies may be even more effective in inhibiting the virus.

The search for a drug that will completely eradicate the virus from the body is bound to take much longer. In the meantime, researchers are exploring drugs to boost the immune system, which in turn may strengthen the patient's ability to resist the opportunistic infections and cancers associated with the disease.

**BILSTAD:** The attention and resources that are being brought to bear on AIDS, in both the private and public sectors, is unprecedented. We now know more about this retrovirus than we do about many other viruses that have been known for decades to cause human diseases.

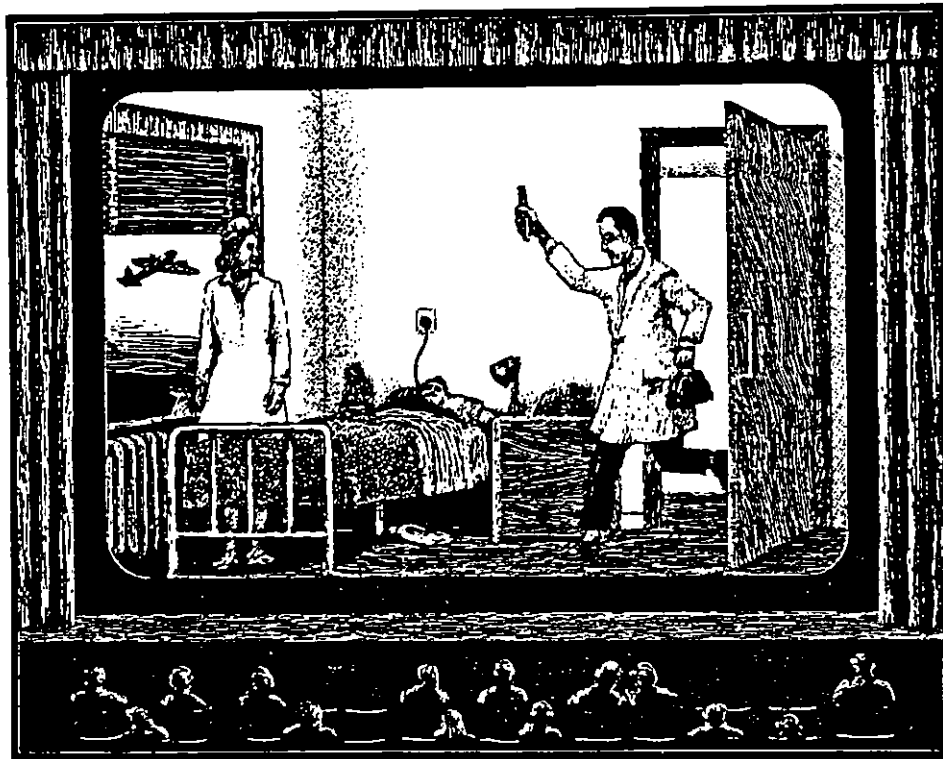
We have a long way to go, but a lot of good people are working on AIDS research. (See article on page 6.) There is no question that the fight against this disease has caught the attention of not only the American people, but of the worldwide medical and scientific community as well. I am confident that in time we will overcome this disease. ■

# FDA FINDS NEW WAYS TO

# SPEED

# TREATMENTS TO PATIENTS

by Ken Flieger



***M**oviegoers in the 30s and 40s were regularly treated to the high drama of a dying patient whose only hope lay in an experimental drug—usually called a “serum”—that had to be flown through a raging storm, at night, to the patient’s bedside. In the Hollywood scenario, the “serum” always arrived in the nick of time, the patient was saved, the brave young doctor was acclaimed a hero with a brilliant future, and the world got a miraculous new weapon in the battle against death and disease.*

*MUSIC UP—FADE TO BLACK—ROLL CREDITS*

\* \* \*

Such movies are, of course, fantasy. But underlying their dated and, by today’s standards, corny plot lines is the widely held belief that when nothing else can help, desperately ill patients ought to have access to investigational treatments that show some evidence of being useful. Concerned health professionals and consumers alike have long maintained that even though possibly important new drugs or biologicals haven’t yet com-

pleted the complex and often lengthy path to FDA approval, physicians should nonetheless be able to use them in willing patients who can't benefit from established therapy.

And, in fact, thousands of people receive investigational products, not only in carefully controlled clinical trials, but also in innovative programs aimed at giving them all the medical help possible.

Using investigational agents in a sort of last-ditch effort to help desperately ill and dying patients is not new to medicine. FDA has permitted the emergency use of unapproved, investigational products for many years. Under the general rubric "compassionate use," the agency has permitted sponsors of investigational agents to provide them to doctors not involved in controlled clinical trials for use in individual patients who might be helped by the treatment.

In 1987, FDA changed its regulations on investigational new drugs (INDs) to specifically authorize treatment use of such agents. The term "Treatment IND" highlights the fact that an investigational agent is being administered not primarily to gain information about its safety and effectiveness, as in a controlled study, but to treat certain seriously ill patients.

The change in terminology is emblematic of a shift in the way FDA, the Congress, the pharmaceutical industry, health professionals, and health activists view the role of drug development and drug regulation in this country. All agree that a major goal of drug regulation must be to speed the journey from laboratory to bedside of important new drugs for devastating illnesses.

The shift involves more than just wider treatment use of unapproved agents. It also encompasses steps to accelerate FDA's process for reviewing applications to bring new drug and biological products to the market. Without compromising the approval requirements for safety and effec-

tiveness of new drugs and biologics, FDA has taken numerous steps to shorten the time devoted to pre-approval drug testing. This streamlining of the process is geared to eliminating unnecessary, duplicative studies, and expediting the review of innovative agents for the most serious or life-threatening conditions.

Through published guidelines and meetings with sponsors, FDA reviewers help drug developers plan studies designed to generate the information FDA needs to make decisions about approvability. In addition, under a new congressional mandate, the agency will be able to collect user fees from product developers and manufacturers to cover the costs of expediting the review of prescription drug applications. (See "User Fees to Fund Faster Reviews," page 19.)

#### Treatment INDs

The first class of drugs to generate interest in treatment use outside formal clinical trials consisted of beta-blocking agents used in certain forms of heart disease. During the mid-1970s, many thousands of patients were treated with beta blockers for advanced, life-threatening heart and lung conditions for which no effective alternative treatment existed. In one instance, more than 600 cardiologists treated some 20,000 patients with the anti-arrhythmic drug amiodarone before it was approved for marketing as Cordarone in late 1985.

By far the most celebrated use of a Treatment IND involved expanding the availability before approval of zidovudine, commonly known as AZT, to people with AIDS. Initial (phase 1) testing of the drug in 33 patients with AIDS, carried out between July and December of 1985, yielded encouraging results. Phase 2 trials to assess the drug's safety and effectiveness began in February 1986. About 300 people with AIDS at several centers around the country were randomly se-

lected to receive either AZT or a placebo.

These studies were abruptly halted in September 1986 when it was discovered that 16 patients receiving placebo had died, while only one death had occurred among those receiving AZT. Within a week of receiving this information, FDA authorized a treatment protocol for AZT. As a result, more than 4,000 AIDS patients were treated with AZT before its approval as the first anti-AIDS drug under the brand name Retrovir in March 1987.

Building on that and other experience with treatment protocols, FDA developed and issued in May 1987 regulations codifying the circumstances under which Treatment INDs can be granted. While the purpose is to make promising investigational drugs available as early as possible to patients with serious or immediately life-threatening diseases, the Treatment IND regulations also ensure that, despite possibly extensive treatment use of an investigational agent, carefully controlled trials will go forward to demonstrate the drug's safety and effectiveness.

The regulations reiterate the requirement that, as with all clinical use of investigational drugs, informed patient consent must be obtained, and the product cannot be promoted or otherwise commercialized. FDA also requires that a product administered under a Treatment IND must be under (or have completed) active clinical investigation, and its sponsor must be pursuing marketing approval with "due diligence."

It's critically important to complete definitive clinical trials, because once an investigational product appears in early studies to offer an important therapeutic advance and becomes available for treatment use, "you may never get another crack at it," says Robert Temple, M.D., director of FDA's Office of Drug Evaluation I. "If a study looks favorable—seems to show an effect on survival in-stance—physicians are very reluctant to

*Without compromising the approval requirements for safety and effectiveness, FDA has taken numerous steps to shorten the time devoted to pre-approval testing.*

redo the study. They want the active drug for their patients."

Ethical concerns make it difficult for physicians to withhold a promising investigational drug that might forestall severe disability or death. But if the study that showed promise was not well-designed—if, for example, there was no control group—what looked like favorable results may prove to be an illusion. "So it's very important to do a good study early—right at the beginning before impressions form that might turn out to be wrong," Temple says.

He points out that the early clinical trial showing AZT to be effective in AIDS patients was a placebo-controlled study, the results of which were dramatic and unequivocal. On the other hand, in the case of ganciclovir, an antiviral drug used to treat an eye infection in AIDS patients, the path to treatment use and ultimate approval was quite different. Early suggestions of ganciclovir's effectiveness led to wide use before controlled clinical trials ever started.

Ganciclovir was approved in 1989 on the basis of a historical comparison with other treatments. But, Temple maintains, approval of ganciclovir was almost certainly delayed for years by the lack of appropriate, controlled clinical investigation.

FDA has indicated, for purposes of Treatment INDs, what constitutes serious or immediately life-threatening illness, what scientific information about the drug's safety and potential usefulness must be in hand, and how physicians can obtain investigational drugs for treatment use.

As of January 1993, 28 agents had been granted Treatment IND status. The conditions for which they have been used include AIDS and its complications, control of infection in kidney transplant patients, severe obsessive-compulsive disorder, Alzheimer's disease, severe Parkinson's disease, various advanced cancers, and

respiratory distress syndrome in premature infants. At press time, 22 of these drugs had been approved by FDA and are on the market.

#### **Other Quick Help**

An older, more targeted treatment-use initiative is aimed at making investigational cancer drugs available to patients who are not participating in controlled clinical trials. Since the mid-1970s, FDA has reviewed drugs for limited distribution by the National Cancer Institute (one of the National Institutes of Health) to provide promising new anti-cancer drugs and drug combinations to cancer patients for whom established therapy is ineffective.

Another mechanism to permit wider availability of experimental agents is the "parallel track" policy developed by the U.S. Public Health Service in response to the AIDS epidemic. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be potentially useful. At press time, one drug (D4T) had been made available under the parallel track mechanism.

#### **Streamlining Review**

Less dramatic, perhaps, than rushing investigational drugs to the desperately ill, but almost certainly of more long-range benefit to society, are measures to streamline FDA's review and approval process and expand the agency's resources for this task. Although not the stuff of which gripping movies are made, these efforts can mean earlier arrival of important new drugs in hospital and community pharmacies for the benefit of everyone who needs them.

One change FDA has adopted in recent years to speed drug review is categorizing new drugs as either standard or priority. Standard drugs are those that offer only minor improvement (or none) over drugs

*One change FDA has adapted in recent years to speed drug review is categorizing new drugs as either standard or priority.*

already on the market. Priority drugs, on the other hand—which may in fact be a new dosage form of, or new use for, an existing drug—are believed to represent potential major advances in health care. Distinguishing the two categories of drugs permits speedier review even before a new drug application is submitted.

FDA and sponsors of priority drugs may meet at the earliest stages of clinical testing to plan studies that will help develop the information necessary for a final decision on a product's approvability. Then, when a marketing application is submitted, FDA can mobilize available personnel and other resources needed to review the often large amounts of technical information contained in a priority new drug application.

In another effort to speed the review of marketing applications, the review process is becoming increasingly computerized. New drug applications that commonly run to thousands of pages are now arriving from sponsors in a form suitable for computer processing. This makes review and communication with the sponsor more efficient, saving time for both FDA and the firm.

#### **Accelerated Approval**

A highly specialized mechanism for speeding the approval of drugs or

biologics that promise significant benefit over existing therapy for serious or life-threatening illnesses—so-called accelerated approval—incorporates several novel elements aimed at making sure that rapid review and approval is balanced by safeguards to protect both the public health and the integrity of the regulatory process itself.

Accelerated review can be used in two very special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when FDA determines that safe use of a product depends on restricting its distribution or use.

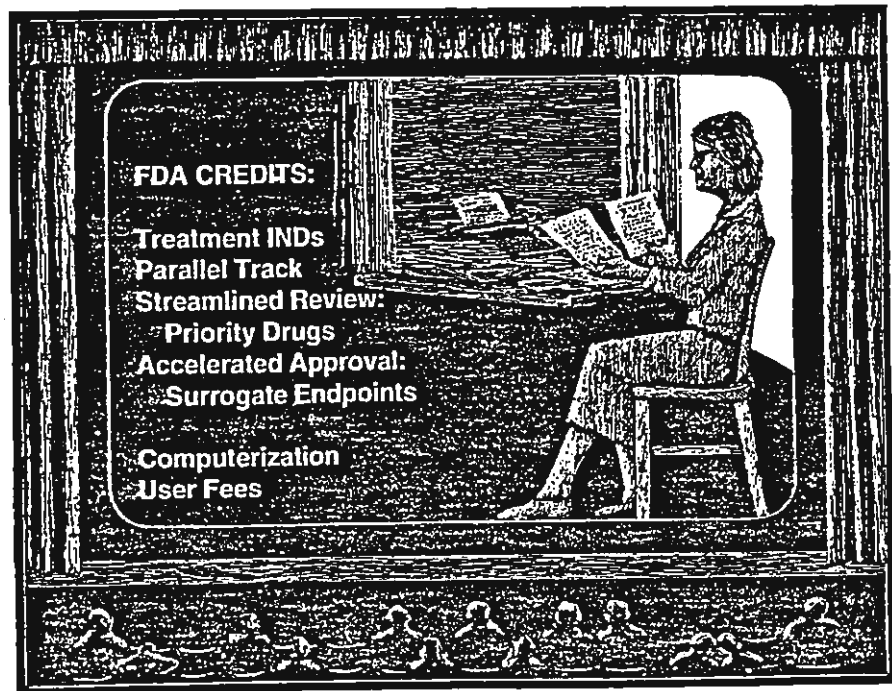
A "surrogate endpoint" is a laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. For example, high blood pressure and elevated serum cholesterol are risk factors for heart and blood vessel disease. Drugs that control blood pressure or cholesterol can reasonably be expected to help control or prevent direct signs of disease, such as angina, congestive heart failure after a heart attack, paralysis following a stroke, and sudden death. Once a drug has been shown effective as measured against such a surrogate endpoint, FDA can grant marketing approval.

As a condition of approval, however, FDA can require the sponsor to carry out post-marketing studies to confirm that the drug does in fact produce a clinical benefit, such as increased survival time. And if further research or experience shows that a product that received accelerated approval cannot safely remain on the market, FDA can order its prompt withdrawal.

As a further safeguard, distribution of accelerated-approval drugs can be limited to institutions that have the capability to use them safely and to physicians with specialized training or experience. The agency can also require that specific medical procedures, such as blood tests, be carried out if they are deemed essential for safe and effective use of the product.

It is clearly too soon to know whether efforts to make drugs and biologics more rapidly and widely available to the desperately ill are contributing to genuine advances in health care. But many thousands of patients who might otherwise be beyond hope are now able to seek help from investigational agents, and all of us stand to gain from a more efficient, more responsive system by which to bring important new agents to market. ■

*Ken Flieger is a writer in Washington, D.C.*



---

Friday  
May 22, 1987

TREATMENT IND

---

Part IV

**Department of  
Health and Human  
Services**

---

Food and Drug Administration

---

21 CFR Part 312

**Investigational New Drug, Antibiotic, and  
Biological Drug Product Regulations;  
Treatment Use and Sale; Final Rule**

**Investigational New Drug, Antibiotic, and  
Biological Drug Product Regulations;  
Treatment Use and Sale; Final Rule**



**DEPARTMENT OF HEALTH AND  
HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 312**

[Docket No. 82N-0394]

**Investigational New Drug, Antibiotic,  
and Biological Drug Product  
Regulations; Treatment Use and Sale**

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing final procedures under which promising investigational new drugs may be made available to desperately ill patients before general marketing begins. These new procedures are intended to facilitate the availability of promising new drugs to patients as early in the drug development process as possible, and to obtain additional data on the drug's safety and effectiveness. The new procedures apply to patients with serious and immediately life-threatening diseases for which no comparable or satisfactory alternative drug or other therapies exist. FDA has clarified the final rule to strengthen the policy objectives of the reproposal while safeguarding against the proliferation of fraudulent products and ensuring the integrity and vitality of controlled clinical trials. FDA is also defining the conditions under which drug manufacturers may charge for investigational new drug products. These procedures are intended to provide sufficient incentives for drug manufacturers to make investigational new drugs available to patients before general marketing begins, but under sufficient safeguards so as to prevent commercialization of the product as well as to ensure the integrity of clinical trials. These actions are based on comments received on the March 19, 1987, reproposal.

**DATE:** The regulation will become effective on June 22, 1987.

**FOR FURTHER INFORMATION CONTACT:** Steven H. Unger, Center for Drugs and Biologics (HFN-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of March 19, 1987 (52 FR 8850), FDA published repropoed regulations governing the conditions under which patients could obtain investigational drugs primarily for treatment use, and the conditions under which investigational drugs could be sold. FDA provided 30 days for public

comment, and, upon request, extended the comment period for an additional 15 days until May 5, 1987. In addition to the many written comments received, the FDA Commissioner held a number of meetings during the comment period with health care professionals, consumer group leaders, representatives from orphan drug organizations, clinicians and clinical investigators from academia, and representatives from the pharmaceutical industry, including those specializing in biotechnology. FDA has benefitted immensely from this full and forthright public discussion of these issues, and the agency has revised portions of the final regulation to reflect the many comments received on the reproposal.

Highlights of the final rule are summarized below, followed by a more detailed response to comments and discussion of the final rule.

**I. Highlights of the Final Rule**

**A. Introduction**

FDA received over 300 comments on the reproposal, representing virtually every affected constituency. These included consumers, consumer group leaders, health professionals and health care providers, representatives of specific disease and orphan drug organizations, State and local health departments, clinical investigators and research institutions, institutional review boards, pharmaceutical manufacturers, and former FDA officials. These comments reflect a broad public acceptance and earnest support for the goal of providing promising new drugs to desperately ill patients as early in the drug development process as possible, and of obtaining additional data on the drug's safety and effectiveness. For this reason, FDA has inserted a statement of this purpose directly into the regulation itself (§ 312.34(a)) to ensure that the regulation is interpreted and applied in a manner consistent with its intended purpose.

These were also a number of specific questions or concerns raised. These fall under four main categories: (1) Protecting against health fraud or premature exposure of patients to untested drugs; (2) ensuring the integrity of clinical trials; (3) ensuring the ethical underpinnings of the drug development process; and (4) providing a clearer description of which costs can be considered in setting the price that could be charged for investigational drugs. Most of these comments were directed towards preventing possible abuses that some believed might have occurred under the reproposal. However, a

number of these comments also suggested the addition of specific safeguards which, if adopted, could serve both to support and strengthen the principal policy goals of the reproposal while minimizing the likelihood of possible abuse. As described below, FDA has made the necessary refinements to the final rule to accomplish these dual objectives.

**B. Treatment Use of Investigational Drugs.**

Like the reproposal, the final rule regarding treatment use provides general criteria for allowing an investigational new drug to be made available to desperately ill patients primarily for treatment use. Minor modifications have been made to these criteria to read as follows: (1) The drug is intended to treat a serious or immediately life-threatening disease; (2) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (3) the drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence (§ 312.34(b)(1)).

Also like the reproposal, in the case of a drug intended to treat a "serious" disease, the final rule provides that the Commissioner may deny a request for treatment use if there is insufficient evidence of safety and effectiveness to support such use (§ 312.34(b)(2)).

In response to comments, FDA has revised the criteria for the granting of a treatment IND for drugs intended to treat immediately life-threatening diseases. In this situation, under the final rule, the Commissioner may deny a request for treatment use if the available scientific evidence, taken as a whole, fails to provide reasonable basis for concluding that the drug: (1) May be effective for its intended use in its intended patient population; or (2) would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury (§ 312.34(b)(3)(i) (A) and (B)).

FDA has also added into the regulation a definition of "immediately life-threatening" to mean a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment (§ 312.34(b)(3)(ii)).

The final rule also clarifies that treatment use of an investigational drug is conditioned on the sponsor and investigator complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR Part 50) and institutional review boards (21 CFR Part 56) and the applicable provisions of Part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports (§ 312.34(c)).

Finally, like the reproposal, the final rule contains provisions for placing a proposed or ongoing treatment protocol or treatment IND on clinical hold (§§ 312.34(d) and 312.42).

#### C. Charging for Investigational Drugs.

Under the final rule, FDA would continue to presume that supplying investigational drugs to subjects participating in clinical trials without charge is part of the normal cost of doing business, and that FDA approval for charging would only be granted upon a showing of why charging is needed for the sponsor to undertake or continue the clinical trial (§ 312.7(d)(1)).

With respect to drugs provided under treatment IND's, the final rule has been revised to authorize sponsors to charge for investigational drugs provided there is adequate enrollment in the ongoing clinical investigations under the authorized IND. This provision is in addition to the three other conditions contained in the reproposal, namely, that the sale does not constitute commercial marketing of a new drug for which a marketing application has not been approved; the drug is not being commercially promoted or advertised; and the sponsor of the drug is actively pursuing marketing approval with due diligence (§ 312.7(d)(2)).

In all cases, the final rule provides that the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug (§ 312.7(d)(3)). This is the same standard currently applied to charging for investigational medical devices.

Finally, like the reproposal, the new rules would allow FDA to withdraw authorization for charging if the conditions underlying the initial authorization were no longer satisfied (§ 312.7(d)(4)).

#### D. Effective Date.

This regulation will become effective for treatment IND/protocols submitted after June 22, 1987.

## II. Responses to Comments

### A. Treatment Use of Investigational Drugs

#### 1. Scope and Criteria

**1. Definitions.** Many comments requested clarification of the term immediately life-threatening disease. Some were concerned that the term "immediately" might literally mean within several days, while other comments were concerned that, as defined, any disease that ultimately could end in death, no matter how many years into the future, could be classified under this category. Comments also requested clarification of the term "serious."

In response to the comments, FDA has defined an immediately life-threatening disease in the regulation as being a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. This does not mean that a clinician would have to make a prognosis with exact precision, but only to provide a general yardstick for decision-making purposes (for example, a reasonable expectation of death within 6 months). FDA will apply a common sense interpretation of the term so that death within more than a year would not normally be considered immediately life-threatening, but also that death within several days or even several weeks would be overly restrictive.

The phrase "or in which premature death is likely without early treatment" is intended to describe those fatal illnesses where death itself may not be imminent but where immediate treatment is necessary to prevent premature death. For example, an anti-retroviral drug might be found on the basis of Phase 2 studies, when used early after infection, to delay progression from the asymptomatic state to AIDS-Related Complex (ARC) and then Acquired Immune Deficiency Syndrome (AIDS). Although this progression would ordinarily take more than 12 months to occur in most patients, this circumstance would be interpreted as fitting the definition of immediately life-threatening.

In the reproposal, FDA identified two disease categories as being immediately life-threatening (advanced cases of AIDS and certain uncontrollable cardiac arrhythmias) and two diseases as being serious (Alzheimer's and multiple sclerosis). FDA received comments that some diseases, particularly multiple sclerosis, become serious only in later stages of the disease and should not be

considered serious, for these purposes, during its earlier stages. Clarification on this point was requested.

FDA agrees that the stage of a disease is important in determining whether it is immediately life-threatening, serious, or not serious within the context of this treatment IND regulation. For diseases such as multiple sclerosis, where some stage of the disease would not be considered serious, the regulation would not be applicable to those stages. In approving an investigational drug for a treatment IND, FDA will seek to define the intended patient population and, in medically appropriate cases, will limit treatment use to particular stages of a disease or to patients with a particular set of symptoms.

To illustrate these categories further, the following diseases or stages of diseases would normally be considered to be immediately life-threatening:

- a. Advanced cases of AIDS;
- b. Advanced congestive heart failure (New York Heart Association Class IV);
- c. Recurrent sustained ventricular tachycardia or ventricular fibrillation;
- d. Herpes simplex encephalitis;
- e. Most advanced metastatic refractory cancers;
- f. Far advanced emphysema;
- g. Severe combined immunodeficiency syndrome;
- h. Bacterial endocarditis; and
- i. Subarachnoid hemorrhage;

In addition, the following would normally be considered serious diseases or stages of diseases:

- a. Alzheimer's disease;
- b. Advanced multiple sclerosis;
- c. Advanced Parkinson's disease;
- d. Transient ischemic attacks;
- e. Progressive ankylosing spondylitis;
- f. Active advanced lupus erythematosus;
- g. Certain forms of epilepsy;
- h. Nonacidotic or hyperosmolar diabetes; and
- i. Paroxysmal supraventricular tachycardia.

FDA recognizes these are illustrative and not complete lists.

**2. No alternative therapy.** A number of comments addressed the proposed criterion that there be no satisfactory alternative drug or other therapy available to treat the disease. Many comments supported this criterion as a necessary prerequisite to allowing treatment use of an investigational drug. Several comments, however, requested clarification of this criteria. Specifically, these comments were concerned that FDA should not interpret this criterion in an overly restrictive way so as, for example, to preclude granting of a

treatment IND where there is any approved drug or therapy available to treat the disease in question.

FDA continues to believe that the absence of alternative therapy should be prerequisite to granting a treatment IND, because one of the major principles underlying the treatment IND policy is that these drugs would be necessary to fill an existing gap in the medical therapies available. However, FDA agrees that there should be flexibility in applying this concept so as best to serve desperately ill patients. For example, the mere fact that the disease in question has existing approved therapy does not mean that the approved treatments are satisfactory for all patients.

Accordingly, FDA has clarified this criterion in the final rule by stating that there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population (§ 312.34(b)(1)(i)). The word "comparable" has been included in the criterion of no alternative therapy, as have the phrases "that stage of" the disease and "in the intended patient population" to emphasize that FDA will not be unduly restrictive in interpreting this criterion. FDA would therefore view the criterion of no comparable or satisfactory alternative therapy as being met when there are patients who are not adequately treated by available therapies, even if the particular disease does respond in some cases to available therapy. This criterion would be met, for example, if the intended population is for patients who have failed on an existing therapy (i.e., the existing therapy did not provide its intended therapeutic benefit or did not fully treat the condition); for patients who could not tolerate the existing therapy (i.e., it caused unacceptable adverse effects); or for patients who had other complicating diseases that made the existing therapy unacceptable (e.g., concomitant disease making available therapy contraindicated) for the patient population.

3. *Criteria for immediately life-threatening disease.* Virtually all the comments supported the criteria for drugs intended to treat serious diseases. Many comments, however, objected to the proposed criteria for drugs intended to treat immediately life-threatening diseases, especially as those criteria related to evidence of therapeutic benefit. Although many of these comments agreed with having separate criteria for immediately life-threatening (versus serious) diseases, many interpreted the wording of the reproposal as requiring the

Commissioner to prove a negative, i.e., the lack of effectiveness, a burden that the Commissioner, according to these comments, would unlikely be able to meet. Other comments stressed the need to emphasize that the Commissioner needs to have sufficient information to make the specified determinations, as had been stated in the preamble to the reproposal. Most of the comments addressing this issue recommended that the criterion be changed to require that there be some evidence of possible effectiveness (e.g., a reasonable scientific basis for believing that the drug may be effective) before allowing treatment use of an investigational drug for an immediately life-threatening disease. Otherwise, these comments argued, the regulation could have the unintended effect of allowing worthless, dangerous, or fraudulent drugs to be marketed to victims of life-threatening illnesses. Finally, some comments questioned the need to provide separate criteria for immediately life-threatening diseases and proposed, instead, adoption of the criteria proposed for serious diseases (e.g., sufficient evidence of safety and effectiveness) for both disease categories.

Because of the different risk-benefit considerations involved in treating such diseases, FDA continues to believe there needs to be a separate standard for drugs intended to treat immediately life-threatening diseases. However, FDA also is persuaded that, to ensure that the intended policy of providing only truly "promising" drugs to desperately ill patients is met, it is necessary to clarify the language in the final rule to require evidence that provides a reasonable basis for believing that the investigational drug may be effective. FDA emphasizes that this standard needs to be interpreted in the context of a treatment IND to treat patients suffering from immediately life-threatening illnesses so that the level of evidence needed is well short of that needed for new drug approval—and may be less than what would be needed to support treatment use in diseases that are serious but not immediately life-threatening. What the final rule does provide for is a standard of medical and scientific rationality—a requirement for sufficient scientific evidence on the basis of which experts could reasonably conclude that the drug may be effective in the intended patient population.

Such scientific evidence could arise from a variety of sources. As stated in the preamble to the reproposal, FDA expects that data from controlled clinical trials will ordinarily be available at the time a treatment IND is

requested. However, FDA is committed to reviewing and considering all available evidence, including results of domestic and foreign clinical trials, animal data, and, where pertinent, *in vitro* data. FDA will also consider clinical experience from outside a controlled trial, where the circumstances surrounding an experience provide sufficient indicia of scientific value.

As stated in the preamble to the reproposal, in making such a determination, the Commissioner obviously must have sufficient information, and must make use of all available information. It follows that, under the final rule, it is expected that the Commissioner will be provided with sufficient data to make the specified determination.

Accordingly, the final rule has been revised to provide that the Commissioner may deny a request for treatment use of an IND for an immediately life-threatening illness if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug (1) may be effective for its intended use in its intended patient population; or (2) would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury (§§ 312.34(b)(3)(i) (A) and (B)).

## 2. Safeguards

4. *Overview.* FDA's objectives in regulating the clinical testing of new drugs are to protect the rights and safety of human subjects of such testing while, at the same time, facilitating the development and marketing of beneficial drug therapies. In reproposing rules on treatment uses for investigational drugs, FDA was aware of the need to safeguard these objectives even while promoting the availability for treatment use of promising new therapies. Some of these safeguards—particularly those designed to protect the rights and safety of human subjects—were already in place as part of the general IND and related regulations; other safeguards were specifically designed to complement the reproposed treatment IND rules.

The most significant of these safeguards, all of which are retained in this final rule, include the following:

a. *Informed consent.* Authorization to use an investigational drug for treatment is conditioned on the licensed practitioner obtaining the legally effective informed consent of the patient. Informed consent is critical to the protection of the rights and safety of

the human subjects. There are clearly significant risks in taking all experimental drugs, including drugs intended for treatment use. Patients must be informed about the potential benefits and risks of drug use to help them decide whether the risks are appropriate and acceptable in their particular situation. Of course, this decision must be made under appropriate medical supervision. The regulations governing informed consent, 21 CFR Part 50, apply to the administration of drugs under an authorized treatment IND/protocol.

b. *The IND system.* It is important to emphasize that the treatment IND process takes place within the larger IND system. This means, for example, that the obligations and responsibilities of the sponsor of a clinical trial also apply to a sponsor of a treatment protocol or treatment IND. This would include, for example, the obligation to submit important adverse reactions to FDA in IND safety reports. Of equal importance, the responsibilities of the licensed medical practitioner using an investigational drug for treatment use are the same as those imposed on an investigator conducting a clinical trial. In addition, as for all investigational drugs, an investigational drug for treatment use must be manufactured in adequate manufacturing facilities to ensure good quality control.

c. *Protection of the integrity of the clinical testing process.* The final rule incorporates a number of safeguards that are intended to ensure that the premarketing availability of drugs for treatment use does not create incentives for delay in the timely testing, development, and submission for marketing approval of promising therapies. FDA is keenly aware that it can not let the treatment IND process become either a substitute for the research necessary to bring a drug to commercial marketing or a substitute for marketing itself.

FDA received a number of the comments on the adequacy of the safeguards discussed in the reproposal. These comments and agency responses are discussed below.

5. *License medical practitioner.* Under the reproposal, drugs for treatment use are provided to "licensed medical practitioners" or "treating physicians." Some comments suggested that the obligations of the "licensed medical practitioner" or "treating physician" were not adequately delineated in the reproposal and therefore requested such clarification.

The "licensed medical practitioner" or "treating physician" is the "investigator" for purposes of the treatment protocol

regulations and may, under some circumstances, be the "sponsor-investigator" for purposes of treatment IND's. As an investigator, the licensed medical practitioner must comply with all investigator responsibilities described in the IND regulations (Part 312) and in Parts 50 and 56. This means that under a treatment protocol the practitioner must, among other responsibilities, assure that the investigational drug is used in compliance with the treatment protocol, promptly report to the sponsor (or, if the practitioner is also the sponsor of the IND, to FDA) all reportable adverse drug experiences, and take all other necessary steps to safeguard the handling and distribution of the investigational drug. For treatment IND's the licensed medical practitioner is the sponsor-investigator. As sponsor-investigator, the licensed practitioner is responsible for meeting all applicable sponsor and investigator responsibilities under Parts 50, 56, and 312.

6. *Qualifications of practitioners.* Several comments questioned whether the proposed regulation provided adequate assurances of the qualifications of the licensed medical practitioners. One comment observed that section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(i)) limits distribution of investigational drugs to experts qualified by scientific training and experience to investigate the safety and efficacy of drugs. The comment contended that "licensed medical practitioners" are not necessarily experts qualified within the meaning of the statutory language.

FDA believes that the regulatory scheme adopted in this final rule adequately ensures that practitioners who obtain drugs for treatment use are well qualified. A sponsor who wants to provide an investigational drug to a practitioner for treatment use under a treatment protocol is obliged to select only those practitioners who are qualified by training and experience to use the investigational drug (21 CFR 312.53(a)). A sponsor must obtain a signed investigator statement from the licensed practitioner containing a full statement of the practitioner's training and experience to qualify the practitioner to use the investigational drug. FDA expects sponsors to exercise care in selecting practitioners to take part in a treatment protocol. When a licensed practitioner is the sponsor-investigator of a treatment IND (i.e., when there is no commercial sponsor to evaluate the qualifications of the practitioners), FDA will conduct its own

assessment of the practitioner's qualifications.

7. *Informed consent.* Several comments expressed uncertainty about the applicability of the informed consent requirements to treatment IND's and treatments protocols. In addition, comments asked whether, when granting a waiver of Institutional Review Board (IRB) review requirements, FDA was also waiving informed consent requirements.

Under FDA regulations, 21 CFR Part 50, informed consent of the patient or the patient's legally authorized representative is required prior to the administration of an investigational drug. In obtaining the patient's informed consent, the physician must provide the patient with information in lay language that truthfully explains the possible benefits and potential risks involved in receiving the investigational drug. (The other items of information that must be provided the patient are enumerated in the informed consent regulations in Part 50 (see 21 CFR 50.25).) FDA regards the informed consent of the patient receiving a drug for treatment use as a crucially important safeguard of the patient's rights, safety, and welfare.

To emphasize the importance of informed consent, the final rule has been revised to make clear that authorization to use an investigational drug for treatment is conditioned on the sponsor and all licensed practitioners meeting the requirements of the agency's informed consent regulations.

Finally, with respect to the concern expressed about informed consent in the context of an IRB waiver, it is worth repeating that FDA requires assurances that adequate informed consent is obtained, whether or not IRB review is waived. The requirement for informed consent is independent of the requirement for IRB review and is not subject to waiver.

8. *IRB Review.* A number of comments expressed concern about the agency's stated willingness to waive IRB review for treatment protocols and treatment IND's. In both the original June 1983 proposal and the March 1987 reproposal, FDA asserted that IRB waiver would frequently be appropriate in the treatment use context because there would be adequate guarantees of subject protection through the informed consent process. Many comments disputed this assertion. These comments contended that, even if some of the functions of the local IRB could be performed by FDA (or by a central or "national" IRB), many important responsibilities within the province of

the IRB could only adequately be exercised by a local IRB.

FDA has reconsidered its previous decision to encourage requests for waiver of IRB review for treatment IND's and treatment protocols. The agency agrees with those comments that contended that there is much to be gained in having a local IRB conduct an initial and continuing review of the treatment of an investigational drug. IRB's are well placed to determine the adequacy of informed consent. Knowledgeable about the reputation and competence of local practitioners whose work they oversee, these IRB's may also be better able to provide greater insight into the potential benefits of treatment than can be gained by review by a distant IRB or by FDA. Also the need for review may be greater when practitioners are permitted to charge for investigational drugs. For these reasons, FDA has removed the presumption of IRB review waiver from the final rule.

It should be emphasized, however, that although the treatment IND provisions do not solicit waiver requests, waivers in appropriate cases are still available from FDA under the IRB regulations (21 CFR 56.105). As noted above, the waiver provisions do not apply to the informed consent requirement.

FDA anticipates using the waiver provision only where it would be in the best interest of subjects and where alternative mechanisms for assuring the protection of subjects are adequate. In the past, waivers have not ordinarily been granted for IND's when local IRB's are available to review the research. Most waiver requests have been for research conducted outside the United States, and, in those cases, the waiver requests have usually been to waive part, but not all, of the IRB requirements.

In the past, FDA has considered a waiver request to be in the best interest of subjects when preliminary results of clinical studies demonstrate strong initial support for the effectiveness of the drug; when patients must have immediate access to the drug; and when requiring local IRB review is not feasible. Any such waiver would require a finding of adequate alternative mechanisms to protect human subjects. These adequate alternative mechanisms might entail the initial and continuing review and approval of the IND by a committee that does not meet all of the IRB requirements, but that assumes those responsibilities normally held by local IRB's. Finally, any such waiver would require FDA's review and acceptance of the protocol and the model informed consent form.

Finally, FDA has always stated that its grant of a waiver request does not preclude a local IRB from exercising its prerogative to initiate its own review.

**9. Drug quality control.** Several comments asked whether the current good manufacturing practice (GMP) regulations applied to investigational drugs intended for treatment use.

FDA is committed to ensuring that drugs distributed under a treatment IND or treatment protocol are manufactured under adequate manufacturing facilities to ensure good quality control. In this regard, it should be emphasized that investigational drugs, like drugs approved for marketing, have always been subject to the agency's GMP inspection requirements (21 CFR Parts 210, 211, 606 et seq.). This is so even though investigational drugs are often produced in small batches in laboratories or pilot plant settings.

In the past, FDA has not routinely inspected clinical production runs in small laboratory settings or in pilot plants, although it has occasionally conducted inspections of large-scale operations that manufacture batches of drug for the larger Phase 3 studies and treatment IND's. In expanding the availability of investigational drugs for treatment uses, FDA believes that it is appropriate as an additional safeguard of the quality of such drugs to increase its monitoring of clinical batch production. Under this new policy, FDA will conduct an assessment of current good manufacturing practices at the plant where the investigational drug is produced whenever there is good cause to believe that the existing facilities may not be sufficient to ensure the quality and consistency of the investigational drug. The assessment will focus on the nature of the process to be employed in the manufacture of the treatment drug. In cases "for cause," FDA may delay authorization to distribute a drug for treatment use until a GMP plant inspection has been satisfactorily concluded. Where such an inspection is necessary, FDA will conduct it expeditiously.

**10. Active pursuit of marketing approval.** The reproposal conditioned the authorization to distribute a drug for treatment use on the investigational drug being subject to a controlled clinical trial and on the sponsor's active pursuit of marketing approval of that drug with due diligence. A number of comments asked FDA to clarify these provisions. One comment noted that the pursuit of marketing approval with due diligence would be difficult to enforce, observing that marketing approval is a necessarily complex procedure with many opportunities for delay.

In making treatment IND/protocol authorization contingent on the existence of an ongoing control clinical trial and on the sponsor's active pursuit marketing approval, FDA intended to assure that the treatment IND process would not create disincentives to the expeditious development and marketing of promising therapies. In the words of the reproposal, these provisions were designed to ensure that the drug developer make a good faith effort to seek timely and expeditious marketing approval through actions meant to advance the progress of the IND and subsequent marketing approval.

In interpreting this provision further, it is not only important that the drug developer's efforts be taken in good faith; it is also important that the sponsor's efforts stand a chance of being successful. In particular, FDA expects that the sponsor's clinical studies will be the kind of adequate and well-controlled studies that can reasonably be expected to provide data acceptable to FDA in determining the safety and efficacy of the investigational drug. The agency will, therefore, interpret the final rule to mean that the controlled trials that serve as the underpinning for the treatment IND must meet FDA's regulatory standards for adequate and well-controlled studies (21 CFR 314.126). This means that the controlled clinical trial should be designed in such a way as to reflect those attributes of an adequate and well-controlled study that are enumerated in § 314.126.

For purposes of this rule, the phrase "activity pursuing marketing approval with due diligence" is intended to encompass a drug developer's good faith effort to pursue drug development and marketing approval in a timely manner. In determining whether a sponsor is actively pursuing marketing approval, FDA will take into consideration all relevant factors. For example, in FDA's view, a necessary component of marketing approval with due diligence is the sponsor's compliance with all IND obligations, especially adverse reactions and annual reporting obligations. In addition, "actively pursuing marketing approval with due diligence" will be measured by the sponsor's success in meeting whatever developmental goals are part of the sponsor's own drug development plan. Particular attention will be paid to the speed with which subjects are enrolled in ongoing clinical trials. The agency will also focus on the sponsor's success in reaching the other major milestones of drug development. These milestones would ordinarily include timeliness in the completion of animal studies, establishment of a full-

scale manufacturing facility, and preparation and submission of a complete marketing application.

FDA is aware that "active pursuit" of marketing approval and "due diligence" are terms found in other regulatory schemes under FDA's jurisdiction. Specifically, "active pursuit" of marketing approval is a condition of approval to export unapproved new drugs and biologics under the Drug Export Amendments of 1986, and a "due diligence" standard is applied to applicants for patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984. FDA advises that the meaning of "actively pursuing marketing approval with due diligence" under this final rule, though related to the drug export and patent term restoration contexts, is fully governed by the discussion of this concept in this preamble. This discussion is not intended to affect the interpretation of these related phrases under the other regulatory provisions noted above.

Finally, FDA notes that under the reproposal, both the sale and the treatment IND provisions contained a due diligence requirement, but expressed in slightly different words. In this final rule, in the interest of uniformity, both provisions require that the sponsor be "actively pursuing marketing approval with due diligence."

11. *Completed studies.* Several comments suggested that the reproposal might be read as prohibiting FDA from authorizing a treatment use after completion of all controlled clinical studies.

Clearly, drugs that have completed the clinical trial process, but have not yet been approved for marketing, should be eligible for consideration for a treatment IND/protocol. FDA, therefore, agrees with these comments and has revised § 314.34(b)(1)(iii) accordingly.

### 3. Legal Authority

12. In response to the reproposal, several comments asserted that FDA does not have authority under the act to permit the use of investigational drugs for treatment purposes. These comments asserted that such use is inconsistent with the grant of authority in section 505(i) of the act allowing FDA to exempt from otherwise applicable provisions of the law new drugs intended "solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." Several comments stated also that treatment IND/protocols are inconsistent with the holding of the Supreme Court in *United States v. Rutherford*, 442 U.S. 554 (1979) that the

new drug approval requirements of the act encompass drugs intended for treating terminal diseases.

Most of the comments questioning the legality of the treatment IND/protocol provisions did so in the context of challenging the standard for obtaining approval of a treatment IND/protocol for an immediately life-threatening disease. These comments stated that, as drafted, the proposal appeared to require approval of a treatment IND/protocol when there was no evidence of the drug's safety or effectiveness. As described above, however, the final rule has been revised to make clear that a request for a treatment IND/protocol may be denied if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug (1) may be effective for its intended use in its intended patient population; or (2) would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

In response to those comments asserting that, regardless of the criteria for approval, FDA in general lacks authority to permit treatment INDs/protocols, the agency continues to adhere to the position expressed in the preamble to the reproposal (52 FR 8851), that there is adequate authority under the act to provide for a treatment IND/protocol. Section 505(i) of the act confers broad authority upon the Secretary (by delegation to FDA) to promulgate regulations governing the clinical investigation of new drugs to protect the rights, safety, and welfare of human subjects and otherwise to promote the public health. The language of section 505(i) of the act authorizing regulations for drugs intended solely for investigational use is intended to ensure that unapproved drugs are not commercialized before marketing approval, and not to prohibit some use of an investigational drug in a treatment-investigational setting. The treatment IND/protocol serves an investigational purpose by generating information on matters concerning the drug's safety and efficacy. For example, information about less common side effects may be revealed during study under a treatment IND/protocol and can be used to write more informative labeling for the product at the time of its approval. The requirements for a treatment IND/protocol include submission of information in advance of treatment, the submission of safety reports and other information following drug administration, informed consent, IRB review and adherence to other applicable provisions of Part 312,

including distribution of drugs through qualified experts and maintenance of adequate manufacturing facilities. Thus, FDA continues to believe that there are sufficient investigational aspects to these treatment IND/protocols to justify agency authorization of such uses.

The treatment IND/protocol provisions of the final rule, including the provisions for immediately life-threatening diseases, do not violate the Supreme Court's holding in *Rutherford*. The provisions of the final rule governing treatment IND/protocol clearly continue to extend to patients suffering from terminal diseases the protections inherent in the new drug provisions of the act. The court in *Rutherford* noted that the act explicitly provides for the carefully regulated use of drugs not yet proven safe and effective. The treatment IND/protocol provisions of this final rule provide for such carefully regulated use in an investigational/treatment setting. Thus, the treatment IND final rule is not inconsistent with but rather supported by the holding in *Rutherford*.

One comment noted that under the Supreme Court's opinion in *Hynson, Westcott & Dunning*, all evidence other than evidence from adequate and well-controlled clinical investigations is anecdotal and as such may not be relied on to support new drug approval. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973). The comment contended, therefore, that such evidence should not be relied upon to permit treatment use. *Hynson* describes the standard of evidence necessary to support new drug approval—that is, approval for commercial marketing. *Hynson* does not establish an evidentiary standard for approval of an IND or a treatment IND. Further, an important goal of the treatment IND/protocol provisions is to facilitate the availability of promising new drugs to patients with serious and immediately life-threatening disease conditions for whom there are no comparable or satisfactory alternative drug or other therapies. Adoption of criteria for approval of a treatment IND/protocol that would restrict the evidence that the agency could consider solely to evidence from adequate and well-controlled clinical trials, which may be available only at the end of the development process, would not serve the purpose of allowing treatment use at an earlier stage than that provided by commercially approved drugs. Therefore, for this reason and for the reasons stated in the preamble to the reproposal (52 FR 8851), the agency disagrees with this comment.

## 4. Other Issues

13. *Indications for Treatment Use.* A comment asked whether treatment IND/protocols would be available for indications other than those being studied under clinical trials.

FDA expects that drugs for treatment use will only be offered for indications that are the same as, or very similar to, those under study in a controlled clinical trial. As noted previously, the decision to permit an investigational drug for treatment use is based, in large part, on the data that emerge from these clinical trials. In determining whether a treatment IND/protocol should be authorized, the available data must be relevant to the proposed treatment use. Although FDA is not establishing a requirement that the treatment use be for an indication that is identical to that in the controlled study, the need for relevant data will mean that treatment uses will only be available for indications the same as or very similar to those that are under study in the clinical trial. The intended use of the drug is one of the items that needs to be identified in the treatment protocol or treatment IND application.

14. *FDA's review.* Under the reproposal, a treatment use under a treatment IND or treatment protocol may begin 30 days after the submission is received from the sponsor. No affirmative FDA approval of the sponsor's request is required. Several comments suggested that no treatment use should be allowed until FDA has had the opportunity to complete its review and affirmatively "approve" the sponsor's request.

The 30-day review period has been part of the IND review process since the adoption of the IND regulations in 1963. FDA believes that the 30-day period available for review under the final rule will be adequate time to complete a review of a submission.

15. *Other IND's.* Several comments identified a number of categories of drugs that the agency has previously authorized for distribution to treat patients that, according to the comments, would not satisfy some or all of the technical criteria required for a treatment IND or treatment protocol. Drugs that have been so distributed include orphan drugs for non-serious diseases, "compassionate" IND's, and IND's for drugs where marketing is not likely to be pursued, such as for drugs intended to treat certain tropical diseases. The comments asked that the final rule be revised expressly to authorize the continued distribution of these drugs under an IND.

FDA believes that these concerns raise issues that are beyond the scope of this rulemaking. This final rule is not intended to restrict the premarketing availability of the categories of investigational drugs that are identified in the comments. FDA will conduct a review of this issue as necessary.

16. *Status of an investigational drug for treatment under the Controlled Substances Act.* A comment from the Administrator of the Drug Enforcement Administration (DEA) asked FDA to reaffirm that investigational drugs, including investigational drugs authorized for distribution for treatment uses, are not drugs in "currently accepted medical use in treatment in the United States" within the meaning of the Controlled Substances Act.

In scheduling a substance for control under the Controlled Substances Act, the Administrator of the DEA must make a finding as to whether that substance has a "currently accepted medical use in treatment in the United States" (21 U.S.C. 812(b)). DEA has relied upon the recommendations of the Assistant Secretary for Health in making such determinations. In making its recommendation to the Assistant Secretary, FDA has consistently interpreted "currently accepted medical use in treatment in the United States" to mean lawfully marketed in the United States under the Federal Food, Drug, and Cosmetic Act. Nothing in this final rule alters FDA's position, nor does FDA interpret "currently accepted medical use in treatment in the United States" to include use of investigational drugs as provided for in this final rule. FDA has stated repeatedly that drug availability under a treatment IND serves an investigational as well as a treatment purpose (§ 312.34(a)). Moreover, FDA's insistence on adequate informed consent in all cases underscores the significant difference between drugs approved for marketing and those available only under a treatment IND.

#### B. *Charging for Investigational Drugs*

17. *Overview.* FDA received a large number of comments on the sale provision in § 312.7(d) of the reproposal. Some of these comments, primarily from newer, smaller pharmaceutical firms, supported the sale provisions as repropounded. However, the majority of comments expressed varying degrees of concern as to how the sale provision would be implemented and its potential effect on patients, their families, and on the practical and ethical aspects of drug research. These concerns focused, for example, on whether allowing for sale of investigational drugs would help promote health fraud; whether sale

would make it more difficult to enroll patients in clinical trials; whether the price charged should be reduced or eliminated; whether the analysis of "manifestly unfair" would lead to price setting by FDA; and whether charging for investigational drugs would present ethical difficulties for local institutional review boards. Some comments also questioned FDA's legal authority in this area. Comments expressing such concerns came from a wide variety of groups, including pharmaceutical firms, clinical research institutions, associations representing patients with serious and life-threatening diseases, consumer groups, and institutional review boards.

FDA's policy on sale of investigational drugs was discussed in the March 19, 1987, reproposal. That reproposal sought to define the circumstances under which it would be appropriate for drug sponsors to charge patients for investigational drugs, both during clinical trials and under a treatment IND. FDA continues to believe that appropriate circumstances can be so defined, and that these criteria should be less restrictive for investigational drugs being made available under a treatment IND than for those utilized in a clinical trial. In response to comments, however, FDA has revised the final rule so that charging for an investigation under a treatment IND would be conditioned upon adequate enrollment of ongoing clinical investigations, and to provide that the sponsor, under either a clinical trial or treatment IND, may not commercialize the drug by charging a price larger than that necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational drug. FDA believes these refinements should remove the major concerns expressed by the various comments. These refinements are discussed below.

18. *Legal Authority.* In response to the reproposal, several comments asserted that FDA lacks authority to permit or regulate the sale of investigational drugs. These comments asserted that sale of an investigational drug is contrary to the statutory scheme in section 505 of the act prohibiting the commercial marketing of unapproved new drugs. A number of comments stated that the combination of the provisions in the reproposal expanding treatment use and allowing sale of investigational drugs is contrary to the intent of Congress in enacting the 1962 Drug Amendments to require prior approval of the safety and effectiveness of a drug before marketing. One comment noted that, although not

explicitly prohibiting the sale of an investigational drug, in enacting the 1962 Drug Amendments Congress plainly contemplated continuation of the pre-1962 practice of disallowing such sale.

The agency believes that it has authority under the act to permit charging for an investigational new drug as set forth in this final rule. Charging for investigational new drugs is not prohibited by the act, and there is authority to permit charging for an investigational drug in appropriate circumstances. As stated in the preamble to the reproposal, there are compelling public health reasons that justify permitting sponsors to charge for investigational drugs distributed under an approved treatment IND/protocol. As explained further below, the reproposal, which allowed sale at a price not manifestly unfair, has been changed so that a sponsor may only recover costs. Therefore, unless indicia of commercialization are present, such as, for example, promotion or advertising, the agency concludes that it is consistent with the statutory scheme and the language of section 505 to permit sponsors to charge for the costs of investigational drugs distributed under a treatment IND/protocol, under the provisions of the final rule.

With respect to congressional intent in enacting the 1962 Drug Amendments, the legislative history of the amendments reveals, among other things, an intent to avoid repetition of another tragedy similar to thalidomide. The focus of congressional debate and inquiry was not on sale per se of investigational drugs, but rather on ways to ensure adequate animal testing of drugs prior to human administration and to ensure that new drugs are adequately tested and approved for safety and effectiveness prior to commercial distribution. The final treatment IND/protocol regulation, as revised, contains adequate safeguards against such premature release of drugs.

In addition, during passage of the 1962 Amendments, Congress was aware of FDA's then proposed IND regulations. 108 Cong. Rec. 17378 (1962) (statement of Sen. Hruska). Those proposed regulations included a sale provision stating the presumption that sale is commercialization. However, the proposed regulations also offered sponsors the opportunity to demonstrate why sale of a particular investigational drug should not be regarded as commercialization. Thus, Congress was aware that there were circumstances under which sale would not be considered commercialization and,

nevertheless, refrained from amending the act to explicitly prohibit sale.

One comment contended that any sale of an investigational biological product is expressly prohibited by section 351 of the Public Health Service Act (42 U.S.C. 262), which states that no person may "sell, barter, exchange, or offer for sale" any unlicensed biological products. However, biological products undergoing development, but not yet ready for a product license, are regulated under section 505(i) of the act (21 CFR 601.21). As described above, there is authority in section 505(i) to permit sale of an investigational drug, when such sale does not constitute commercialization. Thus, the prohibition against sale of an unlicensed biological product does not preclude the sale of an investigational biological product for which an IND has been submitted when such sale is in conformance with the regulations governing investigational new drugs at 21 CFR Part 312.

Several comments stated that the interplay of the provisions in the reproposal permitting sale of an investigational drug prior to final new drug approval with the provisions for approval of treatment IND's for life-threatening diseases with less than the substantial evidence of safety and effectiveness necessary for new drug approval create an opportunity for the marketing of governmentally sanctioned quack remedies which is inconsistent with the Supreme Court's opinion in *United States v. Rutherford*, 442 U.S. 544 (1979). In *Rutherford*, the Court held that the new drug approval requirements of the act applied to drugs intended to treat persons with terminal diseases and upheld FDA's determination that Laetrile was an unapproved new drug that could not be shipped in interstate commerce. *Rutherford* at 2475. However, the treatment IND/protocol and sale provisions of the final rule are not inconsistent with *Rutherford*. The Court in *Rutherford* noted that application of the new drug approval provisions to therapies for terminal diseases did not foreclose resort to experimental drugs by patients for whom conventional therapy was unavailable. *Id.* at 2478. The Court noted that the act makes explicit provision for carefully regulated use of certain drugs not yet demonstrated safe and effective. *Id.* at 2479. The final rule, while permitting cost recovery for certain investigational drugs, maintains the prohibition against commercialization; distribution of a drug under an approved treatment IND/protocol, therefore, continues to be a carefully regulated distribution. Treatment use of an investigational drug

is conditioned on the sponsor complying with all the safeguards inherent in the IND process including informed consent, IRB review and the applicable provisions of Part 312, such as distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports. The treatment IND/protocol provisions and the provisions for cost recovery, operating together, are consistent with the Court's opinion in *Rutherford*.

One comment stated that under section 704 of the act (21 U.S.C. 374), FDA lacks authority to inspect the financial records of companies. The agency disagrees that it lacks authority to inspect data and information relevant to the cost recovery provisions of the final rule. In any event, however, the agency will consider a sponsor's request for or notification of the sale of an investigational drug as a consent by the sponsor to inspection and copying of information and data relevant to a verification that the charge for the investigational drug is restricted to the cost of the drug's manufacture, research, development, and handling.

19. *Protection against health fraud.* A number of comments were concerned that sale of investigational drugs would provide an unintended opportunity for the proliferation of health fraud. These comments were based largely on the interplay of the proposed criteria for treatment IND's for immediately life-threatening illnesses (discussed above) and the proposed provision on sale.

As noted above, because FDA has revised the criteria for permitting a treatment IND for immediately life-threatening illnesses, the agency believes concerns over potential health fraud have been fully addressed. As revised, § 312.34(b)(3)(1) now provides that the Commissioner may deny a request for treatment use of an investigational drug for an immediately life-threatening illness under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug (1) may be effective for its intended use in its intended patient population; or (2) would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

20. *Recoverable costs.* A number of comments addressed to what extent, if any, FDA should restrict the price charged for investigational drugs. Some comments argued that any degree of price control by FDA was a matter for concern as the agency lacked the



necessary expertise to exercise such authority properly and that it would be misuse of the agency's resources to seek to develop such expertise. Other comments favored an FDA mechanism for limiting the cost of investigational drugs, adding that the costs of investigational drugs should be reasonable and must be effectively controlled or eliminated. Many of the comments expressed concern that the "manifestly unfair" standard of the reproposal was too vague to enforce and would likely result, however unintentionally, in patients being charged excessive prices for investigational drugs.

FDA agrees that any charges for investigational drugs should not be excessive. The agency also agrees, however, that it should not be put in a position of being a price regulator and has, therefore, drafted the final rule to minimize the degree to which it will have to act in this area. Accordingly, the agency has added to § 312.7(d)(3) to the final rule, which states that a sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover the costs associated with the manufacture, research, development and handling of the investigational drug. This provision is the same as that applicable to investigational medical device area since 1980 (21 CFR 812.7(b)) and provides a preferable standard to "manifestly unfair" which has been deleted from the regulation. The standard in the final rule would apply to charges under both a clinical trial and under a treatment IND. FDA would limit its expenditure of resources by requesting sponsors to include in their requests for prior approval (clinical trials) or prior notifications (treatment IND) a certified statement that, consistent with generally accepted accounting principles, the requested price is not greater than that necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational drug.

**21. Incentives to pursue marketing approval.** Some comments questioned whether a sponsor or investigator, if allowed to sell drugs for treatment use, would have less incentive to pursue marketing approval.

FDA believes there are three provisions in the final rule that greatly reduce or eliminate this possibility. First, the requirement for "active pursuit" (discussed earlier) requires that the sponsor make timely progress towards submission of a marketing application. Second, the provision in § 312.7(d)(2) specifies that sponsors can

charge for investigational drugs under a treatment IND provided there is adequate enrollment of the ongoing clinical trials. Finally, as noted above, the final rule limits sponsors to recovery of specified costs. Accordingly, FDA believes that drug sponsors, for many reasons, will have the incentive to pursue marketing approval as quickly as possible.

**22. Procedures.** Several comments argued that the procedures for requesting authorization to sell an investigational drug should be the same for a treatment IND as for a clinical trial. Other comments stated that the final regulation should specify a period of time, preferably within 30 days, for FDA to respond to request to sell drugs in clinical trials.

FDA believes that because of the different considerations underlying charges for an investigational drug in a clinical trial and a treatment IND, different procedures are warranted. Under the final rule, charging for investigational drugs during a clinical trial would normally not be allowed, and, to do so, the sponsor must obtain prior FDA approval upon a showing of why such charges are necessary to undertake or continue the clinical trial. As stated in the reproposal, obtaining such prior approval requires the sponsor to overcome the presumption that providing investigational drugs during clinical trials is normally considered part of the cost of doing business. In contrast, providing an investigational drug to patients under a treatment IND is in addition to the normal clinical trial process necessary to gain marketing approval. In these circumstances, FDA believes that charging should be allowed provided adequate enrollment of ongoing clinical trials has occurred. Because the presumption under a treatment IND is in favor of charging, FDA believes that only prior notification to the agency, not prior approval, is warranted.

As for specifying in the regulations that FDA should respond within a specified period of time to requests to charge for drugs used in clinical trials, FDA does not agree that such an approach is warranted. As explained above, such requests must show why cost recovery is necessary to assure development of the drug. The agency expects this documentation will be prepared differently in different instances and will vary in content and amount. Therefore, setting a time limit might not allow for adequate review. In any event, if the drug is intended to treat a serious or life-threatening illness, FDA will give high priority to responding

promptly to a request to charge for the drug in a clinical trial.

**23. Sale during clinical trials.** Some comments suggested that the provision for sale of investigational drugs in clinical trials, as described in the preamble to the reproposal, discriminated in favor of smaller and newer pharmaceutical firms.

FDA did not intend to discriminate in favor of smaller and newer firms with respect to charging for investigational drugs in clinical trials. As stated previously, FDA believes that cost recovery is justified in clinical trials only when necessary to further the study and development of promising drugs that might otherwise be lost to the medical armamentarium. The agency believes that this situation is most likely to arise in the context of new products derived through biotechnology which are produced by small, medium, and large firms alike.

**24. Equitable Distribution of Investigational New Drugs and Equitable Selection of Test Subjects.** A number of comments raised concerns that charging for investigational drugs used in either clinical trials or in a treatment IND would be unfair for patients who could not afford the drugs.

FDA recognizes that in some instances, when a drug is particularly expensive to manufacture and a sponsor either demonstrates the necessity to charge for the drug in clinical trials or decides to charge for the drug under a treatment IND, certain members of the patient population may not be able to afford the drug. FDA notes that the opportunity to charge for investigational drugs has existed in FDA's regulations since 1963. These concerns are not new. No significant problems have arisen in the past, however. FDA would also point out that sponsors are not required to charge, and several pharmaceutical manufacturers have indicated that they probably will not charge, regardless of the sale provision. Lastly, the concern that some patients would not have earlier access to promising new drugs fails to recognize that in some instances, without the authority to recover costs, no one would have access to these new drugs and no one would benefit from the additional information gained in a treatment IND. For all of these reasons, FDA believes it is appropriate to authorize sale, with the safeguards provided in the final rule.

Several comments suggested that permitting sale of investigational new drugs raises a question of the equitable selection of subjects. Specifically, this comment questioned whether the Institutional Review Board (IRB) would

be able to determine whether selection of subjects was equitable if only those who could afford to pay were included in research involving promising experimental drugs or, conversely, if only those who could not afford to pay for the drug under treatment IND were included in the research.

With regard to concerns if charges are imposed for clinical trial participants, FDA notes that under the final rule, charging for an investigational drug in a clinical trial will only be permitted if the sponsor can demonstrate that such charges are necessary to undertake or continue the clinical trial.

With regard to concerns if there are charges for treatment use drugs, FDA believes they are addressed adequately by the new proposed Federal Policy for Protection of Human Subjects (51 FR 20204). Under this policy, an IRB is advised to be "particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disturbed persons, or economically or educationally disadvantaged persons." Thus, a major role in ensuring equitable selection will be played by the local IRB (21 CFR 56.111(a)(3)).

These concerns are also addressed by the final rule's provisions that sale authorization under a treatment IND is contingent on adequate enrollment in clinical trials, and that treatment IND's are contingent on the sponsor's active pursuit of marketing approval with due diligence.

**25. Safeguards against promotion.** Several comments requested clarification of certain language in § 312.7(d)(2), which outlines conditions under which a sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND—specifically, the terms "commercial marketing," "commercially promoted or advertised," and "due diligence." The comments believed that clarification of these terms was necessary to prevent misinterpretation or abuse. A comment suggested that FDA provide publicly available guidelines to define the term "commercially promoted or advertised." One comment argued that prohibitions against commercial marketing and advertising would be meaningless in context of the publicity surrounding treatments developed for AIDS, for example.

Informal guidance with respect to what would constitute commercial promotion and advertising for investigational drugs has been issued in the past by the Division of Drug Advertising and Labeling in FDA's

Office of Drug Standards—most recently in August 1986. FDA believes that updated guidance in this area may be needed with the publication of this regulation and will take action to develop such guidance as may be appropriate.

FDA's understanding of commercial promotion does not place limits on the free exchange of scientific information (e.g., publishing results of scientific studies, letters to the editor in defense of public challenges, investigator conferences). However, responses by sponsors or investigators to unsolicited media inquiries or statements made in the exchange of scientific information should (1) make clear that the drug is investigational; (2) make no claims that the drug has been proven to be safe or effective; and (3) be truthful and nonmisleading when measured against available information on the drug—and fairly represent available information—as set forth in materials such as investigators' brochures and patients' informed consent sheets.

FDA emphasizes its willingness to discuss with sponsors and investigators any questions they may have as to whether contemplated activities may amount to commercial promotion.

Finally, the term "due diligence" in the regulations at §§ 312.7 and 312.34 is discussed earlier in this preamble.

**26. Third-party reimbursement.** Comments were divided on the issue of whether patients should absorb the cost of investigational drugs. Some comments felt that it would be fair to charge patients for experimental therapies. The majority, however, noting that third party payors do not normally reimburse for experimental therapies, expressed concern as to the effect charging would have on patients and on their families. A number of comments stressed the precarious financial positions—and consequent inability to pay for investigational drugs—of many patients with life-threatening illnesses such as AIDS. Others were concerned that families of desperately ill patients could be bankrupted by the cost of experimental therapies. Several comments stated that the Federal Government should reimburse these costs. Two comments requested that FDA defer final action until the Health Care Financing Administration (HCFA) has addressed the issue of Medicare and Medicaid reimbursement for experimental therapies.

FDA is mindful of the straitened financial circumstances of many desperately ill patients; however, the subject of third party reimbursement is outside the agency's jurisdiction and expertise. The agency notes that one

pharmaceutical firm commented on its willingness as a sponsor to assist patients in finding possible third party reimbursement through such sources as health insurance carriers, government grants, and philanthropic foundations.

**27. Withdrawal of authorization for sale.** Finally, several comments argued that FDA should establish procedures for withdrawing authorization for sale of an investigational drug. Some of the comments argued that withdrawal of permission to sell is analogous to termination of an IND and should be subject to similar procedures, i.e., provide notice to the sponsor with an opportunity for the sponsor to supply an explanation in response justifying the pricing, either in writing or during an informal conference; and provide an opportunity for a regulatory hearing if FDA does not accept the sponsor's explanation.

FDA does not agree that withdrawal of authorization for sale of an investigational drug is analogous to the withdrawal of an IND. In the context of a treatment IND, the sponsor would still be able to provide the investigational drugs to patients, so that authorization for sale is independent of the authorization for the treatment IND itself. The ability of a sponsor to be able to continue distributing the drug without charging is at least plausible since the criteria for charging in this situation do not include economic need. FDA is not persuaded of the need to include formal procedures for withdrawal of sale authorization in the regulations. In instances where the agency finds compelling reason to withdraw sale authorization, FDA will take such action in a manner appropriate to the particular instance, taking into consideration the condition or conditions underlying the authorization that are no longer being met, and giving prior notice to the sponsor. Moreover, FDA will proceed with the utmost caution in situations where withdrawing authorization for sale might have a direct adverse effect on the patients themselves.

### III. Economic Impact

In accordance with Executive Order 12291, FDA has previously considered the potential economic effects of this final rule. As announced in the reproposal, the agency has determined that the rule is not a major rule as determined by the Order. Similarly, under the Regulatory Flexibility Act, the agency previously considered the potential effects that this rule would have on small entities, including small businesses. In accordance with section

605(b) of the Regulatory Flexibility Act, the agency has determined that no significant impact on a substantial number of small entities would derive from this action. FDA has not received any new information or comments that would alter its previous determinations.

#### IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### V. Paperwork Reduction Act of 1980

Sections 312.7(d) and 312.35 contain collection of information requirements that were submitted for review and approval to the Director of the Office of Management and Budget (OMB), as required by section 3504(h) of the Paperwork Reduction Act of 1980. The requirements were approved and assigned OMB control number 0910-0014.

#### List of Subjects in 21 CFR Part 312

Drugs, Medical research.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, Part 312 is amended as follows:

#### PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR Part 312 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); 21 CFR 5.10, 5.11.

2. In § 312.7 by revising the section title, by revising paragraph (d) and by adding a parenthetical statement at the end of the section to read as follows:

#### § 312.7 Promotion and charging for investigational drugs.

(d) *Charging for and commercialization of investigational drugs*—(1) *Clinical trials under an IND.* Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

(2) *Treatment protocol or treatment IND.* A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under § 312.31. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

(3) *Noncommercialization of investigational drug.* Under this section, the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.

(4) *Withdrawal of authorization.* Authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0014)

3. By adding regulatory text to § 312.34 to read as follows:

#### § 312.34 Treatment use of an investigational new drug.

(a) *General.* A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during

Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the "treatment use" of a drug includes the use of a drug for diagnostic purposes.

(b) *Criteria.* (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

(2) *Serious disease.* For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

(3) *Immediately life-threatening disease.* (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(A) May be effective for its intended use in its intended patient population; or

(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(ii) For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

(c) *Safeguards.* Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing

informed consent (21 CFR Part 50) and institutional review boards (21 CFR Part 56) and the applicable provisions of Part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

(d) *Clinical hold.* FDA may place on clinical hold a proposed or ongoing treatment protocol or treatment IND in accordance with § 312.42.

4. By adding § 312.35 to Subpart B to read as follows:

**§ 312.35 Submissions for treatment use.**

(a) *Treatment protocol submitted by IND sponsor.* A sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug under § 312.34 shall submit to FDA a treatment protocol. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:

(i) The intended use of the drug.  
(ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

(iii) A brief description of the criteria for patient selection.

(iv) The method of administration of the drug and the dosages.

(v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is to be supported by the following:

(i) Informational brochure for supplying to each treating physician.

(ii) The technical information that is relevant to safety and effectiveness of the drug for the intended treatment purpose. Information contained in the sponsor's IND may be incorporated by reference.

(iii) A commitment by the sponsor to assure compliance of all participating investigators with the informed consent requirements of 21 CFR Part 50.

(3) A licensed practitioner who receives an investigational drug for treatment use under a treatment protocol is an "investigator" under the protocol and is responsible for meeting all applicable investigator responsibilities under this part and 21 CFR Parts 50 and 56.

(b) *Treatment IND submitted by licensed practitioner.* (1) If a licensed

medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:

(i) A cover sheet (Form FDA 1571) meeting § 312.23(g)(1).

(ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with § 312.23. A sponsor of a clinical investigation subject to an IND who supplies an investigational drug to a licensed medical practitioner for purposes of a separate treatment clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.

(iii) A statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor.

(iv) A treatment protocol containing the same information listed in paragraph (a)(1) of this section.

(v) A statement of the practitioner's qualifications to use the investigational drug for the intended treatment use.

(vi) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(vii) Agreement to report to FDA safety information in accordance with § 312.32.

(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and 21 CFR Parts 50 and 56.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0014)

5. In § 312.42 by adding paragraph (b)(3) to read as follows:

**§ 312.42 Clinical holds and requests for modification.**

\* \* \*

(b) \* \* \*

(3) Clinical hold of a treatment IND or treatment protocol.

(i) *Proposed use.* FDA may place a proposed treatment IND or treatment protocol on clinical hold if it is determined that:

(A) The pertinent criteria in § 312.34(b) for permitting the treatment use to begin are not satisfied; or

(B) The treatment protocol or treatment IND does not contain the information required under § 312.35 (a) or (b) to make the specified determination under § 312.34(b).

(ii) *Ongoing use.* FDA may place an ongoing treatment protocol or treatment IND on clinical hold if it is determined that:

(A) There becomes available a comparable or satisfactory alternative drug or other therapy to treat that stage of the disease in the intended patient population for which the investigational drug is being used;

(B) The investigational drug is not under investigation in a controlled clinical trial under an IND in effect for the trial and not all controlled clinical trials necessary to support a marketing application have been completed, or a clinical study under the IND has been placed on clinical hold;

(C) The sponsor of the controlled clinical trial is not pursuing marketing approval with due diligence;

(D) If the treatment IND or treatment protocol is intended for a serious disease, there is insufficient evidence of safety and effectiveness to support such use; or

(E) If the treatment protocol or treatment IND was based on an immediately life-threatening disease, the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(1) May be effective for its intended use in its intended population; or

(2) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

\* \* \*

Frank E. Young,

Commissioner of Food and Drugs.

Dated: May 20, 1987.

Don M. Newman,

Acting Secretary of Health and Human Services.

[FR Doc. 87-11932 Filed 5-21-87; 9:17 am]

BILLING CODE 4160-01-M

**Food and Drug Administration**

---

Friday  
October 21, 1988

SUBPART E

---

**Part VI**

**Department of  
Health and Human  
Services**

---

**Food and Drug Administration**

---

**21 CFR Parts 312 and 314  
Investigational New Drug, Antibiotic and  
Biological Drug Product Regulations;  
Procedures for Drugs Intended To Treat  
Life-Threatening and Severely Debilitating  
Illnesses; Interim Rule**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****Food and Drug Administration****21 CFR Parts 312 and 314**

[Docket No. 88N-0359]

**Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses**

**Editorial Note:** This reprint incorporates a correction published in the *Federal Register* of Tuesday, November 1, 1988.

**AGENCY:** Food and Drug Administration.

**ACTION:** Interim rule; opportunity for public comment.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing interim regulatory procedures designed to speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and effectiveness. These procedures are intended to facilitate the development, evaluation, and marketing of such products, especially where no satisfactory alternative therapies exist. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedures apply to products intended to treat acquired immunodeficiency syndrome (AIDS), some cancers, and other life-threatening or severely-debilitating illnesses. FDA is issuing these procedures as an interim rule with opportunity for public comment.

**DATES:** Interim rule effective October 21, 1988; comments by December 20, 1988.

**ADDRESS:** Written comments to the Dockets Management Branch (HFA-305) Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:**

Steven H. Unger, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049,

or  
Steven F. Falter, Center for Biologics Evaluation and Research (HFB-130), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, 301-295-8046.

S-031999 002(01)(20-OCT-88-11:45:17)

**SUPPLEMENTARY INFORMATION:**

Expediting the availability of promising new therapies has been a major priority of FDA over the past several years. In the *Federal Register* of May 22, 1987 (52 FR 19466), FDA issued new regulations designed to increase the availability to desperately ill patients of promising investigational new drug (IND) and biological products before general marketing begins. This rulemaking initiative, known as the treatment IND program, was endorsed by the President's Task Force on Regulatory Relief, chaired by Vice President George Bush. The final rule has received broad support from the medical and patient communities. The significance and utility of the treatment IND program has also been recognized and endorsed by the President's Commission on the Human Immunodeficiency Virus (HIV) Epidemic.

The treatment IND regulations became effective on June 22, 1987. Since that time, seven promising experimental therapies have been made available to patients stricken with AIDS, cancer, Parkinson's disease, and other serious conditions. In February 1988, the American Medical Association and FDA cosponsored a major national conference intended to educate physicians and health care organizations about the treatment IND program. FDA has also publicized specific treatment IND approval actions in both medical and lay journals (Refs. 1 through 8).

The treatment IND program is part of FDA's comprehensive efforts to facilitate the development and availability of significant new therapies. For example, through its implementation of the Orphan Drug Act, enacted in 1983, FDA has given special emphasis to potential new therapies for rare diseases or conditions. Since 1983, FDA has granted orphan drug designation to over 200 products, many of which are for life-threatening illnesses. (Orphan drug designation provides the commercial sponsor with certain economic incentives to encourage drug development, including tax credits for the cost of clinical development and exclusive marketing rights for the designated indication upon marketing approval.) FDA has approved for marketing 27 such orphan products, including therapies to treat such life-threatening illnesses as leukemia and AIDS.

FDA has also instituted a number of management improvements designed to expedite the evaluation of AIDS-related products in particular. These include establishment of a top "1-AA" priority for the review of all AIDS products, and

the creation of two new divisions—one for drugs and one for biologicals—to give special focus to the review of such products. FDA's actions have led to the approval in record time of the first drug, zidovudine (formerly called AZT), to treat the AIDS virus, as well as approval for human testing of the first potential AIDS vaccines.

Building on these achievements, on August 3, 1988, Vice President Bush, in his capacity as chairman of the Presidential Task Force on Regulatory Relief, requested FDA to develop procedures for expediting the marketing of new therapies intended to treat AIDS and other life-threatening illnesses. This charge recognized the urgency felt by desperately ill patients and their families. The charge was directed to FDA as the Federal agency that regulates the transfer of the fruits of biomedical research to the marketplace.

The procedures contained in this notice respond to the Vice President's charge. In developing these procedures, FDA met informally with representatives of AIDS interest groups as well as with representatives of consumer, health professional, academic, orphan drug, and industry organizations. FDA also met informally with leadership of the National Institutes of Health.

As described further below, FDA is issuing these new procedures as an interim rule, effective immediately, with an opportunity for public comment. Highlights of the interim rule are summarized below, followed by a section-by-section description of the new procedures.

**I. Highlights of the Regulations**

New procedures are being codified as part of FDA's IND regulations, by adding a new Subpart E consisting of §§ 312.80 through 312.88, and by adding a conforming amendment to FDA's new drug application (NDA) regulations, new paragraph (c) of § 314.25. The purpose of these new procedures (§ 312.80) is to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening or severely-debilitating illnesses, especially where no satisfactory alternative therapies exist. The procedures themselves focus on the entire drug development and evaluation process—from early preclinical and clinical testing, through FDA evaluation of controlled clinical trials and marketing applications, to postmarketing surveillance—in order to treat the entire process as a coherent whole and thereby significantly increase its overall efficiency.

The scope of the new procedures (§ 312.81) will apply to new drugs, antibiotics, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating illnesses. Within the context of these procedures, the term "life-threatening" is defined to include diseases where the likelihood of death is high unless the course of the disease is interrupted (e.g., AIDS and cancer), as well as diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival (e.g., increased survival in persons who have had a stroke or heart attack). The term "severely-debilitating" refers to diseases or conditions that cause major irreversible morbidity (e.g., blindness or neurological degeneration).

A key component of the procedures is early consultation between FDA and drug sponsors (§ 312.82) to seek agreement on the design of necessary preclinical and clinical studies needed to gain marketing approval. Such consultation is intended to improve the efficiency of the process by preventing false starts and wasted effort that could otherwise result from studies that are flawed in design. Most important, at the end of early (phase 1) clinical testing, FDA and the sponsor will seek to reach agreement on the proper design of phase controlled clinical trials, with the goal that such research will be adequate to provide sufficient data on the product's safety and effectiveness to support a decision on its approvability for marketing. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members.

If the preliminary analysis of test results appears promising, FDA may ask the sponsor (§ 312.83) to submit a treatment protocol to be reviewed under the treatment IND regulations. Such a treatment protocol, if submitted and granted, would serve as a bridge between the completion of early stages of clinical trials and final marketing approval.

Once phase 2 testing and analysis is completed by the sponsor and a marketing application is submitted, FDA will evaluate the data utilizing a medical risk-benefit analysis (§ 312.84). As part of this evaluation, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease, the absence of satisfactory alternative therapy. In making decisions on whether to grant marketing approval

for products that have been the subject of an end-of-phase 1 meeting under this rule, FDA will usually seek the advice of outside expert scientific consultants or advisory committees.

As a conforming amendment, a new paragraph (c) is being added to § 314.125 of FDA's NDA regulations. This paragraph is designed to make clear that FDA's evaluation of marketing applications for drugs to treat life-threatening and severely-debilitating diseases will incorporate the criteria being added to § 312.84. These criteria include the adoption of a medical risk-benefit analysis when assessing the safety and effectiveness of these drugs.

Finally, when approval or licensing of a product is being granted, FDA may seek agreement from the sponsor (§ 312.85) to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, and use of the drug over a longer period of time.

These procedures are modeled after the highly successful development, evaluation, and approval of zidovudine, the first drug approved to treat the AIDS virus. Close consultation between FDA, the sponsor, and the National Institutes of Health resulted in efficient preclinical animal testing (2 to 4 weeks in duration), focused phase 1 clinical testing, and a well-designed and conducted multi-center phase 2 clinical trial that provided dramatic evidence of increased survival in patients with advanced cases of AIDS. Given such evidence, FDA approved a treatment protocol in 5 days, and marketing approval in 107 days. Concurrent with approval, the sponsor agreed to conduct phase 4 research studying the effects of zidovudine in patients at an earlier stage of the disease. In total, the drug development and evaluation process, which takes an average of 8 years from initial human testing under an IND to final marketing approval, took only 2 years for zidovudine. Although the total development time will vary with different drugs, FDA believes that the approach contained in these new procedures has great potential for increasing significantly the efficiency of the drug development and evaluation process for the drugs affected.

Moreover, to the extent that the Commissioner determines that clinical trials to treat life-threatening or

severely-debilitating diseases are already underway and are consistent with the requirements of these rules, upon his own initiative and in cooperation with the drug sponsor, he may recommend that a marketing application be submitted under the new procedures.

In conjunction with these procedures, FDA may, in certain circumstances, undertake focused regulatory research (§ 312.86) addressing critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. The FDA Commissioner and other agency officials will also actively monitor (§ 312.87) the progress of the conduct and evaluation of clinical trials for products covered by these procedures, and will be involved in facilitating their appropriate progress.

The final provision of these procedures (§ 312.88) references applicable safeguards inherent in existing FDA regulations to ensure patient safety during clinical testing and the safety of products following marketing approval. These safeguards include FDA requirements regarding informed consent and institutional review boards. These safeguards further include the review of animal studies prior to initial human testing, and the monitoring of adverse drug experiences during the IND, marketing application, and postmarketing phases.

FDA believes that this program, taken as a whole, establishes a new and innovative approach to stimulating the development of particularly important drugs, while at the same time building on past practices that have proven to be successful.

## II. Effective Date and Opportunity for Public Comment

For the reasons described below, FDA is issuing these procedures as an interim rule, with an opportunity for public comment. Because of the urgency associated with life-threatening illnesses, the agency intends to begin implementation of these procedures immediately, but will consider modifications to them based on issues raised during the comment period and experience gained under the interim rule.

The program established in this interim rule is intended to bring about a significant improvement in the efficiency of the development, evaluation, and marketing of new therapies for life-threatening and severely-debilitating illnesses, while preserving appropriate guarantees for safety and effectiveness. Although the program is important, it

builds upon managerial and regulatory options available under existing practices and procedures. The opportunity for early consultation with sponsors on the design of clinical trials, for example, is permissible under the existing investigational new drug review provisions of FDA's regulations. Because the new program represents a fundamental commitment to expediting the development of innovative products, it is appropriate to identify and describe the components of that program and to codify them for ready reference by affected persons. Moreover, the amendment to Part 314, requiring consideration of risk-benefit criteria in decisions to approve or disapprove these drugs, is consistent with the flexibility granted to the Agency under the statute in determining whether substantial evidence of safety and effectiveness has been demonstrated.

To the extent that the elements of the program announced today are regarded as new rules, they are within the exception to the Administrative Procedure Act notice-and-comment requirement for general statements of policy and rules of agency organization, procedure, and practice (5 U.S.C. 553(b)(A)). Moreover, if the new program is regarded as substantive rulemaking, the Commissioner hereby finds good cause for not providing notice and an opportunity to comment prior to its effectiveness. The importance of developing new therapies for life-threatening diseases has been highlighted in recent years by the AIDS crisis. In addition, the sustained search by drug researchers for treatments for many other diseases, including Alzheimer's disease and cancer, merits immediate attention. FDA believes that, as promising new therapies for these diseases are identified, they must be developed by sponsors and evaluated by the agency as expeditiously as possible. It would therefore be contrary to the public interest to delay the implementation of this program pending the time necessary to engage in the APA's notice-and-comment procedures, and such delay would also be unnecessary because the program derives from existing regulations that have already been the subject of notice and an opportunity for comment (5 U.S.C. 553(b)(B); 21 CFR 10.40(e)).

FDA believes, however, that it should invite and consider public comment on its practices and procedures for reviewing investigational new drug, new drug approval, and biologics license applications, including those described in this notice.

### III. Contents of the Program

#### A. Purpose

The drug development process is generally thought of, in simplified terms, as consisting of three phases of human testing to determine if a drug is safe and effective: Phase 1 with 10 to 50 patients to study how the drug is tolerated, metabolized, and excreted; phase 2 with 50 to 200 patients in which the safety and efficacy of the drug are first evaluated in controlled trials; and phase 3 with 200 to 1,000 or more patients to confirm and expand upon the safety and efficacy data obtained from the first two phases. (For purposes of this discussion, the word "drug" is meant to include new drugs, antibiotic drugs, and biological products.)

A recent study of new drug development has documented the percentage of drugs whose development is discontinued after each of these phases. Of the 174 new chemical entities that entered phase 1 testing under U.S. IND's between 1976 and 1978, 70 percent successfully completed phase 1 and moved on to phase 2, while 33 percent successfully completed phase 2 and moved on to phase 3. At this point the dropout rate slowed considerably, as 27 percent successfully completed phase 3 and were submitted to FDA in the form of a marketing application, and 20 percent actually received marketing approval from the agency (Ref. 9).

The three phases describe the usual process of drug development, but they are not statutory requirements. The basis for marketing approval is the adequacy of the data available; progression through the particular phases is simply the usual means the sponsor uses to collect the data needed for approval. The statute itself focuses on the standard of evidence needed for approval, as derived from adequate and well-controlled clinical investigations, with no mention of phases 1, 2, and 3. FDA believes that if sufficient attention is paid to the quality and amount of data obtained in phase 2, it should be possible to identify early those drugs that represent safe and effective treatments for life-threatening and severely-debilitating diseases—and to develop the evidence needed for their marketing—in the course of carrying out the first controlled trials.

This program is based on that premise. For drugs intended to treat life-threatening and severely debilitating illnesses, it should be possible to reduce the total premarket drug development time by designing and conducting phase 2 controlled trails that are capable of providing necessary data on the drug's safety and effectiveness. FDA would

analyze data from such studies utilizing medical risk-benefit considerations appropriate for drugs intended to treat life-threatening or severely-debilitating illnesses. The treatment IND, as appropriate, could continue to serve as a bridge between phase 2 trials and the point of marketing approval. Drug sponsors might also conduct postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. The FDA Commissioner and other agency officials would actively monitor the process to ensure that such products are developed by the sponsor and analyzed by the agency as expeditiously as possible.

Section 312.80 of the rule summarizes the program's purpose: to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening or severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated in FDA's new drug application regulations (§ 314.105(c)), while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. In promulgating this interim rule, FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. The procedures contained in this rule reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedures outlined in this notice should be interpreted consistent with this statement of purpose.

#### B. Scope

Section 312.81 of the rule outlines the scope of this rule. The rule applies to new drug, antibiotic, and biological products being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

A "life-threatening" disease is defined as one in which the likelihood of death is high unless the course of the disease is interrupted (e.g., progression from asymptomatic HIV infection to



symptomatic HIV infection, or further progression to a later stage of AIDS; metastatic cancer; amyotrophic lateral sclerosis (e.g., amyotrophic lateral sclerosis). This use of the term "life-threatening" plainly includes any disease whose progression is likely to lead to death, especially in a short period of time (e.g., 6 months to 1 year). This section also applies to any condition in which a study is to be carried out to determine whether the treatment has a beneficial effect on survival (e.g., increased survival after a stroke or heart attack).

The term "severely-debilitating" is defined as a disease or condition that leads to major irreversible morbidity (e.g., severe functional deficits in multiple sclerosis, Alzheimer's disease or progressive ankylosing spondylitis; prevention of blindness due to cytomegalovirus infection in AIDS patients).

With respect to "severely-debilitating" illnesses, the procedures contained in this rule are applicable to those instances where the studies proposed will examine the treatment's capacity to prevent or reverse what would otherwise be irreversible damage, such as putting ankylosing spondylitis into remission and stopping joint damage and deformity, or preventing blindness. It is in such studies that

efficiency in study design and an early answer to key questions on safety and effectiveness are especially critical. The agency notes that there are many other studies that examine symptomatic relief (e.g., pain of ankylosing spondylitis) rather than irreversible morbidity. While products being studied for symptomatic relief of a serious disease would likely qualify for treatment IND consideration under § 312.34(b)(2), they would not be covered by the procedures contained in this interim rule.

In all of the cases covered by these new procedures, when the end points of clinical study relate to survival or prevention of major disability, they are of such great importance that it is imperative that the first controlled clinical trials be designed and conducted as well as possible. If this is not done, preliminary reports of success from poorly designed studies might make it difficult ever to carry out the proper trials. FDA believes it is clearly in the public interest to assure in such situations, to the extent possible, that the first clinical trials be designed so that the true merit of the drug or biologic can be evaluated as promptly as possible. FDA will also expedite the registration of eligible orphan products and provide additional incentive for their development.

The agency recognizes that the scope of these procedures is subject to interpretation, and the examples given above are illustrative only. FDA intends to be flexible in its implementation of this program and, subject to available resources, provide early advice when it is sought. The agency encourages sponsors to consult with FDA on the program's applicability to particular products.

### C. Elements of the Program

1. *Early consultation.* A key component to be addressed is early consultation, which is covered in § 312.82 of the rule. In 1987, FDA codified the practice that, upon request of a drug's sponsor, FDA medical staff will hold a conference with the sponsor at the end of phase 2 testing. (See § 312.47(b)(1).) The goal of this conference is to reach agreement on a plan of phase 3 testing that will provide the needed remaining evidence of the drug's safety and efficacy to gain marketing approval. If, however, the evidence obtained from well-planned and well-executed phase 2 research is sufficient under the statute for marketing approval, there may be no need for additional phase 3 premarket testing, and the drug can become available much more rapidly than usual.

This is most likely to occur for drugs to treat life-threatening illnesses where the relatively small amount of data available at this stage may nevertheless be sufficient for approval. For example, phase 2 research was sufficient for approval of zidovudine the only drug approved thus far to treat the AIDS virus. Zidovudine was developed and approved in record time, largely because further premarketing (phase 3) studies were not needed to support safety and effectiveness following completion of a highly successful well-controlled multicenter phase 2 study that demonstrated dramatic effects on survival.

There have been other circumstances, particularly in the oncology area, where early (phase 2) results were such that additional studies were not needed to conclude that the drug was effective and that its benefits outweighed its risks. For example, the licensing of alpha interferons to treat hairy cell leukemia was based on phase 2 trials that showed partial or complete remission of the disease in 75 to 90 percent of patients.

To build upon these successes, FDA is instituting a process for conferences to be held at the end of phase 1 (rather than waiting until the end of phase 2) with the sponsors of drugs and biologics intended to treat life-threatening and severely-debilitating illnesses, especially where there are no

satisfactory alternative therapies. The purpose of these conferences will be to review the product's phase 1 test results and phase 2 plans for clinical testing. If enough is known about the drug at that time, agreement would be reached on a phase 2 testing program (e.g., the design of the studies, the number of patients to be tested, the end points to be used, and the proposed mode of replication), that would be sufficient to establish the drug's safety and effectiveness. Where the data resulting from these phase 2 studies prove sufficient to allow a determination that, on the basis of risk-benefit considerations detailed further below, the drug is safe and effective, FDA will approve the drug without further preapproval studies. In this case, phase 2 thus obviates the need for further research in phase 3, if the phase 2 trials prove successful. Of course, when the results of phase 2 research do not provide evidence that fulfills the statutory criteria for approval, further preapproval studies will be necessary.

Because the end-of-phase 1 conference serves the same function (except earlier in the process) as an end-of-phase 2 conference would otherwise serve, FDA will apply the same procedures to both meetings, as codified in § 312.47(b)(1). This includes provision for documenting the agreements reached at the meeting. In order to provide the broadest possible expertise available, FDA may invite to the meeting one or more of its advisory committee members or other scientific consultants. The sponsor may, of course, also bring scientific consultants to the meeting.

With respect to study design, the agency recognizes that there has been some confusion about the role of placebo-controlled studies in patients with a life-threatening disease. FDA believes that a requirement for placebo-controlled studies is *not* appropriate in those situations where there is known to be an effective therapy, for the stage of disease or condition under investigation, that can improve survival or prevent irreversible morbidity. For example, in the case of symptomatic AIDS or advanced AIDS-related complex (ARC), where zidovudine is known to improve survival, it would not be appropriate to compare a new drug with placebo. Rather, the new drug should be compared with zidovudine. It would also be possible to compare the new drug plus zidovudine with zidovudine alone, but in neither case would it be necessary to deny patients therapy with zidovudine which is known to improve survival. In contrast, where no therapy has been shown to be effective, it is scientifically and ethically appropriate

to randomize patients to test drug and placebo. This was done with zidovudine and, by providing early and clear evidence of benefit in terms of improved survival, enabled FDA to confer the rapid approval that made the drug widely available to AIDS patients.

The Institute of Medicine, in its recent report entitled, "Confronting AIDS: Update 1988," emphasized the importance of controlled clinical trials as the "fastest, most efficient way to determine what treatments work" (Executive Summary at page 19; Report at page 139) (Ref. 10). As the report continues, "Conducting well-designed trials from the beginning will benefit more patients, sooner, than any other approach. Poorly designed trials, or administering drugs without controls and 'observing' the course of the disease, risk being inconclusive or drawing incorrect conclusions." (Report at page 139) (Ref. 10). FDA fully supports the early initiation of well-designed phase 2 controlled clinical trials as the most efficient mechanism of evaluating treatments for the desperately ill.

When planning phase 2 studies, it will be particularly important to make optimal use of pharmacokinetic/pharmacodynamic studies carried out in phase 1. Such phase 1 data are particularly useful in selecting the best dose(s) and dosing intervals for phase 2 testing. Therefore, FDA input should be helpful in the design of phase 1 studies also.

FDA can also make the drug development process more efficient by interacting with the drug sponsor, even before phase 1 testing begins, to help identify the animal studies necessary to assess the toxicity of the new drug and assure that clinical studies can be initiated with reasonable assurance of safety. In consulting with sponsors on animal studies, FDA takes into account the seriousness of the disease to be treated and the nature of the clinical studies planned. In this way, FDA involvement can facilitate the initiation of trials in human patients as early as the safety studies in animals permit, thereby reducing potential barriers to innovation at this early but important stage of new pharmaceutical development.

For example, using this process, some new AIDS drugs have been able to enter clinical testing after animal studies that were 4 weeks long or less in duration, and the preclinical animal studies completed before initial human use of zidovudine were 2 to 4 weeks long. By working closely with the sponsor, FDA can suggest the minimum amount of preclinical testing needed to go forward without compromising the safety of

clinical study participants. Unnecessary animal studies can be avoided, animal lives can be spared, and the sponsor can move the drug into clinical testing in the shortest possible time. Moreover, early FDA involvement can also shorten the time it takes the agency to review and IND submission and lessen the likelihood of FDA placing the application on clinical hold.

**2. Treatment IND's.** Section 312.83 of the rule outlines the role of the treatment IND in the context of this overall program. As codified in §§ 312.34 and 312.35, treatment IND's are intended to permit the wider use of promising experimental drugs for serious and immediately life-threatening illnesses in patients who lack satisfactory alternative therapy. Within the drug development process, treatment IND's can provide a bridge between the completion and initial analysis of promising phase 2 studies and the point of marketing approval. Thus, when early evidence from phase 2 indicates that a drug for a life-threatening or severely-debilitating illness is promising, FDA will actively work with the sponsor to evaluate the appropriateness of a treatment protocol. This approach was used during the development of zidovudine, and allowed wide availability of the drug to over 4,000 patients while the marketing application was being assembled by the sponsor and reviewed by FDA. In addition, FDA will continue to work actively to educate physicians and drug sponsors on how to utilize the treatment IND process most effectively.

**3. Risk-benefit analysis.** Section 312.84(a) of the rule provides that FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

While the statute uses the terms safety and effectiveness, rather than risks and benefits, the decision on whether to approve a drug inherently represents a medical risk-benefit judgment. The agency recognizes that safety and effectiveness are not absolute (i.e., not all drugs are free of risk or have unequivocal benefits), but must be assessed in light of what condition the drug treats. This is particularly true in the case of drugs to

treat life-threatening diseases, where drugs that are quite toxic may nevertheless be considered safe under the circumstances.

In carrying out the statutory mandate, FDA will consider the seriousness of the disease being treated in balancing risks and benefits. For example, as a class, oncologic drugs are highly toxic, but this is acceptable when they are used to treat illnesses for which they represent the only available method of treatment and when they can have a favorable influence on survival or on intractable symptoms. Moreover, dramatic responses (i.e., great benefit), especially on significant end points like survival or progression to an inevitably fatal stage of illness, make it easier to conclude that the benefits of treatment outweigh its risks, even if not all important questions about the drug are answered. Clearly, for a life-threatening illness, a relatively high level of known risk and some uncertainty about potential risk from the drug can be acceptable in exchange for the improved survival provided by effective drug treatment for a condition that, left untreated, would result in death. Similarly, for the same life-threatening illnesses, evidence of effectiveness must be weighed against risks of the drug and the knowledge that death would result in the absence of treatment.

Section 312.84(b) of the rule provides that the agency will usually seek the advice of outside expert consultants or advisory committees in reaching its conclusions. That section also provides that FDA will notify the members of the relevant standing advisory committee of the filing of a marketing application covered by this rule, and its availability for review.

In seeking to utilize phase 2 data for final decisionmaking, FDA would be trying to increase the likelihood that a safe and effective drug, especially one that affects mortality or major irreversible morbidity, would be shown safe and effective in the shortest possible time by assuring that the initial studies are adequate to do this—i.e., to provide evidence, even though derived from a limited data base, that would be sufficient to reach a benefit-risk judgment. FDA's goal is to be able to reach a scientifically defensible decision based on the results of well-designed phase 2 controlled clinical trials. If, on the basis of phase 2 testing, a therapy is found to effectively treat a life-threatening disease for which no other therapy exists, it would not be appropriate to continue premarketing research into phase 3. However, poorly

designed phase 2 studies serve to retard the drug development process.

If FDA concludes that the data presented are not sufficient for marketing approval, § 312.84(b) of the rule provides that FDA will issue a letter to the sponsor describing the deficiencies in that application, including why the results of the research design agreed to under § 312.82 of this rule, or in subsequent meetings, did not provide sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

To increase the likelihood that phase 2 testing can provide sufficient results, sponsors could need to plan phase 2 studies that are somewhat larger and more extensive than is currently the norm, including a mode for replication of key findings. Moreover, to avoid missing an effect by using too little drug, or to avoid studying a dose that proves toxic, it may be necessary to study several doses in the first formal trials, an approach that may require a larger study but can plainly save time, thereby enabling physicians to treat patients with life-threatening illnesses more rapidly. However, it should be appreciated that a drug has only minor or inconsistent therapeutic benefits, its positive effects may be missed in this stage of clinical testing, even if the drug ultimately proves to be beneficial following more extensive phase 3 trials.

The issue of replication requires careful consideration. The requirement in the statute for adequate and well-controlled "clinical investigations" (21 U.S.C. 355(d) (emphasis added)) has long been interpreted to mean that the effectiveness of a drug should be supported by more than one well-controlled clinical trial and carried out by independent investigators. This interpretation is also consistent with the general scientific demand for replicability to ensure reliability of study results. Therefore, as a general requirement, the clinical trials submitted in a marketing application—including trials on products covered by this rule—must include studies by more than one independent investigator, each of whom has studied a number of patients adequate to generate statistically reliable results.

When applying the statutory requirement of "adequate and well-controlled investigations" to a drug for a life-threatening or severely-debilitating disease, FDA will consider the quality of the data submitted, including the assurance of the data's consistency, reliability, and reproducibility. There

have been a few unusual instances in which a particularly persuasive multi-center study has been accepted in support of a claim of increased survival because the study was, due to its design and dramatic and reliable results, considered highly persuasive; therefore, replication was not required for ethical reasons. One such example was the approval of zidovudine to treat AIDS patients (discussed earlier in this preamble). A second example involved the approval of timolol for reduction of post-infarction mortality, where a major effect on mortality was demonstrated in a large multi-center study. The timolol study was very persuasive because of excellent design, minimal or no problems during execution of the study, and a high degree of statistical significance associated with the critical finding.

In both these instances, the sufficiency of a multi-center study for marketing approval was based on the research being well-designed and well-conducted, and a dramatic increase in survival of the patients using the drug. Under these circumstances, FDA believed it would be unethical to repeat the trial. FDA would consider applying the same principle to other such cases in which the outcome of a multi-center study demonstrated a consistently dramatic increase in survival among independently evaluable study sites and where repetition of the study would be unethical. However, the agency cautions that persuasively dramatic results are rare and that two entirely independent studies will generally be required. Sponsors should therefore plan in advance a strategy for replication of key findings through a second well-controlled study. Such replication need not delay approval where a sponsor carries out all necessary clinical studies concurrently.

Finally, § 312.84(d) of the rule provides that marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in 21 CFR Part 314 or Part 600, as well as those in this interim rule. FDA has also added a conforming amendment to § 314.125 of the new drug application regulations, noting that for drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88, the criteria contained in paragraphs (b)(3), (4), and (5) of § 314.125 shall be applied according to the considerations contained in § 312.84.

While FDA can contribute to the design of the controlled clinical trials, and actively urge that such trials be pursued, the agency has no direct

control over the pace at which trials are initiated and completed. Success of drug development depends on the willingness of the sponsor and clinical investigators to devote the necessary time and resources to complete the studies expeditiously.

*4. Phase 4 studies.* Section 312.85 of the rule describes the role of phase 4 studies in this program. If FDA approval is gained on the basis of limited, but sufficient, clinical trials, it will usually be important to conduct postmarketing (phase 4) clinical studies that will extend the knowledge about the drug's safety and efficacy and allow physicians to optimize its use. For example, in the case of zidovudine, early appearance of a dramatic improvement in survival of the treated patients was taken as clear evidence that, for the relatively advanced HIV-infected patients treated, the benefits clearly outweighed the risks. Although significant side effects of zidovudine were found, the clinically demonstrated benefit of prolonged survival clearly outweighed those risks.

This does not mean that all important questions were answered at the time of approval of zidovudine and that research into its use could end. It was critical to examine—after marketing—its use in earlier stages of the disease, where its toxicity might outweigh its benefit (i.e., in earlier stages of the disease, survival is much greater without treatment so that there is less improvement possible, but toxicity might be just as severe). It was also important to explore dosing regimens that might be less toxic and equally effective. In addition, as with any drug, it is important to consider whether there are long-term adverse effects that might "take away" the early gain. As with zidovudine, FDA has generally been able to obtain a voluntary agreement with drug sponsors about the need to do such followup studies and the nature of their design, because sponsors also recognize important gaps in the data base and believe they need to be filled. Section 312.85 of the rule codifies this practice.

*5. Focused FDA regulatory research.* The responsibility for conducting the preclinical and clinical testing needed to gain marketing approval clearly rests with the drug's sponsor. This rule does not alter that responsibility. Recognizing the lack of available therapy for certain life-threatening and severely-debilitating illnesses, § 312.86 of the rule provides that in certain circumstances FDA may, in its discretion, undertake research on critical rate-limiting aspects of the preclinical, chemical/manufacturing,

and clinical phases of drug development and evaluation. For example, FDA often needs specific information upon which critical regulatory decisions are made—e.g., manufacturing standards and assays for vaccine or biotechnology products. Recent examples include FDA potency testing of vaccines and development of assay methods for drug bioavailability. FDA is prepared to intensify this practice on a limited basis as a means of meeting a public health need in facilitating the development of therapies to treat life-threatening illnesses, rather than merely waiting passively.

**6. Active monitoring of conduct and evaluation of clinical trials.** Section 312.87 of the rule provides that the Commissioner and other agency officials will actively monitor the progress of the conduct and evaluation of clinical trials and be involved in stimulating their appropriate progress. Recognizing that people with life-threatening diseases face a catastrophic condition that requires special attention, it is imperative that the conduct of clinical trials and FDA's evaluation of them proceed as expeditiously as possible. FDA actions would include, for example, contacting the sponsor directly when clinical trials are not proceeding on schedule. FDA may also convene special meetings of its advisory committees, as necessary, rather than waiting for the next scheduled periodic meeting.

Finally, FDA, in conjunction with other Public Health Service agencies, will utilize, to the extent possible, clearinghouse mechanisms for informing physicians and patients of investigational therapies for life-threatening illnesses. Existing mechanisms of this type will be augmented, as appropriate.

**7. Safeguards for patient safety.** If successfully implemented, this program will expedite the availability and approval of new therapies for life-threatening and severely-debilitating illnesses while assuring that the products are shown safe and effective under the law. Section 312.88 of the rule references safeguards inherent in FDA regulations that ensure the safety of clinical testing and the safety of products following marketing approval. These include the requirements for informed consent (21 CFR Part 50) and institutional review boards (21 CFR Part 56). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23); IND safety reports during the conduct of clinical trials and treatment IND protocols (§ 312.32); safety update reports during

the review of marketing applications (§ 314.50); and adverse drug reaction reports after products are approved for marketing (§ 314.80).

In addition to these regulatory safeguards designed to assure patient safety, FDA's practices and procedures provide additional safeguards to assure the quality and integrity of the drug development and review process. These include conducting on-site audits of key studies and/or clinical investigators to assure authenticity of the data submitted to FDA, and inspections of manufacturing facilities before marketing approval is granted to assure that manufacturers are able to produce properly formulated compounds.

#### *D. Environmental Impact*

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### *E. Economic Impact*

FDA has considered the economic impacts of this interim rule and concludes that additional costs resulting from this rule will be negligible, and to the limited extent that they may occur, they will likely be more than off-set by the societal benefits of this rule.

The compression of the drug development process set forth in this rule for life-threatening and severely-debilitating illnesses presents a trade-off for affected sponsors. They would be relieved of conducting the customary phase 2/phase 3 clinical studies if they participate in early study design consultation with FDA, conduct a sufficiently comprehensive phase 2 study, and stand ready to conduct any necessary phase 4 studies. Considering the probable time savings of this process, it is expected that the net cost of clinical development and regulatory review for a sponsor will remain constant or possibly decrease. Even if costs were to increase slightly, the societal benefits would more than likely compensate for any added costs since a considerable patient population would be receiving the life-saving benefits of the expedited therapy over an extended period of time that would not otherwise be realized.

Accordingly, FDA concludes that this interim rule is not a major rule as defined by Executive Order 12291, which would require a regulatory flexibility analysis. Furthermore, this rule is not expected to impose substantial impacts on a significant

number of small entities which would require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

#### *F. Paperwork Reduction Act of 1980*

This interim rule does not contain new collection of information requirements. Section 312.88 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980. Sections 312.23 and 312.32 were approved under OMB control number 0910-0014. Section 314.50 was approved under OMB control number 0910-0001. Section 314.80 was approved under OMB control number 0910-0230.

#### **References**

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Young, Frank E., and Stuart L. Nightingale, "FDA's Newly Designated Treatment IND's," "Information on Treatment IND's as They Become Available to the Practitioner," *Journal of the American Medical Association*, 260:224-225, 247, 1988.
2. Young, Frank E., John A. Norris, Joseph A. Levitt, and Stuart L. Nightingale, "The FDA's New Procedures for the Use of Investigational Drugs in Treatment," *Journal of the American Medical Association*, 259:2267-2270, 1988.
3. "Drugs Hold Hope for Parkinson's Obsessive-Compulsive Patients," *FDA Consumer*, September 1988:31.
4. Young, Frank E., "Experimental Drugs for the Desperately Ill: A Progress Report," *FDA Consumer*, May 1988:2-3.
5. "Updates," *FDA Consumer*, February 1988:2-3.
6. Young, Frank E., "New Drug Development in the United States," *FDA Consumer*, November 1987:4-5.
7. "Updates," *FDA Consumer*, September 1987:5-6.
8. Young, Frank E., "Experimental Drugs for the Desperately Ill," *FDA Consumer*, June 1987:2-3.
9. Office of Planning and Evaluation Study 77, "The Outcome of Research on New Molecular Entities Commencing Clinical Research in the Years 1976-78," FDA, May 1988.
10. "Confronting AIDS: Update 1988," Institute of Medicine, 1988.

#### **List of Subjects**

##### *21 CFR Part 312*

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety

**21 CFR Part 314**

Administrative practice and procedure, Drugs, Reporting and cordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, Parts 312 and 314 are amended as follows:

**PART 312—INVESTIGATIONAL NEW DRUG APPLICATION**

1. Subparts E and F are redesignated as Subparts F and G, respectively, and new Subpart E is added consisting of §§ 312.80 through 312.88 to read as follows:

**Subpart E—Drugs Intended To Treat Life-threatening and Severely-debilitating Illnesses**

- Sec.
- 312.80 Purpose.
- 312.81 Scope.
- 312.82 Early consultation.
- 312.83 Treatment protocols.
- 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.
- 312.85 Phase 4 studies.
- 312.86 Focused FDA regulatory research.
- 312.87 Active monitoring of conduct and evaluation of clinical trials.
- 312.88 Safeguards for patient safety.

Authority: Secs. 501, 502, 503, 505, 506, 507, 1, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); 21 CFR 5.10, 5.11.

**Subpart E—Drugs Intended To Treat Life Threatening and Severely-debilitating Illnesses****§ 312.80 Purpose.**

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated § 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side

effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

**§ 312.81 Scope.**

This section applies to new drug, antibiotic, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:

- (1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and
- (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

**§ 312.82 Early consultation.**

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach

agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing. The procedures outlined in § 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

**§ 312.83 Treatment protocols.**

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§ 312.34 and 312.35. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in § 312.42(b)(3)(ii)).

**§ 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.**

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under § 312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under § 314.101 or Part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue (for a drug) a not approvable letter pursuant to § 314.120 of this chapter, or (for a biologic) a deficiencies letter consistent with the biological product licensing procedures. Such letter, in describing the

deficiencies in the application, will address why the results of the research design agreed to under § 312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in Part 314 or Part 600 of this chapter, as well as those in this subpart.

**§ 312.85 Phase 4 studies.**

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

**§ 312.86 Focused FDA regulatory research.**

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/

manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

**§ 312.87 Active monitoring of conduct and evaluation of clinical trials.**

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

**§ 312.88 Safeguards for patient safety.**

All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (Part 50 of this chapter) and institutional review boards (Part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§ 312.32), safety update reports during agency review of a marketing application (§ 314.50 of this chapter), and postmarketing adverse reaction reporting (§ 314.80 of this chapter).

**PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG**

2. The authority citation for 21 CFR Part 314 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); 21 CFR 5.10, 5.11.

3. Section 314.125 is amended by adding paragraph (c) to read as follows:

**§ 314.125 Refusal to approve an application.**

(c) For drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88 of this chapter, the criteria contained in paragraphs (b) (3), (4), and (5) of this section shall be applied according to the considerations contained in § 312.84 of this chapter.

Frank E. Young,  
*Commissioner of Food and Drugs.*  
Otis R. Bowen,

*Secretary of Health and Human Services.*

Dated: October 18, 1988.

[FR Doc. 88-24457 Filed 10-19-88; 10:18 am]

**Editorial Note:** This reprint incorporates a correction published in the *Federal Register* of Tuesday, November 1, 1988.

BILLING CODE 4160-01-M

**Food and Drug Administration**

---

Wednesday  
April 15, 1992

PARALLEL TRACK

---

Part V

**Department of  
Health and Human  
Services**

---

Food and Drug Administration  
Public Health Service

---

21 CFR Part 312

Investigational New Drug, Antibiotic, and  
Biological Product Applications; Clinical  
Hold and Termination; Final Rule

Expanded Availability of Investigational  
New Drugs Through a Parallel Track  
Mechanism for People With AIDS and  
Other HIV-Related Disease; Notice

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Public Health Service**

**Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and Other HIV-Related Disease**

**AGENCY:** Public Health Service, HHS.

**ACTION:** Notice Final Policy Statement.

**SUMMARY:** The Public Health Service (PHS) is announcing a final policy to make promising investigational drugs for AIDS and other HIV-related diseases more widely available under "parallel track" protocols while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out. The "parallel track" initiative establishes an administrative system designed to expand the availability of promising investigational agents and to make these agents more widely available to people with AIDS and other HIV-related diseases who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.

**FOR FURTHER INFORMATION CONTACT:** Donald Pohl, Office of AIDS Coordination (HF-12), Food and Drug Administration/PHS 5600 Fishers Lane, Rockville, MD 20857, 301-443-0104.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of May 21, 1990 (55 FR 20856), the PHS published a proposed policy for the expanded availability of investigational new drugs through parallel track for people with HIV infection and AIDS. 1,210 comments were received; of these, 200 were unique while the other 1,010 were form letters.

As with the proposed policy, the final policy was developed by a PHS workgroup composed of representatives from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Office of the General Counsel, and the National AIDS Program Office (NAPO), with significant input from community advocates, community physicians, clinical researchers, and industry representatives.

**I. Comments**

**A. Expansion to Other Life-Threatening Diseases**

Many comments supported the expansion of the parallel track mechanism to other life-threatening diseases. A number of comments stated that the policy as it applies to AIDS and other HIV-related disease should be

evaluated before applying the policy to other diseases, while some comments supported immediate expansion to other diseases. Comments from individuals as well as manufacturers and professional associations expressed the view that the parallel track policy for AIDS and other HIV-related disease should serve as a pilot project to work out specific appropriate administrative procedures. Some individuals stated that a policy similar to parallel track for other life-threatening diseases should be developed only after consultation with advocates for patients with those other diseases.

A variety of regulatory mechanisms exists to make promising investigational agents more widely available for serious and life-threatening diseases.

These specific processes (such as the NIH AIDS Research Advisory Committee (ARAC) and the specific National Human Subjects Panel described below) are not applicable to other life-threatening diseases. This parallel track policy describes processes specifically for AIDS and other HIV-related diseases. However, PHS invites patient groups, physicians and sponsors interested in developing a similar process for other life-threatening diseases to work with PHS on issues concerning expanding the parallel track mechanism for other life-threatening diseases.

Currently, other mechanisms exist for making investigational drugs available prior to approval to persons with life-threatening diseases for which there is no satisfactory alternative therapy. Under the treatment IND procedures, eligible patients can have access to investigational drugs intended to treat serious or life-threatening diseases that meet established criteria. For cancer patients in particular, FDA and the National Cancer Institute (NCI) have described a special category of drugs, "Group C" drugs, which may be provided to eligible patients through protocols outside the controlled clinical trials prior to approval. In many instances it appears these mechanisms adequately address demand for early access.

PHS intends to evaluate the parallel track experiences specifically to determine whether worthwhile benefits are provided in addition to those available under mechanisms such as the treatment IND or Group C approaches. The evaluation would also include a consideration of whether parallel track has had detrimental effects on individuals or on the ability to determine the safety and effectiveness of promising therapies.

Even though a combination of safeguards has been built into this policy (including careful product selection, informed consent, patient and physician education, a national human subjects protections review panel, community involvement, and oversight), allowing increased availability of drugs prior to definitive evidence of either safety or efficacy carries potential risks for the participants.

**B. NIH AIDS Research Advisory Committee (ARAC)**

**1. Role of the ARAC in Review of Drugs for Parallel Track**

Some comments endorsed the proposed role of the AIDS Research Advisory Committee (ARAC) in reviewing sponsors' requests and in making recommendations regarding parallel track protocols. Other comments requested further clarification of the ARAC's role in the parallel track process. Two comments stated that sponsors should not have the option of bypassing ARAC review.

As outlined in the policy, IND sponsors will submit parallel track proposals to FDA as amendments to existing INDs. The sponsor may be the manufacturer of the drug or another organization conducting drug trials. Unless the sponsor objects, FDA will refer the parallel track proposal to the ARAC for consideration. Requests for ARAC review will be processed and scheduled by National Institute for Allergy and Infectious Diseases (NIAID) Committee staff. After review of the proposal, the ARAC will make a recommendation to the Director, NIAID. The Director of NIAID will then forward a recommendation through the Director of NIH to the FDA Commissioner.

In this process, the ARAC serves as an expert advisory panel composed of persons with HIV-related disease, physicians, non-government scientists, and representatives of activist organizations. In addition to reviewing and making recommendations on parallel track proposals generated by IND sponsors, the ARAC may make recommendations, based upon available evidence, concerning termination of parallel track protocols. While the ARAC plays a vital role in the review of parallel track protocols, the policy will still allow sponsors to request that their protocols not be reviewed by the ARAC.

**2. Non-Sponsor Requests for ARAC Consideration**

A number of comments stated that in addition to sponsors, any interested person should be able to petition the



ARAC to consider the appropriateness of parallel track protocols for specific drug products.

An entity which is authorized to distribute the drug, which has access to all data necessary to support an IND, and which is willing and able to carry out the responsibilities of the sponsor of an investigational new drug application is necessary for the initiation of a parallel track protocol. As discussed in the proposed policy statement, deliberations about whether or not a specific drug is appropriate for parallel track study can best be accomplished through the review of a detailed parallel track protocol in conjunction with the controlled clinical trials protocols for that same drug.

Information needed to evaluate the benefits and risks of a drug is ordinarily information that is proprietary to the drug manufacturer. Unless the sponsor of an investigational drug indicates a willingness to provide the necessary information and to conduct a parallel track study, the ARAC would be frustrated in its attempt to review a drug for appropriateness for parallel track availability.

The NIH, as part of its research mandate, has a public responsibility to ensure that research showing high promise is pursued and supported. Therefore, the NIH can be requested to take on the obligation of developing a drug lacking private sector sponsorship, and in that role also assume any responsibilities for implementing a parallel track program. The decision to assume these obligations would, of course, be guided by the available resources and competing needs for those resources. The ARAC, which has programmatic advisory responsibilities for NIAID, might be consulted in such decisions.

There may be extraordinary circumstances in which a non-sponsor has sufficient information about the drug and its potential usefulness for the intended patient population and condition to be treated, and about the clinical trials to permit meaningful review of a parallel track proposal. In such circumstances, the non-sponsor could request NIAID to refer the matter to the ARAC for review and recommendation. If NIAID determined that a meaningful review and recommendation could be accomplished, it could refer the matter for ARAC consideration. Because PHS expects that such circumstances would be rare, the policy statement has not been amended to refer specifically to such requests by non-sponsors.

### 3. ARAC's Role in Defining "Standard Treatment"

A number of comments stated that the ARAC should have the authority to define "standard treatment" as applied to the eligibility criteria for each parallel track protocol. The ARAC may make recommendations with respect to any aspect of a proposed parallel track protocol, including the section dealing with eligibility criteria. The ARAC may review the description of standard treatment, as well as the descriptions of when it will be considered that standard treatment "cannot be tolerated" or is "no longer effective".

As with the other aspects of approval for parallel track protocols, FDA has the authority to make the final determination on the acceptability of the eligibility criteria in the protocol. In making determinations regarding parallel track protocols, FDA will consider the ARAC's recommendations on each issue. Further discussion of "standard treatment" appears below, at F. "Eligibility Criteria." Even when a sponsor elects not to have ARAC review, FDA may elect to consult ARAC on the appropriateness of the description of standard therapy.

### 4. ARAC as the Interim National Human Subjects Protections Review Panel (National Human Subjects Panel)

Several comments raised concerns about the proposal to have an ad hoc subcommittee of the ARAC function as an interim national human subjects protections review panel. PHS has determined that it would be more appropriate to have the AIDS Program Advisory Committee (APAC) at NIH serve as this interim panel. The comments regarding this interim group and other institutional review board (IRB) issues are described more fully below under M. "Human Subjects Protections."

### C. Review Criteria

Some comments criticized the proposed parallel track review criteria and process as overly complex and likely to delay access to experimental treatments. One comment stated that the ambiguity of the criteria makes it difficult to assess the potential impact of the policy on drug availability. The proposed policy statement listed eight categories of information that the FDA and the ARAC would ordinarily consider in reviewing a proposal to make an investigational drug available through a parallel track protocol. In general, PHS believes that this is the minimum information needed to enable the decision makers to assess potential

risks and benefits to the recipients of the drug in parallel track studies and the potential effect on the controlled trials.

Unless the information specified for review is available, PHS does not believe that it would have sufficient information to justify exposing large numbers of subjects to the investigational drug through parallel track protocols. By enumerating the kinds of information to be provided, PHS believes that a sponsor can more readily prepare an acceptable parallel track proposal, which the FDA and the ARAC can review without delays to request additional needed information. If adequate, the expanded access studies can be permitted to go forward expeditiously.

The policy statement describes in general terms the kinds of information needed to support a parallel track proposal; it allows flexibility and room for appropriate adaptation to the unique circumstances of particular drugs or patient populations. Involving the FDA, the NIH, and the ARAC in the review process is intended to provide a variety of expert opinions on the merits of a parallel track proposal. PHS believes that the procedures provide a reasonable approach to dealing with the complexities of expanded access and should not result in any undue delay in drug availability.

### D. Impact of Parallel Track on Clinical Trials

Some comments suggested that parallel track studies should be delayed for a period of time to allow for Phase 2 controlled trial accrual. One comment stated that the controlled trial enrollment should be completed before a drug is made available through parallel track. Others expressed the view that individuals enrolled in expanded access trials were ineligible for controlled trials, and the low accrual rates in controlled trials were due instead to overly restrictive enrollment criteria.

The proposed policy statement indicated that Phase 2 controlled clinical trial protocols are to be approved by the FDA and patient enrollment initiated prior to or simultaneously with release of drugs for expanded availability under the parallel track protocol. As discussed in the proposed policy statement, PHS recognizes that well controlled clinical trials are crucial to establishing the safety and effectiveness of new treatments. It is therefore extremely important that the parallel track studies not delay or compromise the controlled trials to support product approval.

The combination of specific enrollment criteria and the timing of beginning enrollment in the controlled trials and the parallel track studies should adequately prevent the parallel track studies from having a detrimental effect on the controlled trials. As some of the comments pointed out, patients are not eligible for parallel track protocols unless they cannot participate in the controlled trials. Once the controlled clinical trials have been approved, the eligibility criteria for those trials are clear. If the eligibility criteria for the parallel track protocol are honored, the start of accrual in the parallel track protocols should not interfere with accrual in the controlled trials. PHS recognizes, however, that if physicians enroll patients in the parallel track protocol who are in fact eligible for a controlled trial, accrual in the controlled trials may be adversely affected. PHS will consider methods of monitoring parallel track enrollment to determine whether eligibility criteria are being followed.

PHS believes that it is important that patient enrollment in the controlled trials be initiated prior to or simultaneously with release of drug for expanded availability under a parallel track protocol. PHS does not believe that it is necessary to require that the enrollment in the controlled trials be completed before beginning accrual in the parallel track protocols. Accrual in large studies can take many months or longer before complete enrollment; in the absence of extraordinary circumstances, such a delay in beginning studies with different eligibility criteria would not be appropriate. In some situations it may be appropriate for accrual in the controlled trial to have already begun before initiating the expanded access trials. Such determinations should be made based upon the circumstances of the particular drug patient population.

Regardless of when accrual in the controlled trial begins, if there is evidence that the parallel track study is interfering with the successful enrollment in, and completion of, the controlled trials, FDA may terminate the parallel track study. (See discussion below at 0. "Terminating Protocols.") In addition, PHS is prepared to appropriately revise this policy if a more systematic interference of controlled trials becomes obvious.

**E. Protocol Development**

A number of comments asked for assurance that there would be input from people with AIDS, the FDA, the ARAC, community physicians, the primary care physicians in the design of

parallel track protocols. One comment requested that specific criteria for the design of protocols be required.

As discussed in the proposed policy statement, FDA regulations set forth the general elements required to be contained in protocols for studies of investigational drugs (21 CFR 312.23(a)(6)). The sponsor would develop the protocol, which is then reviewed by others, including the ARAC, under parallel track procedures. Representation of people with HIV disease and community and primary care physicians on the ARAC provides one opportunity for input of these groups in the development of the protocol design. The FDA will review the design of the protocol as part of determining the acceptability of the sponsor's parallel track submission. Sponsors of parallel track studies who desire waiver of local IRB review under 21 CFR parts 56 and 45. CFR part 46 may include such requests in their submissions.

**F. Eligibility Criteria**

**1. Patient's Inability To Take Standard Treatment**

Several comments stated that the non-response to Zidovudine (ZDV/AZT) or Dideoxyinosine (ddI) as well as intolerance should establish eligibility of a patient for a parallel track study. Similarly, a number of comments stated that a drug available under a treatment IND should not be considered "standard treatment" for purposes of the parallel track eligibility criteria. Conversely, another comment stated that a patient should be intolerant of AZT or geographically distant from clinical trials to qualify for parallel track.

A basic premise regarding drugs under consideration for parallel track protocols is that there is not yet sufficient evidence of the drug's safety and effectiveness to support approving the drug for marketing.

Because of the increased uncertainties as to a product's safety and effectiveness when drugs are made available at such an early stage of the development of safety and effectiveness information, it is appropriate that enrollment in parallel track studies be limited to those patients who cannot take therapies already shown to have acceptable benefit/risk ratios. Approved products have been found to have acceptable benefit/risk ratios for labeled indications based upon adequate and well-controlled studies as well as other available information. PHS believes that in most circumstances it will be clear that the available information supports the conclusion that

only patients who cannot take or do not respond to either an approved drug or one available under a treatment IND, for the same clinical condition for which the parallel track investigational drug is being studied, should be eligible for the parallel track protocol.

Nevertheless, PHS also believes that those preparing and reviewing the proposed protocol should have flexibility in determining what constitutes standard treatment for the particular condition and patient population identified in the proposed parallel track study, in order to take into account unique circumstances. To allow the determination to be made on a case-by-case basis, PHS has removed from the policy statement the parenthetical phrase defining standard therapy as "a drug approved for marketing or available under a treatment IND for the same clinical condition for which the investigational drug is being studied." PHS expects that in many circumstances standard treatment would include both approved drugs and drugs available under a treatment IND. With regard to the eligibility of those patients who do not respond to standard therapy or drugs available under treatment IND, this determination will also be made on a protocol specific basis. For many protocols, the criterion of "the patient cannot take standard treatment because it is . . . no longer effective" will most likely include circumstances under which the drug was never effective.

**2. Patient's Health Status**

A number of comments expressed concern that people who are HIV-positive and asymptomatic should have access to experimental therapies before they become clinically ill.

The proposed policy statement included as a criterion of patient eligibility that the patient have clinically significant HIV-related illness or be at imminent health risk due to HIV-related immunodeficiency. HIV-positive individuals who are not manifesting clinical symptoms may still be at imminent risk because of their immune status. Such individuals may be eligible for appropriate parallel track protocols.

Each parallel track protocol will identify the intended patient population, as well as the condition being studied. The parallel track policy permits submission and acceptance of appropriate protocols for studies of asymptomatic individuals at imminent health risk due to HIV-related immunodeficiency.

### 3. Access to Parallel Track Studies for Underserved Populations

A number of comments expressed concern that parallel track studies be accessible to underserved populations, especially women and minorities. Others also raised questions about the eligibility of those who cannot afford standard therapy to participate in parallel track studies.

The eligibility criteria for a parallel track protocol should not arbitrarily exclude specific patient populations without adequate scientific justification. The question of access to parallel track studies for all eligible patients who wish to participate can be addressed to some extent through educational programs. The educational program, which is to be addressed in each protocol, includes education of physicians, patients, IRBs, community-based health institutions, community and migrant health centers, the general public, and affected communities. Educational initiatives in community health centers and drug treatment centers, as well as in such programs as the AIDS Clinical Trials Groups (ACTG) and the Community Program for Clinical Research on AIDS (CPCRA), should facilitate enrollment from all eligible groups.

Involvement of community physicians and community-based programs should help to provide access to parallel track studies for traditionally underserved populations. The system for collecting and reporting data should be efficient and not unnecessarily burdensome to encourage community physician participation (see "Patient Data" section).

PHS believes that economic status is not an appropriate criterion for enrollment in clinical trials and that economic issues should be addressed through other means. However, PHS recognizes that economic problems impede access to therapy for low-income patients. There are public health care programs, not within the purview of PHS, established to make approved drugs available to those patients who need the drugs but cannot afford to pay for them. A further discussion of cost issues related to parallel track studies appears below at L. "Economic Concerns."

#### G. Geographic Concerns

Most of those who commented on geographic concerns stated that a benefit of parallel track would be to make therapies available outside of urban centers. One comment stated that the geographic dispersion of patients in parallel track protocols might compromise the value of the data

collected. Another comment stated that expanded access should be restricted to a limited number of patient subsets—including those denied access to clinical trials due to geographic location.

Parallel track studies are intended to provide access to promising investigational drugs for patients who cannot participate in the controlled trials while generating data on the safety and effectiveness of the drug. The proposed policy statement included undue hardship among the reasons for inability to participate in the controlled trials and defined undue hardship as including excessive travel time to the study site.

PHS recognizes that the geographical dispersion of the clinical investigators can create some difficulties in collecting the data from parallel track trials. However, all participating physicians will be required to report data as specified in the protocol, and the sponsor will be responsible for gathering and organizing the data. Appropriate design and conduct of the data collection process should minimize the problems created by geographical dispersion. Additional concerns about data collection are discussed below at L. "Patient Data."

Although PHS agrees that parallel track studies should be available for those who cannot participate in controlled trials because of geographical distance, PHS does not believe that parallel track studies should be restricted by geographic location. For example, patients who live near the location of a controlled trial site may be ineligible to participate in the controlled trials for other reasons. They may not meet the entry criteria, they may be too sick, or the controlled trials may be fully enrolled. PHS believes that these patients should not be excluded from parallel track studies solely because of geographic proximity to the study site of the controlled trials.

#### H. Physician Criteria

Some comments addressed the qualifications for physicians who participate in parallel track studies. Of these comments, some stated that participating "physicians" should include physician groups, clinics, and community-based health care facilities because many patients have no primary physician. Other comments raised questions about the training of physicians, specific minimum qualifications, and incentives for physicians to participate.

As discussed in the proposed policy statement, physicians administering investigational drugs under parallel track protocols become clinical investigators subject to all the

obligations and responsibilities of investigators. The protocol should specify the minimum qualifications for participating physicians and the process by which a physician may be accepted by the sponsor as a clinical investigator under the expanded availability protocol.

Physician groups, clinics, and other community-based facilities are eligible if they meet the specified qualifications. The data collection and reporting procedures, as well as the education and training programs, for participating physicians should be designed to ensure an adequate and appropriate study without creating unnecessary burdens or disincentives for the physicians. The opportunity to provide a treatment option for patients who cannot participate in the controlled trials or take standard therapy should be a significant incentive for physicians to participate in parallel track studies.

#### I. Patient Data

The comments identified a number of concerns regarding data collection, including the need for well-defined data collection requirements and a cost efficient, time efficient, uncomplicated data collection system. Some comments urged permitting community research groups to collect data on effectiveness as well as safety. Other comments raised concerns about the confounding of results due to patient noncompliance with protocols and difficulty analyzing data without control group study designs. Some comments requested that FDA consider data generated in parallel track studies in granting marketing approval. In addition, questions were raised about who will pay for the cost of data collection, who will analyze the data, and what incentives exist for physicians to submit data.

PHS agrees that well-defined data collection requirements should be specified in the parallel track protocol. The system for collecting and reporting data should be efficient and not unnecessarily burdensome for the participating physicians. All participating physicians will be required to report safety data.

PHS agrees that parallel track protocols may appropriately provide for community research groups or other specified investigators to collect data on effectiveness as well as safety. The nature and extent of effectiveness data collection may vary in different clinical settings.

The sponsor will analyze the parallel track data and report the results to FDA under the IND. Ongoing review of available data will be provided by a

availability of investigational new drugs through a parallel track mechanism for people with AIDS and HIV-related diseases follows:

#### *Introduction*

Through this notice, the Public Health Service is announcing a final policy under the Food, Drug and Cosmetic Act (the Act). The purpose of this policy is to permit promising investigational agents to be made available to people with AIDS and HIV-related diseases who are not able to take standard therapy, or for whom standard therapy is no longer effective, and who are not able to participate in ongoing controlled clinical trials. Through this policy, promising new drugs would be made available through studies without concurrent control groups to monitor drug safety that are conducted in parallel with the principal controlled clinical investigations (hence the name "parallel track").

This policy, developed by the Public Health Service with significant input from community advocates, industry representatives, the research community, and other interested members of the public, represents a further step in expanding availability of promising investigational drugs under the Act to those persons with AIDS and HIV-related diseases who are without satisfactory alternative therapy and who cannot participate in the controlled clinical trials. Because some investigational drugs for these conditions may be more widely available at a very early point in the drug development process, this procedure recognizes the need for participating physicians and their patients to consider what is and is not known about the risks and benefits of a variety of potential therapeutic agents when making clinical decisions.

Patients and physicians must recognize that products available under this procedure will be in the very early stages of product development and will only be made available to provide potential therapeutic options to those people with serious and life-threatening HIV-related disease who have no satisfactory alternative therapy. It must be clearly understood that the earlier availability of experimental treatments on a wide scale exposes larger number of patients to greater uncertainty and the risk of unforeseen and serious reactions.

There are many issues and problems related to providing potential therapies to individuals with HIV-related diseases. Although certain problems have been addressed in this document, others, in particular some that are not

within the purview of the Public Health Service still require attention, but will not be discussed in this publication. For example, this policy does not deal with aspects of the health care system that can affect the availability and affordability of parallel track mechanisms to underserved groups. It also does not address the role of third-party payers in covering the costs of medical services associated with the use of parallel track drugs, nor does the policy address the liability of manufacturers sponsoring a parallel track drug. While the Public Health Service recognizes the importance of these issues, and will attempt to facilitate a broader consideration of them, they are beyond the scope of this policy.

In the development of this policy, it was recognized that well conducted clinical trials are crucial to the development of new treatments. While the goal of making promising investigational agents more widely available to persons with HIV infection and no therapeutic alternatives is an important one, controlled clinical trials that yield definitive information on the safety and effectiveness of investigational new drugs must continue. This policy includes sufficient safeguards and oversight to ensure that it neither delays nor compromises the controlled clinical trials.

#### *Background*

Normally, the development of a new experimental therapy proceeds through a systematic series of clinical trials that yield data growing from an initial understanding of appropriate dosing, side effects, and initial hints of efficacy, to a substantial body of definitive evidence of safety and effectiveness sufficient to support product marketing. This often lengthy approach is based upon well substantiated and widely accepted scientific and ethical principles and a mandate from society that protection of individuals from undue risks of experimental therapy is essential.

Although the AIDS epidemic has heightened interest in expanded access to investigational drugs, the issue is not new. Persons with life-threatening diseases for which no satisfactory alternative therapy is available have at times requested an investigational new drug prior to the drug's approval by the Food and Drug Administration (FDA). The issue has been dealt with by FDA in the past in both formal and informal ways. In the 1970's a number of large protocols were developed in which physicians, generally at academic referral centers, had access to

investigational drugs for persons with serious or life threatening conditions who were without satisfactory alternative therapy. The drugs in these protocols were usually under active development in controlled trials and some of these protocols involved large numbers of patients. A similar mechanism was developed to provide investigational drugs to persons with cancer.

The FDA and National Cancer Institute (NCI) have described a special category of investigational drugs, "Group C" drugs, which may be provided by oncologists to appropriately chosen patients through protocols outside the controlled clinical trials prior to the drug's approval.

In 1987, FDA incorporated into a final regulation the treatment investigational new drug application (Treatment IND). Under a Treatment IND protocol, eligible patients have access to investigational drugs intended to treat serious or life-threatening diseases. A Treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks, but before marketing approval has been granted. Treatment IND status has been granted for 18 investigational new drugs, 6 of these for AIDS-related conditions.

Under this policy, expanded availability protocols might be approved for promising investigational drugs when the evidence for effectiveness is less than that generally required for a Treatment IND. The expanded availability protocol may include one or more studies without concurrent control groups and may be accompanied by a Treatment IND protocol. All drugs distributed under the parallel track mechanism will be under a study protocol. Data, particularly pertaining to side effects and safety will be collected under these studies. However, most of the data essential for market approval will come from the controlled clinical trials.

As is the case for all investigational uses of drugs, FDA has authority for approving and monitoring the study protocols that are developed under this expanded availability policy. A regulation detailing the FDA's authority to terminate nonconcurrently controlled studies is published elsewhere in this issue of the Federal Register.

#### **Selection of Investigational Therapeutic Agents for Expanded Availability Through Parallel Track**

FDA encourages potential parallel track sponsors (as defined at 21 CFR 312.3(b)) to seek advice and information

from FDA and other scientists outside the agency as early, and as frequently as possible, during the pre-application process.

The FDA authority for the final decisions regarding which investigational agents will be placed in a program for expanded availability. Applications for experimental therapies to be considered for expanded access (parallel track) are to be submitted to FDA as amendments to existing INDs.

(1) FDA will refer all parallel track proposals to the AIDS Research Advisory Committee (ARAC), a committee chartered by the National Institute of Allergy and Infectious Diseases (NIAID) unless the sponsor indicates otherwise. This committee, composed of outside scientists and physicians experienced with AIDS, persons with HIV-related diseases, and others, will review the available data and make a recommendation to the Director of NIAID. After review, the Director of the NIAID will forward a recommendation, through the Director of the NIH, to the Commissioner of the FDA. In all cases, requests to be presented to the ARAC will be screened and scheduled by NIAID Committee Management Staff.

(2) If the sponsor prefers, the formal parallel track proposal can be submitted to the FDA for review without being forwarded to the ARAC.

#### Review Criteria

Ordinarily in reviewing a proposal to make an investigational drug available through a parallel track proposal, the ARAC Committee and FDA will consider whether there is:

1. Sufficient information showing:
  - a. Promising evidence of efficacy based on an assessment of all laboratory and clinical data;
  - b. Evidence that the investigational drug is reasonably safe, taking into consideration the intended use of the drug and the patient population for which this drug is intended; and
  - c. Sufficient data to recommend an appropriate starting dose.
2. Preliminary pharmacokinetic and dose-response data and, ideally, data about interactions with other drugs commonly used in the intended patient population.
3. Evidence of a lack of satisfactory alternative therapy for defined patient populations. In general, the investigational drug should meet a serious unfulfilled health need such that the potential benefits justify the considerable risks of very early expansion of use.
4. A description of the patient population to receive the drug under expanded access. Patient priority

categories based on clinical condition should be determined if the drug may not be available in sufficient quantities to supply all of those who satisfy the basic eligibility criteria.

5. Assurance that the manufacturer is willing and able to produce sufficient amounts of the drug product for both the controlled clinical trials and the proposed expanded availability study.

6. A statement of the status of the controlled clinical trial protocols. Phase 2 controlled clinical trial protocols are to be approved by the FDA and patient enrollment initiated prior to or simultaneously with release of drugs for expanded availability under the parallel track protocol.

7. An assessment of the impact that the parallel track study may have on patient enrollment for the controlled clinical trials and a proposed plan for monitoring progress of the controlled trials.

8. Information describing the informational, educational and informed consent efforts that will be undertaken to ensure that participating physicians and potential recipients have sufficient knowledge of the potential risks and benefits of the investigational agent being studied in the parallel track process.

In general, deliberations about the advisability of expanded availability for a specific drug can be accomplished best during the review of a relatively detailed protocol for expanded availability in conjunction with the review of the protocols for the controlled clinical trials. While a detailed protocol is not required during the initial discussion stage, an outline of the proposed parallel track study should be provided.

Review and approval of a formal IND protocol is to be carried out by FDA, which may elect to involve one or more advisory committees in the review process. The FDA, through its existing regulations and procedures, may also discuss proposed protocols with appropriate consultants to the Agency.

A decision not to allow expanded availability of an investigational drug would not imply a judgement about a drug's ultimate safety or efficacy nor preclude additional controlled trials.

#### Protocol Development and Approval

The protocol for distribution and monitoring of an investigational drug under parallel track (expanded access protocol) is to be developed by the manufacturer or other sponsor. The FDA has regulatory authority for approval of the protocol and, in most cases, will interact with the sponsor during its development.

Elements to be contained in the expanded access protocol are to be the same as those for other protocols of investigational agents in clinical trials (21 CFR 312.23 part (a)(6)). Normally, a protocol submission for a parallel track study would include information about: The administration of the protocol; the sponsor's responsibilities under the protocol; patient selection criteria; phasing in of expanded use; physician selection for participation; dosage level and frequency; data reporting requirements and data collection forms; data monitoring procedures by the sponsor; physician and patient educational materials; patient consent documents; and criteria for terminating the protocol.

#### Eligibility Criteria for Patients To Receive Investigational New Drugs Through Parallel Track

Criteria for patient eligibility are to be included in each protocol for expanded availability. General principles for determining patient eligibility are described below. They are intended to provide flexibility as the specific criteria may vary for different agents and different clinical situations.

The determinants of patient eligibility include all of the following:

1. The patient has clinically significant HIV-related illness or is at imminent health risk due to HIV-related immunodeficiency.
2. The patient cannot participate in the controlled clinical trials because:
  - (a) The patient does not meet the entry criteria for the controlled clinical trials, or
  - (b) The patient is too ill to participate, or
  - (c) Participation in controlled clinical trials is likely to cause undue hardship (e.g. travel time) as defined by the protocol, or
  - (d) The controlled clinical trials are fully enrolled.
3. The patient cannot take standard treatment because it is contraindicated, cannot be tolerated, or is no longer effective. (The terms "cannot be tolerated" and "no longer effective" should be defined in each protocol. Generally these definitions will include a description of the standard therapy including dosages and the minimum duration of treatment to assess clinical utility, the range and severity of adverse reactions that constitute intolerance, and the clinical conditions or laboratory markers that constitute evidence that the therapy is no longer effective). If the basis for enrollment in the parallel track study is that standard treatment is no longer effective, the patient's physician

or physician group would be required under the protocol to certify that the patient is failing clinically despite reasonable efforts to optimize therapy with the standard treatment.

The protocol should establish patient priority categories if a sufficient quantity of the investigational drug is not likely to be available to all those who would satisfy the basic criteria for eligibility.

Because the primary objective of the IND phase of drug development is to establish the safety and efficacy of the drug through controlled clinical trials, it is critical that the sponsor work with participating physicians to assure that reasonable efforts are made to encourage persons to enter controlled clinical trials for which they are eligible. The protocol should specify a process for determining if a person for whom the investigational drug is being requested under the parallel track protocol is eligible for a controlled clinical trial of the drug, and methods for contacting clinical trial directors for possible inclusion.

The expanded availability protocol should not exclude certain patient populations based on age, sex or medical status unless there is adequate justification. Protocols should also consider and address potential problems associated with use of the drug in such special populations. The regulations for human subjects protections are discussed later in this document.

#### Criteria for Physician Participation in Parallel Track

As specified in FDA's IND regulations (21 CFR part 312) physicians administering investigational drugs under parallel track protocols become clinical investigators subject to all the obligations and responsibilities of investigators. The protocol will specify the minimum qualifications for participating physicians and the process by which a physician may be accepted by the sponsor as a clinical investigator under the expanded availability protocol. Physicians are required to certify that the patients meet the requirements of the protocol and that all efforts have been made to optimize standard therapy prior to enrollment in parallel track protocols. Because investigational drugs will be made available through parallel track protocols when relatively little is known about the drug, physicians must be familiar with potential adverse effects, willing to instruct patients in the early recognition of these effects and willing to monitor their patients closely. Participation by all physicians, including those serving rural, inner-city, medically

indigent, and racial and ethnic minority populations should be encouraged.

#### Collection of Patient Data in Parallel Track Protocols

The data to be collected by the participating physicians and reported to the sponsor will be specified in each parallel track protocol. All participating physicians will be required to report safety data, while the nature and extent of efficacy data collection may vary in different clinical settings. The frequency of reporting will be specified in the protocol. Because of the early stage at which investigational drugs are to be made available under a parallel track protocol, and the relative lack of information about risk that is likely to exist, it is critical that participating physicians comply with data reporting requirements to provide important information on the risk of the drug and to assure patient safety.

The data collection forms should be designed to be easy to use and as concise as possible. Appropriate data collection and reporting by the administering physician is a prerequisite for continued drug supply.

#### Monitoring the Protocols

The sponsor of a parallel track protocol should monitor the study closely through a specific monitoring mechanism described in the protocol. The sponsor should establish a Data and Safety Monitoring Board (DSMB) or its equivalent with responsibility for monitoring the parallel track studies and gathering information from all protocols testing the investigational drug. The DSMB or its equivalent may recommend to FDA, the Sponsor, ARAC and other appropriate bodies that the parallel track and/or clinical trial protocols be terminated. (See Terminating Protocols).

The description and mechanism of operation of the DSMB (or other monitoring system) and its precise relationship to the sponsor and other oversight bodies will be specified in the expanded availability protocols.

The sponsor is responsible for submitting reports to the FDA as required in the IND regulations (21 CFR part 312), except where a waiver has been specially granted.

#### Education and Information

An extremely important accompaniment to a parallel track protocol is a program for the education of physicians, patients, IRBs, community-based health institutions, community and migrant health centers, the general public, and affected communities to ensure that participating physicians and potential recipients have

sufficient knowledge of the potential risks and benefits of the parallel track drug as well as the risks and benefits of other treatment options. These programs, as noted in the "Review criteria" section above, should reflect the joint efforts of the PHS, the medical community, industry, academic communities and AIDs-related organizations. These education programs are in addition to the information provided through the informed consent process. Sponsors should specify how their particular education program will be carried out as well as how new information will be collected, analyzed, and publicly circulated.

#### Economic Considerations

Existing IND regulations permit sponsors to request the recovery of costs for certain investigational drugs in clinical studies, in the unusual circumstance in which the trial could not otherwise continue (see 21 CFR 312.7(d)(1)). FDA approval of a request to charge must be obtained.

Sponsors should specify the extent of economic support they would be willing to provide to pursue the expanded access of the investigational agent through the parallel track. They should also specify the degree of support, if any, they would provide for the administration of the drug for the conduct of necessary laboratory and clinical testing to determine product safety and the monitoring, collection, and distribution of drug-specific information through their education programs.

#### Human Subjects Protections

There are two sets of relevant federal regulations for the protection of human subjects which include requirements for local institutional review board (IRB) review and informed consent: the FDA regulations (21 CFR parts 50 and 56) that apply to all investigational drug studies, and HHS regulations (45 CFR part 46) which pertain to institutions that receive HHS support for research involving human subjects.

#### (a) HHS Regulations

Certain requirements of the current HHS regulations cannot reasonably be met for drugs released under the parallel track program. These regulations require local IRB review and approval of each protocol and written Assurance of Compliance from each organization or individual practitioner involved in the research and not affiliated with an assured institution. This is generally not practical for many reasons: (1) Local IRB

review could slow the dissemination of drugs under parallel track policies and procedures; (2) local review could be made by IRBs without sufficient information on which to base a recommendation; (3) local review could result in considerable delays if physicians are required to form their own IRBs; (4) local review might place IRBs in a situation in which it is difficult to monitor activities of physicians for whom they are not otherwise responsible. Consequently, the Secretary of HHS will consider, on a protocol-by-protocol basis, waiving the provisions of 45 CFR part 46.

Other mechanisms, in lieu of local IRB review, to provide for review of the protocol according to established ethical principles and to develop informed consent procedures appropriate to the parallel track program are described below.

#### *(b) FDA Regulations*

Prior to proceeding with a parallel track protocol, a sponsor must comply with FDA's IRB regulations. FDA regulations would allow a waiver where FDA determines that it is in the best interests of the subjects and that a national human subjects panel would provide an adequate mechanism for protecting patients. The Commissioner of Food and Drugs will consider a sponsor's request for waivers of the provisions of 21 CFR part 56 dealing with local IRB review, including § 56.107(a).

#### *(c) National Human Subjects Protections Review Panel*

While local IRBs would always have the option of reviewing expanded availability protocols, a national human subject protections review panel (national human subjects panel) with a broadly-based membership would be established. This panel will provide for patient protection, including approval of consent procedures and documentation and provide for continuing ethical oversight of each parallel track protocol. It will be particularly important for this body to review the proposed informed consent process of each protocol and review an initial "model" informed consent document, and to review the process to update the procedures and the document as knowledge about the investigational drug becomes available. The national human subjects panel will

also ascertain that for each parallel track protocol the sponsor has established an appropriate procedure for data and safety monitoring.

The AIDS Program Advisory Committee (APAC) in NIH will establish an ad hoc subcommittee to carry out the duties of the national human subjects review panel until a permanent body is established. Outside consultants representing the relevant specialties and constituencies will be called on as needed to advise this body. PHS will take steps necessary to create a chartered national human subjects protections review panel with a broadly-based membership.

IRBs would continue to review drugs on the controlled clinical trial side of the "parallel track." In addition, individual institutions have the option to require that their IRBs review the expanded availability protocols when a study is conducted by the institution or its affiliated investigators.

#### **Informed Consent**

It is important that potential participants in the parallel track have as much information as is available in order to make informed decisions. The informed consent process must make clear the risks involved in taking a drug about which relatively little is known. The proposal for agents in the parallel track must describe a detailed process for informed consent, including specific information about patient and physician education. A proposed informed consent document is required to be included with the protocol. There should also be a description of how the informed consent document will be updated and how physicians and patients and the national human subjects panel will be notified of new information (e.g. toxicity, adverse reaction reports) after the initial informed consent document has been put into use.

#### **Terminating Protocols**

Because the parallel track program allows early, widespread distribution of investigational agents prior to full marketing approval, it is necessary to develop criteria to terminate or curtail a parallel track program. In general, these should include the following:

(1) Evidence that subjects are being exposed to unreasonable and significant risks.

(2) Evidence that the parallel track study is interfering with the successful enrollment in, and completion of, adequate and well-controlled studies of this or other investigational drugs.

(3) Evidence that the sponsor is not in active pursuit of marketing approval.

(4) The product has been studied in an adequately controlled clinical trial that strongly suggests lack of effectiveness.

(5) Another product approved or under investigation for the same indication in the same population demonstrates a better potential balance of risks and benefits.

(6) The drug receives marketing approval for the same indication in the same patient population.

(7) Insufficient product exists to conduct both the parallel track protocols and the controlled clinical trials.

(8) The Commissioner of Food and Drugs determines that, in the interest of the public health, the parallel track study should not be continued.

A principal purpose of the Data and Safety Monitoring Board, or its equivalent, would be to examine data to determine if the parallel track and/or clinical trials should be stopped and to make recommendations to the sponsor, FDA, ARAC, and other oversight bodies. A regulation detailing the FDA's authority to terminate these studies, as well as other uncontrolled studies, is published concurrently with this policy statement.

#### **Periodic Review**

A periodic review of the implementation and progress of expanded availability of all investigational drugs being distributed by a parallel track study will be conducted by the PHS. The objective of this periodic review would be to help ensure the continued rapid development and evaluation of therapeutic agents for treatment or prevention of HIV infection and HIV-associated diseases, as well as the safety of participants in these trials.

Dated: April 8, 1992.

**James O. Mason,**

*Assistant Secretary for Health.*

**David A. Kessler,**

*Commissioner, Food and Drug Administration.*

[FR Doc. 92-8624 Filed 4-14-92; 8:45 am]

BILLING CODE 4160-17-M

# Federal Register

---

Friday  
December 11, 1992

ACCELERATED APPROVAL  
(SUBPART H)

---

Part VIII

## Department of Health and Human Services

---

Food and Drug Administration

---

21 CFR Parts 314 and 601  
New Drug, Antibiotic, and Biological Drug  
Product Regulations; Accelerated  
Approval; Final Rule



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

## 21 CFR Parts 314 and 601

[Docket No. 91N-0278]

RIN 0905-AD66

## New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing final regulations under which the agency will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provisions for any necessary continued study of the drugs' clinical benefits after approval or with restrictions on use, if necessary. These new procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment. Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under these procedures will have met the requisite standards for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act) and, thus, will have full approval for marketing.

**EFFECTIVE DATE:** January 11, 1993.

**FOR FURTHER INFORMATION CONTACT:** Marilyn L. Watson, Center for Drug Evaluation and Research (HFD-360), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8038.

**SUPPLEMENTARY INFORMATION:****I. Background:**

In the Federal Register of April 15, 1992 (57 FR 13234), FDA published proposed procedures under which the

agency would accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. FDA provided 60 days for public comment, and, upon request, in the Federal Register of June 18, 1992 (57 FR 27202), extended the comment period for an additional 30 days until July 15, 1992. The final rule incorporates all of the provisions of the proposed rule and provides additional clarification regarding both timing and content of the submissions of promotional materials and regarding the nature of required postmarketing studies. The agency has added a new provision clarifying when certain postmarketing requirements of the rule will be terminated.

Highlights of the final rule are summarized below, followed by a summary and discussion of the comments.

**II. Highlights of the Final Rule**

This final rule establishes procedures under parts 314 and 601 (21 CFR parts 314 and 601) under which FDA will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. These procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic advantage over existing treatment. The preamble of the proposed rule (57 FR 13234) provides a description of other mechanisms available to facilitate access, speed development, and expedite review of therapeutic products (e.g., treatment investigational new drug applications (IND's), subpart E, parallel track). Where appropriate, these mechanisms can be utilized in concert with accelerated approval. The major provisions of the final rule are as follows:

**A. Scope**

The new procedures apply to certain new drug, antibiotic, and biological products used in the treatment of serious or life-threatening diseases, where the products provide meaningful therapeutic advantage over existing treatment (21 CFR 314.500 and 601.40).

**B. Criteria for Approval**

Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under this final rule will have met the requisite standards for safety and effectiveness under the act or the PHS Act and, thus, will have full approval for marketing (21 CFR 314.510, 314.520, 601.41, and 601.42). Ordinarily, products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies, will be considered for approval under the traditional process rather than under accelerated approval.

**C. Postmarketing Studies**

Where a drug's approval under these provisions is based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, the applicant will be required to conduct clinical studies necessary to verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate outcome. The requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval; it is expected that the studies will usually be underway at the time of approval. The proposed regulations have been revised to clarify that required postmarketing studies must also be adequate and well-controlled (21 CFR 314.510 and 601.41).

**D. Restrictions on Use After Marketing**

FDA may grant marketing approval of a drug or biological product shown to be effective where safe use can only be assured if distribution or use is restricted. Under this final rule, FDA may: (1) Restrict distribution to certain facilities or to physicians with special training or experience, or (2) condition distribution on the performance of

specified medical procedures. The restrictions on use will be tailored to the specific safety issue raised by the particular drug or biological product and agreed to by the applicant at the time of approval (21 CFR 314.520 and 601.42). FDA expects that the imposition of these restrictions on distribution will be rare.

#### E. Promotional Materials

The final rule requires submission of planned promotional materials, including promotional labeling and advertisements, both prior to approval (reflecting the initial campaign), and following approval, unless informed by the agency that such submission is no longer necessary, at least 30 days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement (21 CFR 314.550 and 601.45).

#### F. Withdrawal of Approval

The final rule establishes an expedited procedure for the withdrawal of approval if: (1) Postmarketing clinical studies fail to verify clinical benefit; (2) the applicant fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug or biological product; (4) the applicant fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug or biological product is not shown to be safe or effective under its conditions of use (21 CFR 314.530 and 601.43).

#### G. Termination of Requirements

In response to comments, the final rule provides that the requirements set forth in §§ 314.520, 314.530, and 314.550 for new drugs and antibiotics and §§ 601.42, 601.43, and 601.45 for biological products ordinarily will terminate when FDA determines that the results of required postmarketing studies have demonstrated that the drug or biological product has clinical benefit, or, where restrictions on distribution or use have been imposed, when FDA determines that safe use of the drug or biological product can be ensured without such restrictions, e.g., through appropriate labeling. FDA will notify the applicant when these requirements no longer apply (21 CFR 314.560 and 601.46).

#### III. Effective Date

This regulation will become effective on January 11, 1993.

#### IV. Comments on the Proposed Rule

FDA received 54 comments on the proposed rule. The comments came from individuals, specific disease organizations, universities, pharmaceutical manufacturers, trade associations, health professionals, and professional societies. The comments reflect broad support and acceptance of the goal of expediting the approval of drugs intended for the treatment of serious and life-threatening illnesses. A number of comments asked that the proposal be finalized expeditiously without change. Many comments posed specific questions and raised important concerns.

##### A. General Comments

1. One comment suggested that the term "conditional approval" was less confusing and ambiguous than the term "accelerated approval." The comment also referred to the statement in the proposal that "Drugs \* \* \* approved under this proposal will have met the requisite standards \* \* \* under the (act)" and argued that because postmarketing conditions may be imposed, this statement can only be read to say that the requisite standards under the act can only be met by a lower standard of evidence in hand, combined with assurance that further evidence will be obtained.

Another comment expressed concern that the proposal appears to establish a standard for the evaluation of drug product effectiveness that is inconsistent with the substantial evidence requirement of section 505(d) of the act (21 U.S.C. 355(d)), which means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling \* \* \*." The comment argued that, with few exceptions, the agency has consistently interpreted the "substantial evidence" requirement as an instruction that determinations of effectiveness be based on data unambiguously reflecting the clinical status of subjects evaluated under controlled conditions in bona fide clinical experiments. In the absence of compelling empirical evidence documenting that a drug-induced change in a surrogate measure reliably and consistently predicts improved

clinical outcome, a surrogate indicator is no more than a hypothetical construct. The comment asserted that the proposed rule's endorsement of the use of unvalidated surrogate endpoints, therefore, appears to represent a significant departure from traditional agency interpretations of "substantial evidence" within the meaning of the act because it allows belief rather than evidence to serve as the basis for a conclusion about the effectiveness of a new drug.

Three comments asserted that the new regulations are not needed to approve drugs intended to treat serious or life-threatening illnesses. Two comments cited FDA's approval, without new regulations, of didanosine (formerly called ddi) and zalcitabine (formerly called ddc) in combination with zidovudine (formerly called AZT) based on a surrogate marker, i.e., an increase in CD4 cell counts and the "subpart E" procedures at 21 CFR part 312, which address the need for expediting the development, evaluation, and marketing of new therapies intended to treat life-threatening or severely debilitating illnesses as examples of existing mechanisms for the expedited approval of important new drugs. One comment argued that the act requires that drugs be shown to be "safe" and "effective," and proof of effectiveness is not limited by the act to demonstration of an effect on "survival or irreversible morbidity," as the proposed rule seems to assume. The comment further argued that FDA has considerable statutory discretion to define what type of data constitutes proof of effectiveness, and demonstration of an effect on a surrogate marker is one type of such proof.

The agency believes that what the procedures are called is much less important than what the procedures are. The shorthand term selected by the agency reflects the intent of the rule, especially that part related to use of surrogate markers, which is to make drugs that provide meaningful improvement over existing therapies for serious illnesses widely available (through marketing) at the earliest time consistent with the law. The essence of the proposal is thus acceleration, not the imposition of conditions. Approval under these procedures is dependent on compliance with certain additional requirements, such as timely completion of studies to document the expected clinical benefit. The evidence available at the time of approval under this rule will meet the statutory standard, in that there must be evidence from adequate and well-controlled studies showing that the drug will have

the effect it is represented to have in its labeling. That effect will, in this case, be an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit and labeling will refer to the effect on the surrogate, not to effect on clinical outcome.

While the act does not refer to particular endpoints or state a preference for clinical, as opposed to surrogate, endpoints, it is well established that the effect shown in well-controlled studies, must, in the judgment of the agency, be clinically meaningful. Moreover, the safety standard in the act, that a drug must be shown to be safe for its intended use, implies a risk/benefit judgment. The effect shown must be such as to outweigh the risks of the treatment under the conditions of use. Approval under this rule requires, therefore, that the effect shown be, in the judgment of the agency, clinically meaningful, and of such importance as to outweigh the risks of treatment. This judgment does not represent either a "lower standard" or one inconsistent with section 505(d) of the act, but rather an assessment about whether different types of data show that the same statutory standard has been met.

Approval based on surrogate endpoints is not new, although the issue has not previously been considered in regulations. The agency has, in a number of instances, approved drugs based on surrogate endpoints. For example, drugs for hypertension have been approved based on their effects on blood pressure rather than on survival or stroke rate. Similarly, drugs for hypercholesterolemia have been approved based on effects on serum cholesterol rather than on coronary artery disease (angina, heart attacks). But, in those cases there was very good evidence from clinical trials (in the case of hypertension) and from epidemiologic and animal studies (in the case of hypercholesterolemia) that improving the surrogate would lead to or is associated with the desired effects on morbidity and mortality. Even so, there is still today considerable debate about who will benefit from cholesterol lowering. Controlled trials assessing effects on clinical endpoints of morbidity and mortality from use of cholesterol-lowering drugs have been, and are being, conducted.

Reliance on a surrogate endpoint almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known. The expected risk/benefit

relationship may fail to emerge because: (1) The identified surrogate may not in fact be causally related to clinical outcome (even though it was thought to be) or (2) the drug may have a smaller than expected benefit and a larger than expected adverse effect that could not be recognized without large-scale clinical trials of long duration. Reliance on surrogate markers therefore requires an additional measure of judgment, not only weighing benefit versus risk, as always, but also deciding what the therapeutic benefit is based upon the drug effect on the surrogate.

The sections of the final rule that address approval based upon a drug effect on a surrogate endpoint specifically clarify the regulatory approval criteria when the agency relies on a surrogate endpoint that, while "reasonably likely" to predict clinical benefit, is not so well established as the surrogates ordinarily used as bases of approval in the past. Postmarketing studies required to verify and describe actual clinical benefits would also be required to be adequate and well-controlled studies. Sections 314.510 and 601.41 have been revised to clarify this point. If, on completion of required postmarketing studies, the effect on the surrogate is not shown to correspond to a favorable effect on clinical benefit, the rule provides an expedited means of removing the drug from the market.

Approval of didanosine and zalcitabine under current procedures does not show that the rule is of no value. Although approval did rely on a surrogate endpoint that is of the kind specifically addressed by the rule, the fact that studies to define clinical benefit were nearly complete and were being conducted under the auspices of the National Institute of Allergy and Infectious Diseases made it less crucial to have additional guarantees that such studies would be conducted promptly. Moreover, the sponsors of didanosine and zalcitabine agreed prior to approval to expedited withdrawal of the drug from the market if benefit were not shown. The provisions of the final rule will ensure that appropriate safeguards exist for timely generation of data on actual clinical benefit, for appropriate promotional information about labeled indications, and for prompt withdrawal of the drug from the market if clinical benefit is not confirmed.

2. Pointing to a statement in the preamble to the proposed rule that it is in the public interest to make promising new treatments available at the earliest possible point in time for use in life-threatening and serious illnesses, one comment expressed concern that the proposed rule may lead to the marketing

of large numbers of clinically ineffective, but pharmacologically active, drugs and this may not be in the interest of the public health. The comment argued that early access to so-called "promising" drugs is not the same as early access to safe and effective drugs, and the number of potential markers that may be advanced as surrogates of clinical outcome is exceedingly large. The comment suggested that it may be more appropriate to seek adoption of the proposed requirements through an amendment to the act.

FDA agrees with the contention that providing people who have serious or life-threatening illnesses with numerous clinically ineffective drugs would not be helpful. However, the agency does not agree that the rule can be expected to have this result. Although studies using surrogate endpoints may provide less assurance of clinical benefit than studies using clinical endpoints, FDA believes compliance with all of the elements of the accelerated approval program will not result in the marketing of large numbers of clinically ineffective drugs. The new procedures apply to a limited group of circumstances, namely, to drugs intended for serious or life-threatening illnesses when the drugs provide a meaningful therapeutic benefit over existing therapy. Reliance on a surrogate endpoint is not equivalent to reliance on any evidence of pharmacologic activity. The endpoint must be reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.

Whether a given endpoint is, in fact, reasonably likely to predict clinical benefit is inevitably a matter of judgment. FDA, using available internal and external expertise, will have to make informed judgments in each case presented, just as it does now. The agency acknowledges that there are well-recognized reasons for caution when surrogate endpoints are relied on. Certain putative surrogates have ultimately been shown not to correspond to clinical benefit. Perhaps the most noteworthy example is the failure of antiarrhythmic agents in the Cardiac Arrhythmia Suppression Trial (CAST) to improve survival by depressing ventricular ectopic beats; effective suppression of ectopic beats was associated with increased mortality.

A sponsor must persuasively support the reasonableness of the proposed surrogate as a predictor and show how the benefits of treatment will outweigh the risks. Such presentations are likely to be persuasive only when the disease to be treated is particularly severe (so

that considerable risk is acceptable) and/or when the surrogate endpoint is well supported. In addition, it will be the sponsor's clear obligation to resolve any doubts as to clinical value by carrying out definitive studies.

FDA does not agree that it would be more appropriate to seek an amendment to the act than to adopt the proposed requirements. As discussed in the preamble to the proposed rule as well as elsewhere in this preamble to the final rule, existing provisions of the act and the PHS Act authorize promulgation of the requirements in the final regulations.

3. One comment expressed concern that because the proposed rule would establish conditions on a drug's approval, third-party payors may decline reimbursement because the so-called approval would have attributes of investigational status.

The agency expects that, because drugs approved under the accelerated approval process meet the statutory standards for safety and effectiveness, they would be eligible for reimbursement under State Medicaid programs or other third-party plans. Drug products granted accelerated approval will not be, under the law, investigational, as suggested by the comment.

4. One comment asked if all drugs considered for accelerated approval must be reviewed by an advisory committee. The comment stated that because advisory committees meet infrequently, waiting for the next meeting may slow down the approval process.

FDA is not required to consult with an advisory committee before approving an application under these accelerated approval regulations, or any other regulation. However, FDA intends to consult the appropriate committee in most instances. Advisory committee meetings can usually be scheduled to avoid significant delays in the review process. The agency will consider any request by an applicant for referral of the application to an advisory committee.

#### B. Scope

5. Four comments asked for further clarification of what diseases are covered by the rule. One comment stated that the terms "serious," and "life-threatening," are defined in the proposal by reference to 21 CFR 312.34, followed by a brief statement explaining the role of judgment and examples of diseases that are currently judged to be

serious. The comment asked that FDA also describe: (1) Diseases that are not currently included in the category of "serious," (2) examples of diseases that are currently judged "life-threatening," and (3) examples of diseases that are not currently included in the category "life-threatening."

One comment contended that the statement in the preamble that "seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one" too narrowly limits diseases covered by the proposed rule (57 FR 13234 at 13235). The comment argued that some "less severe" diseases, even if treated, may progress to a more serious state, and that these diseases should also be covered by the rule. On the other hand, two comments argued that the language in the preamble that classifies diseases as "serious" was overly broad and subjective and far too large a number of illnesses could be eligible as being "serious."

FDA discussed the meaning of the terms "serious" and "life-threatening" in its final rules on "treatment IND's" (52 FR 19466 at 19467, May 22, 1987) and "subpart E" procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every "serious" and "life-threatening" disease that would be within the scope of this rule. In FDA's experience with "treatment IND's" and drugs covered by the "subpart E" procedures there have not been problems in determining which diseases fall within the meaning of the terms "serious" and "life-threatening," and FDA would expect no problems under this accelerated approval program. The likelihood of progression to a serious condition with available treatments would also be considered in assessing whether the disease is within the scope of the final rule. The preamble to the proposed rule (57 FR 13234 at 13235) referred to chronic illnesses that are generally well managed by available therapy, but can have serious outcomes for certain populations or in some or all of their phases. Applicants are encouraged to consult with FDA's reviewing divisions early in the drug development process if they have questions about whether their specific product is within the scope of this rule.

The concerns expressed in these and other comments about considering too many illnesses eligible for consideration under the accelerated approval procedures may arise from the underlying fear that reliance on surrogate endpoints will become routine, the "normal" way drugs are brought to the market. This fear is groundless. The vast majority of drugs are directed at symptomatic or short-term conditions (pain, heart failure, acute infections, gastrointestinal complaints) whose response to drugs, if it occurs, is readily measured and where there is no need to consider or accept surrogate endpoints. Surrogates, with few exceptions, are of interest in the following situations: (1) Where the clinical benefit, if there is one, is likely to be well in the future; and (2) where the implications of the effect on the surrogate are great because the disease has no treatment at all or the drug seems to treat people with no alternative (e.g., because they cannot tolerate the usual effective treatment). In the first case, great care is needed, and would be given, as there would generally be no experience linking an effect on the surrogate to clinical success, and there have been conspicuous examples of lack of linkage (CAST, referred to above; drugs that increase cardiac output in patients with heart failure but that decrease survival; imperfect agreement of effects on coronary artery patency and effects on survival in patients with myocardial infarction; lack of beneficial effect on bone fracture rate despite favorable effects on bone density in patients with osteoporosis). FDA and outside experts will be aware of these examples as proposed surrogates are considered. The implications are especially great when considering prophylactic therapy, i.e., treatments to prevent chronic illness (coronary artery disease, cancer), in an essentially well population. In the second case, there will generally have been experience (with the standard therapy) to evaluate in considering linkage of the surrogate to benefit; this was, for example, the case with didanosine, where evidence from zidovudine studies of the relationship of an effect on CD4 lymphocytes and clinical outcome could be assessed. Similarly, there is considerable experience to show that durable complete responses in many cancers correspond to improved survival, so that an agent inducing them in refractory illness or in primary

disease that had previously been poorly responsive would generally be seen as reasonably likely to provide a clinical benefit.

6. One comment stated that epilepsy is a serious and life-threatening condition and asked that it be included within the scope of the proposal. The preamble cited, among other illnesses, depression and psychoses as examples of chronic illnesses that can have serious outcomes even if they are generally well managed. One comment asserted that neither depression nor psychosis is a disease, nor is either one serious or life-threatening. The comment stated that depression and psychosis are diagnoses. The comment urged the agency to remove them from the definition of life-threatening "illnesses" or "diseases."

With respect to epilepsy, FDA notes that in the "treatment IND" final rule (52 FR 19466 at 19467, May 22, 1987), the agency listed "certain forms of epilepsy" as an example of a disease or stage of disease that would normally be considered "serious." Certain forms of epilepsy may also be considered "serious" under the accelerated approval program. It is unlikely, however, that a surrogate endpoint would be utilized in such a case, as seizure frequency, a clinical endpoint, is readily measured.

FDA's reference to depression and psychoses was intended to give examples of conditions or diseases that can be serious for certain populations or in some or all of their phases. While drugs for the treatment of depression and psychosis would be examples of those that could be covered by the accelerated approval program, it is not the use of surrogate endpoints that would be expected; the symptoms and signs of these diseases are readily studied. On the other hand, some of these drugs have been quite toxic (e.g., clozapine for refractory psychoses) and might be considered for approval with restrictions to ensure safe use.

7. Two comments asked how FDA will decide that a drug is eligible for accelerated approval. One comment asserted that the decision should be an option for the applicant to consider, not a decision for FDA to make unilaterally. Pointing to a statement in the preamble (57 FR 13234 at 13235) that FDA reserves the right not to apply accelerated approval procedures when it believes in good faith that the drug's foreseeable use is reasonably likely to be outside the scope of "life-threatening diseases without meaningful therapeutic benefit over existing therapy," the comments argued that, if there are patients with life-threatening conditions

that can benefit from expedited approval, the needs of the patients should determine the procedures used to approve the drug. One comment contended that applicants of products considered candidates for accelerated approval may have their drug or biological product "forced" into the accelerated approval process and be forced to conduct a program of studies to substantiate that surrogate endpoints actually predict significant clinical benefits.

The medical reviewing divisions within FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will determine the type of regulatory review that FDA may apply to an application. FDA encourages sponsors to meet with FDA early in the drug development process to discuss the applicability of the accelerated approval program to their product; however, FDA reserves the discretion to determine whether these procedures are applicable to a specific product.

With respect to the preamble statement cited by one comment, the comment misreads the preamble statement, which does not say that FDA will, in all cases, apply FDA's traditional approval mechanisms rather than this accelerated process for drugs where a majority of the drug's foreseeable uses are outside the scope of "life-threatening" diseases without meaningful therapeutic benefit over existing therapy. The statement merely informs applicants that FDA will consider the possible impact of widespread use of a drug for uses other than the one supporting accelerated approval; drugs approved under this program would often have only small safety data bases so that widespread off-label use might have serious implications. The agency does not believe that such a situation would regularly lead to exclusion from these provisions.

FDA does not agree that applicants seeking approval to market drug and biological products that would be candidates for accelerated approval will be forced to use the accelerated approval mechanism. It is true, however, that some proposed surrogate endpoints would not be considered acceptable bases for approval without assurance that the clinical studies to show clinical benefit will be conducted. A sponsor that wishes the application to be considered under the traditional approval process may request and receive such consideration.

The agency wishes to clarify the circumstances in which the accelerated

approval regulations will apply. Sections 314.500 and 601.40 describe aspects of the scope of these regulations. Moreover, these regulations are intended to apply to applications based on surrogate endpoints whose validity is not fully established, to applications based on clinical endpoints that leave unanswered major questions about the product's effect on ultimate outcome, and to applications for products whose safe and effective use requires limitations on distribution or use. In all other situations, accelerated approval requirements will not apply.

Where approval is based on a surrogate endpoint that is accepted as validated to predict or correlate with clinical benefit, the product will be considered under the traditional process, and the postmarketing requirements under accelerated approval will not apply. Approvals of products for serious or life-threatening illnesses based on clinical endpoints other than survival or irreversible morbidity will usually also be considered under traditional procedures. Approvals based on such clinical endpoints will be considered under the accelerated approval regulations only when it is essential to determine effects on survival or irreversible morbidity in order to confirm the favorable risk/benefit judgment that led to approval. Applications for products for serious or life-threatening illnesses that provide a meaningful therapeutic benefit over existing therapy will receive a priority rating and expedited review, even when not considered under the accelerated approval procedures.

The agency also wishes to clarify that whenever an application is approved under § 314.510 or § 601.41, postmarketing studies confirming the product's clinical benefit will thus be required. Therefore, in order to eliminate potential confusion, the agency has amended §§ 314.510 and 601.41 to clarify these points.

FDA also recognizes that over time a particular surrogate, once acceptable as a basis for approval only under the accelerated approval regulations, could become recognized as validated by definitive studies (just as high blood pressure, for example, over time became validated as a surrogate with clinical significance). In such cases, a future application relying on such a surrogate would not require postmarketing studies confirming the surrogate's clinical benefit and the application would be considered under traditional procedures.

8. Two comments asked for clarification of the phrase "meaningful

therapeutic benefit over existing therapy" as used in the description of what drugs the accelerated approval program should apply to. Specifically, pointing to an example described in the preamble that a new therapy would be eligible for accelerated approval if there was "a clear improvement" over existing therapy in being more effective or better tolerated, one comment urged FDA to clarify the meaning of "clear improvement"; to discourage applicants of "me-too" products from wasting the agency's time and resources by applying for accelerated approval of such products. The comment also asked that FDA specify that if a new drug is approved under the accelerated approval provisions because the drug exhibits a "clear improvement" over an existing drug that was also granted accelerated approval; then specific restrictions will be placed on the prior approved drug to limit its use only to patients who cannot tolerate the new drug, or whose physicians assess that a change to the new drug might involve significant risks to the patient that outweigh the benefits. One comment asked that the term "meaningful therapeutic benefit over existing therapy" be interpreted and consistently applied to both drugs and biological products.

FDA believes that the examples given to help clarify the phrase "meaningful therapeutic benefit over existing therapy" (ability to treat unresponsive or intolerant patients or improved response compared to available therapy) are readily understood illustrations of the intent of the requirement. A drug that is essentially the same as available treatment (what the comment refers to as a "me too" drug) will not have a credible claim to a meaningful therapeutic benefit over that existing treatment and this should be easily detected.

With respect to restricting use of a drug previously approved under accelerated approval procedures when a new drug granted accelerated approval is a clear improvement over the prior approved drug, this would rarely be appropriate. Although, in some instances, certain therapies are identified as "second-line," this requires essentially unequivocal evidence of an advantage of alternative therapy, not likely on the basis of a surrogate endpoint. Labeling for both drugs will be accurate, however, allowing physicians to prescribe both the newly approved drug and the prior drug properly.

9. One comment asked if a change in the route of administration would be

considered as a meaningful benefit and within the scope of the proposal.

A change in the route of administration may be a candidate for accelerated approval depending upon the particular evidence presented.

10. One comment asked if subpart E drugs currently under investigation will be considered for accelerated approval. The comment assumed that new drug applications (NDA's) and supplemental NDA's considered for accelerated approval will have the highest priority for review.

Subpart E drugs will be considered for accelerated approval if they satisfy both eligibility criteria for accelerated approval, i.e., if they are being developed for the treatment of serious or life-threatening illnesses and the products will provide meaningful therapeutic benefits to patients over existing treatment. As discussed above, applicants should consult with FDA early in the development process to determine the nature of the regulatory review. Early consultations are a critical part of subpart E procedures. Drugs being reviewed under accelerated approval procedures will receive high priority review. However, applications for drugs for acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV)-related conditions will receive the highest priority review.

#### C. Criteria for Approval

11. Two comments expressed concern that the proposal did not provide enough detail on what constitutes an appropriate surrogate endpoint. One comment recommended that FDA adopt specific criteria for what constitutes an appropriate surrogate endpoint. The comment suggested that such criteria should include: (1) The surrogate endpoint must be biologically plausible in that it must be consistent with what is known about the pathophysiology and pathogenesis of the disease; (2) the surrogate endpoint must be present or abnormal in a large percentage of people who have the disease; (3) the surrogate endpoint must be a good predictor of the disease progression and should correlate closely with the significant clinical endpoint; (4) there should be a correlation between the quantitative aspect of the surrogate endpoint and the progression of the disease (e.g., the more severe the disease, the more deviant the surrogate endpoint from normal); (5) the regression of the surrogate endpoint should be significantly associated with clinical improvement (e.g., those with the greatest improvement in the surrogate endpoint should also show the greatest clinical effects); conversely, the

lack of regression of the surrogate endpoint should be commonly associated with a lack of clinical improvement; and (6) the incidence of regression or improvement in the surrogate endpoint should be significantly greater in treated than untreated patients.

One comment asked if the use of microalbuminuria data is a surrogate for diabetic nephropathy and if all drugs relying on surrogate endpoints would be eligible for accelerated approval, e.g., an angiotensin receptor antagonist with potential utility for treatment of congestive heart failure. The comment also asked what would happen if postmarketing studies demonstrate beneficial changes of surrogate endpoints but not beneficial clinical endpoints. The comment also asked if FDA will consider publishing guidelines on which surrogate endpoints would be appropriate for the diseases that may be affected by the proposed rule. Another comment expressed the belief that there is no evidence that surrogate endpoints are necessarily good indicators of therapeutic benefit. The comment stated that a drug may have an effect on a surrogate endpoint, but will not make any clinical difference because the advanced stage of the patient's disease precludes any effective therapy or the surrogate marker is not synchronous with the patient's clinical condition.

Another comment asserted that the requirement to base an approval on a surrogate endpoint that is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit other than survival or irreversible morbidity" is not restrictive enough to assure adequate consumer protection. Terms like "reasonably likely" and "or other evidence" allow drug manufacturers too much latitude for claiming that there is a correlation between surrogate endpoints affected by their drugs and clinical endpoints. The comment argued that until a correlation between a surrogate endpoint and a clinical endpoint has been established, a particular surrogate endpoint should only be used to approve subsequent drugs, without adequate clinical evidence, if there is a very strong effect of the drug on the surrogate marker or, if the effect is not sufficiently strong, there is an additional surrogate marker which corroborates the results of the first.

FDA intends to publish informal guidance concerning surrogate endpoints, but does not believe specific requirements for an appropriate surrogate should be specified by

regulation. Any given specifications may not be applicable to a particular case. For example, the thoughtful suggested criteria supplied by the comment would rarely, if ever, be applicable to the first effective drug for a disease, because criterion 5 requires that regression of the surrogate endpoint be associated quantitatively with clinical improvement. If there had never been effective treatment, this would never be known. Yet the surrogate could be persuasive on other grounds, such as a well-documented etiologic relation. In general, it is likely that one or another strongly supportive piece of evidence might outweigh gaps in other areas.

In developing informal guidance on surrogate endpoints, FDA will consider the suggestions in this comment. Interested persons will have an opportunity to comment on any guidance documents in this area developed by the agency. In some cases, new or revised drug class, or disease-specific, clinical guidelines may refer to surrogate endpoints. FDA is not prepared, at this time, to comment on the acceptability of an endpoint that it has not specifically considered, e.g., microalbuminuria.

The final regulations make it clear that not all drugs submitted for approval based on surrogate endpoint data are eligible for accelerated approval (§§ 314.500 and 601.40). The drug in question must be for a serious or life-threatening condition and must provide meaningful therapeutic benefit over existing therapy. In the case of an angiotensin receptor antagonist posed by the comment, there is existing documented life-prolonging treatment for congestive heart failure. An application for a new agent, to be eligible for accelerated approval, would have to show potential benefit over available therapy as well as identify a reasonable surrogate endpoint. This is problematic since no accepted surrogate endpoint for studies to treat congestive heart failure has been identified to date. For example, some drugs with favorable effects on hemodynamic measures in heart failure patients have been clinically ineffective.

The regulations are clear in requiring that, for drugs approved under these provisions based on surrogate endpoints, the postmarketing studies must show clinical benefit, not just the previously shown effect on the surrogate (§§ 314.510, 314.530, 601.41, and 601.43).

Surrogates, or proposed surrogates, are not always good, nor necessarily bad, indicators of therapeutic benefit and must be judged on a case-by-case basis. Even very good surrogates may

not be perfect: Blood pressure lowering has been a better predictor of effect on stroke than on coronary artery disease, cholesterol lowering has had a clearer effect on coronary artery disease than on survival. Moreover, a surrogate may be persuasive for a phase of disease with short expected survival but much less so in an earlier phase of the disease. Caution is always appropriate in evaluating surrogate endpoints and the particular therapeutic setting should always be considered. The agency believes that the evaluation of surrogate endpoint data and the safeguards built into these accelerated approval procedures will provide adequate consumer protection.

12. One comment expressed concern that if there is no accepted surrogate endpoint, an applicant's only option is to conduct a study using some clinical event as an endpoint, which may result in long, large studies that delay approval to the detriment of patients and sponsors. One comment suggested as an alternative that FDA permit approval of a drug based on a study using a clinical endpoint, but accept a less rigorous standard of statistical significance, e.g., 0.20 or 0.15 instead of 0.05. The comment further suggested that the sponsor could then complete postmarketing studies to establish statistical significance at conventional levels. The comment argued that this alternative is totally consistent with FDA's willingness to accept greater uncertainty in approving drugs for serious and life-threatening illnesses.

The intent of the rule is to allow FDA to utilize a particular kind of evidence, an effect on a surrogate endpoint, as a basis for approval, and, where appropriate, to ensure that remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional adequate and well-controlled studies with clinical endpoints. The rule is not intended to place into the market drugs with little evidence of usefulness. Although there is no statutory requirement for significance testing of any particular value, there are well-established conventions for assessing statistical significance to support the statutorily required conclusion that the well-controlled studies have demonstrated that a drug will have the effect it is represented to have. There is nothing about serious or life-threatening diseases that make them uniquely difficult to study. A meaningful effect on survival or morbidity where there is no effective therapy should be readily discerned. Such studies need be long and large only when the effect is small or difficult to detect. In that event,

proper assessment of benefit, and valid weighing of its relation to risks, is especially critical.

13. One comment asked that FDA clarify that one study could be the basis of approval and that one postmarketing study should be all that is needed to establish the link between the endpoint used for approval and some relevant clinical benefit.

FDA interprets the statute and good science, as requiring at least two adequate and well-controlled studies to establish effectiveness. In some instances, drugs have been approved on the basis of a single well-controlled study; this has been done where the study was of excellent design, showed a high degree of statistical significance, involved multiple study centers, and showed some evidence of internal replicability, e.g., similar effects in major study subsets. FDA encourages applicants to discuss with FDA early in a drug's development the basis for the applicant's choice of a specific endpoint and, where applicable, the basis for its belief that a single study would be a sufficient basis for approval. With respect to postmarketing studies, FDA anticipates that the requirement will usually be met by studies already underway at the time of approval. As stated in the proposed rule, the requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for a postmarketing approval of the same drug for the same claim.

14. One comment expressed concern that the preamble to the proposed rule implied that a sponsor of an AIDS drug might have to do a postmarketing study to establish an effect on survival after showing an effect on such endpoints as weight or incidence of opportunistic infection (57 FR 13234 at 13235-13236). The comment stated that FDA's own advisory committee indicated that it was pleased to see an effect from a nucleoside analogue on the incidence of opportunistic infections with AIDS patients but did not suggest that further work should be done to show an effect on mortality. The comment argued that in some cases direct correlation with clinical endpoints such as mortality is difficult to prove and urged FDA to be flexible on this issue to encourage sponsors to go through the accelerated approval process.

Ordinarily, an effect on a meaningful clinical endpoint, e.g., on rate of opportunistic infections in AIDS, is a sufficient basis for approval without need for followup studies. Other endpoints, however, might leave major questions unanswered. For example,

modest effect on weight gain in AIDS without other demonstrated benefit, if considered an adequate basis for approval, while a clinical endpoint, might leave sufficient doubt as to the ultimate value of the effect so that further studies would be necessary. FDA intends to interpret this provision of the regulations with flexibility. This provision should also serve as a reminder, however, that for life-threatening diseases, the ultimate aim of therapy is improved survival as well as improved symptoms.

15. One comment asked FDA to clarify what a sponsor's obligation is to continue supplying medication on a compassionate basis if clinical efficacy is not demonstrated to FDA's satisfaction in postmarketing studies but individual patients appear to be benefiting from use of the drug.

Sponsors are not obligated to supply drugs on a "compassionate basis." Whether, if clinical studies did not show effectiveness, further availability of the drug would be appropriate under any mechanism would be determined case-by-case.

#### D. Promotional Materials

16. Three comments asserted that requiring advance submissions of promotional materials is both beyond FDA's statutory authority and is unnecessary. Although FDA stated in the proposal that it does not intend specifically to approve promotional materials, two comments contended that is the likely effect of advance submission. The comment cited section 502(n) of the act (21 U.S.C. 352(n)), which provides that no regulation promulgated under that provision shall require prior FDA approval of the content of any advertisement "except in extraordinary circumstances," and asserted that the "extraordinary circumstances" language would not apply to drugs approved under the accelerated approval program. One comment argued that submission of promotional material prior and subsequent to approval is unwarranted when dealing with treatments for serious or life-threatening illnesses where dissemination of the most current and timely information is important to the treating physician. One comment questioned why there would be any greater likelihood of misleading promotional claims for products approved under the proposed accelerated approval process than for drugs intended to treat serious or life-threatening diseases that are approved under the normal NDA procedures. The comment also expressed the hope that the proposed requirement for advance

submission of promotional materials was not based upon an assumption that promotional materials for drugs intended to treat serious diseases are more likely to be misleading than promotional materials for other types of drugs because any such assumption would be unfounded. One comment argued that if an advertisement or labeling is inaccurate, the product is misbranded and FDA could then obtain injunctive relief, seize the product, and/or initiate criminal proceedings. Another comment considered requiring advance submission of promotional materials unreasonable because companies are not required to do so now. One comment questioned the legal authority for requiring presubmission of promotional material following approval of a drug product, and the reason for the requirement.

The agency believes that the requirements for submission of promotional materials in the context of accelerated approval are authorized by statute. Subsections 505(d)(4) and (d)(5) of the act provide that, in determining whether to approve a drug as safe and effective, the agency may consider not only information such as data from clinical studies but also "any other information" relevant to safety and effectiveness under the proposed conditions of use. Such information would include information about how the drug would be promoted. In determining whether the drug's proposed labeling would be "false or misleading" under section 505(d)(7) of the act, the agency is similarly authorized to evaluate "all material facts" during the approval process, including the facts about promotion.

FDA is also authorized by section 505(k) of the act to require reporting of information subsequent to approval necessary to enable the agency to determine whether there may be grounds for withdrawing the approval. Among the grounds for withdrawal specified in section 505(e) of the act are that the evidence reveals the drug is not shown to be safe and effective under its conditions of use. In addition, drug approval may be withdrawn if information shows the labeling to be false or misleading. Information on how the drug will be promoted is again relevant to whether the drug's marketing approval should be withdrawn. Section 701(a) of the act (21 U.S.C. 371(a)) generally authorizes FDA to promulgate regulations for the efficient enforcement of the act.

For biological products, additional authority in section 351 of the PHS Act (42 U.S.C. 262) authorizes the promulgation of regulations designed to

ensure the continued safety, purity, and potency of the products. The content of promotional materials is important to the continued safe and effective use of biologicals.

Therefore, the provisions of the final rule requiring submission of promotional materials prior to approval under the accelerated approval procedures and subsequent to such approval are authorized by statutory provisions. FDA might also invoke the authority of section 502(n) of the act (21 U.S.C. 352(n)) to require prior approval of the content of any prescription drug advertisement in "extraordinary circumstances." Whether FDA could appropriately rely on section 502(n) of the act in promulgating §§ 314.550 and 601.45 need not be determined, however, because FDA is not relying upon section 502(n) of the act as legal authority for these (or any other) sections of the accelerated approval regulations.

The agency believes that advance submissions of promotional materials for accelerated approval products are warranted under the accelerated approval circumstances. The special circumstances under which drugs will be approved under these provisions and the possibility that promotional materials could adversely affect the sensitive risk/benefit balance justify review of promotional materials before and after approval. For example, if the promotional materials exaggerate the known benefits of the drug, wider and inappropriate use of the drug could be encouraged, with harmful results.

Similarly, high risk drugs that are approved based on postmarketing restrictions would not have been approved for use without those restrictions because the risk/benefit balance would not justify such approval. If promotional materials were to undermine the postmarketing restrictions, the health and safety of patients could be greatly jeopardized.

Although there is potential harm from any misleading promotion, and there is no reason to believe improper promotion is more likely in this setting than in others, the risk/benefit balance is especially sensitive in this setting. The relatively small data base available and the minimal published information available also can contribute to making the physician and patient populations particularly vulnerable under accelerated approval circumstances.

Reliance on court actions (such as seizures, injunctions, and criminal prosecutions) can be effective in ending false promotions, but can only be initiated after the fact, when harm has already occurred. Corrective efforts can



be helpful but are always somewhat delayed. Under the circumstances of accelerated approval, FDA believes that it is far preferable to avoid problems by reviewing the promotional materials in advance of drug approval and of dissemination of the materials.

17. Two comments supported the provision about submission of promotional materials. One comment urged the agency to require that specific patient information be included in promotional materials to indicate the fact that the drug's clinical benefit has not yet been established. For drugs approved under the restricted use provision, the comment recommended that the labeling specify in detail the exact restrictions placed on the drug. In both cases, the comment recommended that this patient information appear as boxed warnings.

Section 502(n) of the act and regulations at § 202.1(e)(1) (21 CFR 202.1(e)(1)) require prescription drug advertisements (promotional material) to contain, among other things, a true statement of information in brief summary relating to side effects, contraindications, and effectiveness, which would include warnings, precautions, and limitations on use. The information in brief summary relating to side effects, contraindications, and effectiveness is required to be based solely on the approved labeling.

Therefore, to the extent that a drug's labeling reflects the extent of clinical exposure and includes appropriate warnings, a drug's promotional material would also include this information.

FDA regulations governing prescription drug labeling (21 CFR 201.56 and 201.57) require that serious adverse reactions and potential safety hazards, as well as limitations in use imposed by them, be included in the "Warning" section of the labeling. In the case of approval based upon effect on a surrogate endpoint, the "Indications and Usage" section of the labeling would reflect the nature of the demonstrated effect. If the approval is based on use restrictions, the label would also specify the restrictions.

FDA may require boxed warnings if there are special problems associated with a drug, particularly those that may lead to death or serious injury (21 CFR 201.57(e)). The agency does not agree that information related to clinical benefit or use restrictions for accelerated approval drugs would necessarily always require a boxed warning.

As indicated by §§ 314.550 and 601.45 of the final rule, applicants will be required to submit promotional materials prior to approval and in advance of dissemination subsequent to

approval whether the product is a new drug, an antibiotic, or a biological product.

18. One comment contended that FDA review and approval of all promotional pieces before their use will indefinitely delay product marketing campaigns and other patient and physician educational activities, which are essential to market a product, thereby significantly diminishing the advantage of securing an early approval for the applicant. The comment further contended that the requirement to submit "all promotional materials \* \* \* intended for dissemination or publication upon marketing approval" will be overly burdensome for FDA and will unnecessarily slow down the process for review of all materials, not just those for products subject to this proposed rule. The comment recommended that FDA only request for review the primary advertising pieces, such as the introductory letter to physicians, the main detail piece, and the main journal advertisement, but not the secondary materials, e.g., a letter to pharmacists, of the initial promotional campaign.

As previously discussed in this preamble, FDA will be reviewing an applicant's planned promotional materials both prior to approval of an application (reflecting the initial campaign) and subsequent to approval to ascertain whether the materials might adversely affect the drug's sensitive risk/benefit balance. Because all promotional materials, including those referred to by the comment as "secondary" materials, can have significant adverse effects if they are misleading, the agency does not agree that such materials should, as a matter of course, not be requested for review. Insofar as such materials may be directly derived from the introductory letter to physicians, or other materials characterized by the comment as "primary" materials, the additional time to review the derivative materials should not be extensive.

The agency does not agree with the comment's contention that the requirement to submit all promotional materials prior to and subsequent to approval will indefinitely delay marketing campaigns and educational activities or be overly burdensome to FDA reviewers. FDA is committed to rapid review and evaluation of all drugs considered for approval under this rule and will promptly review the promotional materials.

19. One comment suggested a passive, time-limited clearance system for review of advertising after the initial promotional campaign such as that used for review of IND's, which would allow

the sponsor to proceed to use promotional materials after an allotted timeframe, such as 30 days, unless otherwise notified by FDA.

As indicated by this comment and others, additional clarification regarding both timing and content of the submissions of promotional materials seems useful. Therefore, the agency is revising proposed §§ 314.550 and 601.45 to make it clear that, unless otherwise informed by the agency, applicants must submit during the preapproval review period copies of all promotional materials intended for dissemination or publication within the first 120 days following marketing approval. The initial promotional campaign, sometimes referred to as the "launch campaign," often has a significant effect on the climate of use for a new product. As discussed elsewhere in this preamble, the risk/benefit balance of accelerated approval products is especially sensitive, and inappropriate promotion may adversely affect the balance with resulting harm.

There may be some instances in which promotional materials that had not been completed and submitted by the applicant prior to approval would be beneficial in fostering safe and effective use of the product during the first 120 days. Under revised §§ 314.550 and 601.45, FDA would have the discretion to consider such materials at a later time. An applicant who requested permission to include additional materials among those disseminated within the first 120 days following product approval would be notified of FDA's determination. If FDA agreed that dissemination of such materials was acceptable, the materials could then be disseminated or published upon notification.

For promotional materials intended for dissemination subsequent to the initial 120 days under §§ 314.550 and 601.45 FDA would review the submitted materials within 30 days of receipt. This 30-day period is meant to be time-limited, so that the applicant will be assured of no unnecessary delay. It will be important for the applicant to identify the materials being submitted appropriately, so that it is clear that the materials are subject to the 30-day review period. The agency intends to review all such materials promptly, and to notify the applicant of any identified problems as soon as possible. The agency expects that, if the agency notifies the applicant of significant objections to the proposed materials, no materials will be disseminated or published until the agency's objections are resolved. The applicant should plan to allow sufficient time after receiving

FDA's comments for resolving differences and incorporating requested changes in the submitted materials prior to dissemination or publication.

When FDA removes the requirement for advance submission of promotional material, the agency will continue to offer a prompt review of all voluntarily submitted promotional material.

#### E. Postmarketing Restrictions

FDA received many comments on the proposed requirement to limit distribution to certain facilities or physicians with special training or experience, or condition distribution on the performance of specified medical procedures if such restrictions are needed to counterbalance the drug's known safety concerns.

20. Several comments questioned FDA's authority to impose restrictions on distribution or use after an approved drug is marketed. Two comments disagreed with the statutory provisions cited by FDA in the proposed rule as its authority to impose restrictions on distribution or use stating that they refer only to FDA's general authority to ensure that drugs are not misbranded, which is an entirely separate issue. Another comment argued that section 503(b) of the act (21 U.S.C. 353(b)) contemplates that the issues warranting a restriction as to distribution are not factors in whether a drug product is "safe" for purposes of approval, but rather only whether the product must be limited to prescription status. Two comments said that, in the absence of specific statutory authority, the courts clearly have refused to permit FDA to impose restrictions on distribution and cited *American Pharmaceutical Association (APhA) v. Weinberger*, 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), *aff'd sub nom. APhA v. Mathews*, 530 F.2d 1054 (D.C. Cir 1976), a case concerning conditions placed on the approval of the drug methadone.

Some comments asserted that placing restrictions on the distribution of an approved drug to only certain facilities or physicians, or restricting use to certain medical procedures interferes with the practices of medicine and pharmacy, which the comments contended FDA does not have the authority to regulate.

The agency believes that the restrictions to ensure safe use contemplated for approvals under §§ 314.520 and 601.42 are authorized by statute. As discussed in the preamble to the proposed rule (57 FR 13234 at 13237), sections 501, 502, 503, 505, and 701 of the act provide broad authority for FDA to issue regulations to help

assure the safety and effectiveness of new drugs.

The agency does not agree with the comments' contention that the misbranding provisions of the act are irrelevant. Section 502(a) of the act prohibits false or misleading labeling of drugs, including (under section 201(n) of the act) failure to reveal material facts relating to potential consequences under customary conditions of use. Section 502(f) of the act requires drugs to have adequate directions for use and adequate warnings against unsafe use, such as methods of administration, that may be necessary to protect users. In addition, section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Each of these misbranding provisions is intended, at least in significant part, to protect consumers against the marketing of drugs that would not be safe under certain conditions of use. Section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act. The restrictions on use contemplated by §§ 314.520 and 601.42 help to ensure that products that would be misbranded under section 502 of the act are not marketed.

The restrictions on use imposed under section 503 of the act, which relate to prescription use limitations, primarily concern whether a drug is safe for use except under the supervision of a licensed practitioner. While the agency agrees that the restrictions imposed under §§ 314.520 and 601.42 concerning distribution to certain facilities or physicians with special training or experience would be in addition to ordinary prescription limitation, FDA believes these restrictions are consistent with the spirit of section 503 of the act, as well as the other provisions of the act referred to, in ensuring safe use.

New drugs may be approved under section 505(d) of the act only if they are safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. In addition, for approval, a drug's labeling must not be false or misleading based on a fair evaluation of all material facts, which would include details about the conditions of use. For biological products, section 351(d) of the PHS Act also authorizes the imposition of restrictions through regulations "designed to insure the continued safety, purity, and potency" of the products.

The agency disagrees with the comments' implication that the courts' rulings in *American Pharmaceutical Association (APhA) v. Weinberger* mean

there is no statutory authority to impose restrictions on distribution for accelerated approval drugs. The situation considered in that case is readily distinguishable from the situation addressed in §§ 314.520 and 601.42 of the accelerated approval regulations. The APhA case concerned a regulation that withdrew approval of NDA's for methadone, but permitted distribution to certain maintenance treatment programs and certain hospital and community pharmacies. Because methadone is a controlled substance within the provisions of the Controlled Substances Act, which is implemented by the Drug Enforcement Administration with the Justice Department, the district court concluded that the question of permissible distribution of the drug was within the jurisdiction of the Justice Department, not FDA. The Court of Appeals determined that the type of misuse associated with methadone, i.e., misuse by persons who have no intent to try to use drugs for medical purposes, differed from safety issues contemplated for control under section 505 of the act. In contrast, the restrictions contemplated under §§ 314.520 and 601.42 are precisely those deemed necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use. It is clearly FDA's responsibility to implement the statutory provisions regarding new drug approval.

Nor does FDA agree that the provisions placing restrictions on distribution to certain facilities or physicians, or conditioned on the performance of certain medical procedures, impermissibly interfere with the practice of medicine and pharmacy. There is no legal support for the theory that FDA may only approve sponsors' drugs without restriction because physicians or pharmacists may wish to prescribe or dispense drugs in a certain way. The restrictions under these provisions would be imposed on the sponsor only as necessary for safe use under the extraordinary circumstances of the particular drug and use. Without such restrictions, the drugs would not meet the statutory criteria, could not be approved for distribution, and would not be available for prescribing or dispensing. The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases,

approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing.

21. One comment asserted that postmarketing restrictions on distribution to certain facilities or physicians with certain training or experience should be limited to rare occasions in cases of extreme hazard to patient safety in which toxicity of a particular drug may require it, but should not be applied because of insufficient efficacy data. Some comments argued that safety issues in the context of drug use should be addressed through patient management and effective product labeling, not through restricted distribution. In support of this argument, the comments cited the labeling of oncologic drugs, which provides physicians with adequate warnings and recommendations for their use without limiting distribution.

FDA agrees with these comments in part and intends to impose restrictions on distribution or use under this rule only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will not assure the product's safe use. As stated in the preamble to the proposed rule (57 FR 13234 at 13237), FDA believes that the safe use of most prescription drugs will continue to be assured through traditional patient management by health professionals and through necessary safety warnings in the drug's labeling.

22. Two comments asked who will determine if restricted distribution should occur and what facilities or physicians with special training or experience will participate. Several comments expressed concern that restricted distribution and/or conditional use may not include all health care professionals who should participate in safe and effective patient care. Two organizations representing pharmacists asked that FDA develop functional and objective criteria that clearly establish the activities of pharmacists, physicians, and others in the care of patients receiving a drug under restricted distribution. The comments asserted that any health care professional that met these criteria should be allowed to participate in distribution of the drug and care of the patient. One comment recommended that any postmarketing restrictions on distribution or use of a drug approved under the accelerated approval process be developed by appropriate FDA advisory committees or panels expanded to include physicians and pharmacists with expertise in the

therapeutic area being considered and in relevant drug distribution systems. Where appointment of pharmacists to these committees or panels is not feasible, the comment recommended that FDA use pharmacists in a consultant capacity. Another comment argued that current systems for drug distribution incorporate "checks and balances" such that prescribers and pharmacists work together to assure safe use of a drug by a patient. Two comments would oppose any restricted distribution system that allows manufacturers exclusively to deliver prescription drugs directly to patients. One comment asked whether FDA or the applicant would monitor the criteria for restricted distribution sites or physicians.

The medical reviewing divisions within FDA's CDER and CBER will determine if restricted distribution or use should be imposed. FDA will usually seek the advice of outside expert consultants or advisory committees before making this determination, and will, of course, consult with the applicant.

The agency does not agree that FDA should develop criteria that clearly establish the activities of health care professionals in the care of patients receiving a drug approved under this rule and for which restricted distribution has been imposed. Any postmarketing restrictions required under this rule will impose an obligation on the applicant to ensure that the drug or biological product is distributed only to the specified facilities or physicians. FDA will seek the advice of outside consultants with expertise in distribution systems or advisory committees when necessary in determining the need for or type of restricted distribution. The limitations on distribution or use imposed under this rule, including specific distribution systems to be used and the applicant's plan for monitoring compliance with the limitations, will have been agreed to by the applicant at the time of approval. The burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. As appropriate, FDA may monitor the sponsor's compliance with the specified terms of the approval and with the sponsor's obligations.

23. One comment recommended that proposed § 314.520 be modified to include therapeutic outcomes monitoring as a third example of a permissible postmarketing restriction. The comment defined therapeutic outcomes monitoring as the systematic and continual monitoring of the clinical and psychosocial effects of drug therapy

on a patient which achieves the objective of preventing problems with drug therapy. Some comments argued that through therapeutic outcomes monitoring, a physician, a pharmacist, and a patient can work together to prevent problems with drug therapy by being constantly alert to signs of trouble. One comment said that indicator data can be routinely reported to a central collection point for utilization review by health care professionals, followed by educational programs to further improve the efficacy of drug therapy.

The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction. Therapeutic outcomes monitoring does not contribute to that enhancement, and would not be required under this rule.

24. Some comments asked that FDA clarify how products will move from restrictive status to a regular prescription drug status. The comments asserted that all conditions associated with accelerated approval should automatically terminate following completion of confirmatory clinical trials; one comment urged FDA to explicitly state this in the final rule. One comment asserted that restrictions should automatically be removed 180 days after a supplemental application containing the data from the postmarketing study has been filed if FDA has not yet acted upon the supplemental application and the product should be deemed approved as if by "traditional" procedures and all other provisions of the act should apply, e.g., the applicant must have a formal hearing before removal of the product from the market.

FDA will notify the applicant when a particular restriction is no longer necessary for safe use of the product. In the case of drugs approved with a requirement for postapproval studies, FDA would expect that all of the postapproval requirements set forth in this rule, i.e., submission of promotional material and use of expedited withdrawal procedures, would no longer apply after postmarketing studies have verified and described the drug's clinical benefit. Concurrent with the review of the postmarketing studies, if requested, FDA will also review the need to continue any restrictions on distribution that have been imposed. In the case where restrictions on distribution or use have been imposed, such restrictions would be eliminated only if FDA determines that safe use of the product can be assured without them, through appropriate labeling. In

some cases, however, that assurance could not be expected and the nature of the specific safety issue raised by the product might require continued restrictions. FDA has added new §§ 314.560 and 601.46 to state when postapproval requirements will no longer apply and state that the applicant may petition the agency, in accordance with 21 CFR 10.30, at any time to remove specific postapproval requirements.

With respect to the suggested time period for removing restrictions on distribution or use following submission of a supplemental application containing the data from a postmarketing study, FDA does not believe it should prescribe any specific time period. These applications will receive a priority rating and FDA is firmly committed to expedited review of an application considered for accelerated approval and all data submitted from a postmarketing study to verify clinical benefit and believes most reviews will be completed and action taken within 180 days.

25. One comment argued that, as proposed, it is not clear how accelerated approval would apply to drugs which fall under the conditions described in §§ 314.520 and 601.42, which state the postmarketing restrictions on distribution or use that FDA may apply, because the language of these sections explicitly states that the sections apply to products "shown to be effective," which are already adequately covered by the act. To the comment, the language "shown to be effective" implies that full Phase 3 efficacy trials have been conducted, assessed, and deemed to demonstrate that the drug is effective for its proposed use. If the clinical data demonstrate that the product has an acceptable safety profile, the safe use of the drug should be addressed in the product labeling. Thus, the comment argued that §§ 314.520 and 601.42 should not be included in new subpart H of part 314 and subpart E of part 601, respectively, which deal with accelerated approval because these sections explicitly apply to products shown to be effective under a full drug development program.

Sections 314.520 and 601.42 apply not only to drugs and biological products approved on the basis of an effect on a surrogate endpoint but also to drugs and biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses using clinical endpoints and that have serious toxicity. In either case, if the products are so potentially harmful that their safe use cannot be assured through carefully

worded labeling, FDA will approve the products for early marketing only if postmarketing restrictions on distribution or use are imposed. The phrase "shown to be effective" was not intended to distinguish drugs approved under new subpart H from drugs approved under any other subpart of the regulations. All drugs approved will have had effectiveness demonstrated on the basis of adequate and well-controlled studies, whether the endpoint of the studies is a surrogate endpoint or a clinical endpoint.

26. One comment expressed concern that the proposed restricted distribution or use provisions would restrict or eliminate the wholesale distribution of drugs approved through the accelerated approval process.

The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. This rule does not specify how a manufacturer will distribute its product to those receiving the product under the approval terms. FDA will only determine which facilities or physicians may receive the drug, and the applicant will have agreed to this limitation on distribution or use.

27. One comment expressed concern that the proposed postmarketing restriction provision does not preclude a physician to whom restricted distribution applies from prescribing drugs approved under the accelerated approval process for unapproved (off-label) uses.

The comment is correct that this rule does not itself prevent a physician from prescribing a drug granted accelerated approval for an unapproved use. Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved. Physicians may choose to prescribe the drug for a condition not recommended in labeling. Such off-label use would, of course, be carried out under the restrictions imposed under this section. FDA also believes that physicians will be cognizant of the product's special risks and will use such drugs with particular care. The labeling of products approved under this rule will include all necessary warnings and full disclosure labeling would generally reflect the extent of clinical exposure to the drug.

#### F. Postmarketing Studies

28. Three comments argued that FDA does not have the authority to require

postmarketing studies to be performed as a condition of approval based on a "surrogate" endpoint. One comment stated that it is widely accepted that the act empowered the agency to define the type and extent of efficacy data necessary to approve a product application. If a surrogate marker can be shown to be sufficiently related to actual patient benefit, then, the comment asserted, data regarding the effect of a drug on a surrogate marker constitute acceptable proof of efficacy under the act. Two comments urged FDA to continue to ask applicants to agree voluntarily to perform postmarketing studies when medically warranted as is the current policy under the traditional approval process. One comment expressed concern that requiring postmarketing studies may become the norm rather than the exception.

The agency's response to comment 1. explained the circumstances in which FDA might conclude that a drug should be marketed on the basis of an effect on a surrogate endpoint reasonably likely to predict clinical benefit only if studies were carried out to confirm the presence of the likely benefit. As discussed in the preamble to the proposed rule (57 FR 13234 at 13236), FDA believes that it is authorized by law to require postmarketing studies for new drugs and biological products. Section 505(d) of the act provides for the approval of new drugs for marketing if they meet the safety and effectiveness criteria set forth in section 505(d) of the act and the implementing regulations (21 CFR part 314). As discussed in the proposed rule, to demonstrate effectiveness, the law requires evidence from adequate and well-controlled clinical studies on the basis of which qualified experts could fairly and responsibly conclude that the drug has the effect it is purported to have. Under section 505(e) of the act, approval of a new drug application is to be withdrawn if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if new information shows that the drug's labeling is false or misleading.

Section 505(k) of the act authorizes the agency to promulgate regulations requiring applicants to make records and reports of data or other information that are necessary to enable the agency to determine whether there is reason to withdraw approval of an NDA. The agency believes that the referenced reports can include additional studies to evaluate the clinical effect of a drug approved on the basis of an effect on a surrogate endpoint. Section 701(a) of the act generally authorizes FDA to issue

regulations for the "efficient enforcement" of the act.

With respect to biological products, section 351 of the PHS Act provides legal authority for the agency to require postmarketing studies for these products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

The agency notes that it has in the past required postmarketing studies as a prerequisite for approval for some drugs (see 37 FR 201, January 7, 1972; and 37 FR 26790, December 15, 1972).

29. One comment recommended that FDA require that specific timelines for completion of the required postmarketing studies be included in the marketing application. The comment further suggested that, if the sponsor fails to meet its timelines, approval of its application be withdrawn, or in the event it is difficult to withdraw approval of drugs for serious or life-threatening diseases, FDA should establish substantial fines and penalties for sponsors that deliberately withhold information from FDA regarding the preliminary results and the progress of their postmarketing studies, or delay the completion of such studies. The comment also urged FDA to publish in the *Federal Register* identification of manufacturers who are not meeting their obligation to complete the required postmarketing studies on time. These recommendations were prompted by the comment's concern that once a manufacturer is granted approval for its product, the manufacturer will have little incentive to complete postmarketing studies in a timely manner, especially if the preliminary results of such studies indicate that the drug may not be safe and/or effective. Another comment urged FDA to include in the final rule language that requires the participation of pharmacists in postmarketing studies because pharmacists can serve as an additional source of information on therapeutic outcomes of patients taking drugs approved under this rule and monitoring for such drugs.

The agency expects that the requirement for postmarketing studies will usually be met by studies already underway at the time of approval and that there will be reasonable enthusiasm for resolving the questions posed by those studies. The plan for timely completion of the required postmarketing studies will be included

in the applicant's marketing application. In addition, in accord with the annual reporting requirements at § 314.81(b)(2)(vii) (21 CFR 314.81(b)(2)(vii)), an NDA applicant is required to provide FDA with a statement of the current status of any postmarketing studies. FDA declines to impose the sanctions suggested by the comment for failure of an applicant to meet its plans for completion of a postmarketing study. FDA believes this rule applies appropriate regulatory sanctions. Under the proposed rule and this final rule, FDA may withdraw approval of an application if the applicant fails to perform the required postmarketing study with due diligence.

FDA believes that it is not within the scope of this rule to establish the role of pharmacists in postmarketing studies. That role should more properly be defined by the clinical investigator and each institution or facility at which a postmarketing study is conducted.

30. One comment asserted that the proposal sets forth an inherent contradiction between the way FDA evaluates the benefit and risk for drugs today and the way the proposal contemplates. The comment argued that now, if postmarketing data raise questions about the risk associated with a drug product, FDA considers that data along with the other data known about the product, and determines whether, based on the overall knowledge about the drug, there is a need to seek withdrawal of approval. Under this proposal, if the postmarketing study data raised questions about the risk of the product, FDA would seek withdrawal of approval, whether or not the new data really made a fundamental difference to what is known about the benefit and risk of the product.

FDA does not agree that the contradiction described by the comment exists. Under the circumstances of accelerated approval, approval would be based on a weighing of the benefit suggested by the effect on the surrogate endpoint against known and potential risks of the drug. Should well-designed postapproval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval. This evaluation of the data is not different from considerations that would apply in evaluating data in the case of a drug approved under other provisions of the regulations.

31. Two comments expressed the view that the proposed requirement for postmarketing studies may raise

important ethical questions because once a drug product is approved, it may be unethical, depending on the circumstances, for a physician to conduct a study using a placebo control. One comment also contended that a postmarketing study requirement could compromise the NDA holder's ability to enroll sufficient numbers of patients in the study when the new approved drug and possible alternative therapies are widely available to patients.

Usually, and preferably, because of problems suggested in the comment, the requirement for postmarketing studies will be met by studies already underway at the time of approval, e.g., by completion of studies that showed an effect on the surrogate. FDA recognizes that ethical considerations will play a central role in the type of study carried out, a choice that will depend upon the type and seriousness of the disease being treated, availability of alternative therapies, and the nature of the drug and the patient population. There often are alternatives to use of a placebo control, including active control designs and dose-response studies that can satisfy both the demands of ethics and adequacy of design.

32. One comment contended that the term "postmarketing study" is used inconsistently in the proposed rule. The comment argued that "postmarketing study" is an accepted regulatory term of art which, to this point, has referred to studies conducted to confirm safety (not efficacy), after an approval has been granted, whereas in this proposal, a "postmarketing study" refers to a study required to establish clinical efficacy (i.e., a Phase 3 study), but not necessarily safety, although safety data will be collected. To prevent confusion and to differentiate between these required postmarketing confirmatory efficacy studies and safety studies traditionally conducted after approval and to clarify that products granted accelerated approval have been approved on the basis of Phase 2 (surrogate endpoint) data, the comment suggested changing the term "postmarketing study" to "Phase 3 study" in this rule except where traditional postmarketing studies are intended. The comment also suggested that the term "Phase 3 study" be defined as a study required to confirm findings of efficacy based upon surrogate data collected in Phase 2, which will be conducted after an accelerated approval has been granted and will be required before restrictions set forth in § 314.520 are removed.

The agency does not believe that the comment has accurately described accepted meanings of various terms.

The term postmarketing study does not refer to any particular kind of study, but to studies carried out after a drug is marketed, often as part of an agreement by a sponsor to do so. These have included pharmacokinetic, drug-drug interaction, and pediatric studies, studies of dose-response or of higher doses, and studies of new uses. The term is not limited to safety studies. Moreover, Phase 2 and 3 studies are not distinguished by the endpoints chosen. Phase 3 hypertension studies, for example, still measure blood pressure, not stroke rate. The agency believes that the use of the "postmarketing study" in the final rule is appropriate and consistent.

### G. Withdrawal of Approval

33. One comment supported the proposed withdrawal of approval procedure. Other comments asserted that the proposed procedure does not provide the applicant with the procedural safeguard of a formal evidentiary hearing guaranteed by section 505 of the act and the Administrative Procedure Act (APA). As an example, the comments said that based on a finding of a single study failing to show clinical benefit or misuse of any promotional material, an approved new drug would be subject to withdrawal from the market with only a minimal opportunity for the NDA holder to be heard. The comments argued that section 505(e) of the act guarantees applicants "due notice and opportunity for a hearing" on withdrawal of an NDA in compliance with APA hearing standards, thus FDA must conduct hearings on withdrawals of NDA's using the formal adjudicatory procedures of the APA. One comment asserted that, under the proposed procedure, there is the absence of a discernible legal standard, an inability to cross-examine, the prosecuting attorney and judge are one and the same person, and there is a lack of even minimal formal evidentiary procedures. The comment expressed doubt that the proposed procedure would be sufficient to create a record suitable for review by a Court of Appeals, which must be able, on the basis of such a record, to determine whether the approval is supported by "substantial evidence."

FDA believes the withdrawal procedures set forth in proposed §§ 314.530 and 601.43 and in this final rule are consistent with relevant statutes and provide applicants adequate due process. As stated in the proposed rule, in issuing its general procedural regulations, FDA decided to afford NDA holders an opportunity for a formal evidentiary hearing even though the

courts had not decided that such a hearing was necessarily legally required (see 40 FR 40682 at 40691, September 3, 1975). In promulgating its procedural regulations, FDA also determined that a formal evidentiary hearing is not required before withdrawing approval of biological products, but that it would be appropriate to apply the same procedures to biological products as to drug removal (see 40 FR 40682 at 40691).

Through the hearing process in this final rule, as in the proposed rule, applicants will be afforded the opportunity to present any data and information they believe to be relevant to the continued marketing of their product. The proposed process also would have permitted the presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center that initiates the withdrawal proceedings to question any person during or at the conclusion of the person's presentation. As discussed below in response to a comment, FDA has decided to allow up to three representatives of the applicant and of the Center to question presenters. Participants could comment on or rebut information and views presented by others. As with ordinary 21 CFR part 15 hearings, the hearing will be transcribed. Subsequent to the hearing, the Commissioner of Food and Drugs would render a final decision on the matter. The agency believes that the administrative record created through this process would be sufficient for judicial review.

The agency emphasizes that, as part of the approval process under this rule, applicants will have agreed that these withdrawal procedures apply to the drug for which they seek approval; applicants objecting to these procedures may forego approval under these regulations and seek approval under the traditional approval process. Under such circumstances, applicants would not have the benefit of accelerated approval; if the drug were subsequently approved, however, before withdrawal of the approval, the applicant would have an opportunity for a 21 CFR part 12 hearing.

34. One comment noted that the "imminent hazard" provision of section 505(e) of the act allows FDA to suspend approval of a product, immediately, if it is found to pose an imminent hazard to the public health. As an alternative to the proposed withdrawal procedure or in addition to the "imminent hazard" statutory provision, the comment suggested that, when confronted with a dangerous product on the market, FDA

could request that the applicant voluntarily withdraw its product, and most applicants would comply if a legitimate hazard exists.

As noted in the proposed rule, FDA and applicants have often reached mutual agreement on the need to remove a drug from the market rapidly when significant safety problems have been discovered. However, applicants usually have been unwilling to enter into such agreements when doubts about effectiveness have arisen, such as following the review of effectiveness of pre-1962 approvals carried out under the Drug Efficacy Study Implementation (DESI) program. For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that the surrogate endpoint will correlate with clinical benefit or that postmarketing restrictions will enable safe use. If the effect on the surrogate does not translate into a clinical benefit, or if restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health.

35. Under the proposed withdrawal procedures, in addition to other persons, one representative of the Center that initiates the withdrawal proceedings may question participants at a withdrawal of approval hearing. One comment objected to limiting the Center to one representative because detailed knowledge about a drug product is likely to be available from several scientists.

The proposed limitation of questioning to single representatives of the initiating Center and the applicant was intended to make the proceedings manageable. On further consideration, the agency has determined that it would be appropriate and manageable to allow up to three persons to be designated as questioners for the applicant and for FDA. Sections 314.530(e)(2) and 601.43(e)(2) have been revised accordingly.

36. Some comments questioned FDA's ability to withdraw approval under the proposed procedures efficiently or effectively because of: (1) The lack of assurance that the results of postmarketing studies will be promptly provided to FDA; (2) limited agency resources to review study results and act upon them promptly; (3) the difficulties associated with establishing that an approved drug is "ineffective;" and (4) political pressure not to rescind the approval of NDA's for drug products that may lack evidence of effectiveness.

especially if no clearly effective alternative treatments are available. One comment offered the opinion that where a drug shows only modest evidence of benefit, perhaps on a surrogate endpoint, and only shows equivocal evidence of clinical efficacy in postmarketing studies it would be difficult and socially disruptive to withdraw approval and remove the drug from the market if the drug has become well established and accepted, and there is no issue of toxicity. Another comment believed it would be difficult to withdraw approval of a drug that may be beneficial in a subpopulation but which, in fact, has not been shown to be efficacious in broader patient population studies. The comments suggested the need for a lesser sanction.

Another comment suggested that expediting removal of a product from the market could be accomplished by using a procedure like the "imminent hazard" provision of the act, i.e., immediate removal of the drug from the market if any of the conditions listed in proposed § 314.530 were met followed by a hearing.

Although the potential difficulties cited by the comments are real, they are not fundamentally different from determinations FDA regularly must make in carrying out its responsibilities. The new regulations provide for an expedited procedure to withdraw approval; they do not guarantee that results of studies will be wholly unambiguous or that FDA will always be able to prevail in its view as to the need for withdrawal, any more than current withdrawal procedures do. The studies being carried out under these provisions will be conspicuous and important and their completion will be widely known. There is no reason to believe their results would or could be long hidden. A study that fails to show clinical effectiveness does not prove a drug has no clinical effect but it is a study that, under § 314.530, will lead to a withdrawal procedure because it has failed to show that the surrogate endpoint on which approval was based can be correlated with a favorable clinical effect. This may have occurred because the study was poorly designed or conducted; while FDA will make every effort to avoid this, the commercial sponsor has the responsibility for providing the needed evidence confirming clinical benefit. As previously discussed, §§ 314.510 and 601.41 have been revised to clarify that required postmarketing studies must also be adequate and well-controlled. The possibility that an ineffective drug has become "accepted" is not a basis for continued marketing. FDA intends to

implement the provisions of § 314.530 as appropriate; data that are ambiguous will inevitably lead to difficult judgments.

A drug with clear clinical effectiveness in a subset of the population, but not in the population described in labeling, would have its labeling revised to reflect the data. Withdrawal would be inappropriate under such circumstances.

If an imminent hazard to the public health exists, the Secretary of Health and Human Services may suspend approval of an application and then afford the applicant an opportunity for an expedited hearing. In the absence of a significant hazard requiring immediate withdrawal, FDA believes the expedited procedure described in the rule satisfies the need for prompt action while, at the same time, allowing opportunity for discussion and debate before withdrawal.

37. One comment noted that the proposed rule would allow FDA to withdraw approval for failure to perform the required postmarketing studies with due diligence. The comment asserted that the act does not permit FDA to withdraw approval on this ground. Another comment, however, suggested that because proposed §§ 314.530 and 601.43 cite grounds for withdrawal of approval that are not grounds under the act, the language of these proposed sections should be revised to use language that closer aligns to that used in the act, e.g., describe a "postmarketing study" in statutory language.

FDA reaffirms the position expressed in the preamble to the proposal (57 FR 13234 at 13239) that there is adequate authority under the act to withdraw approval of an application for the reasons stated under proposed §§ 314.530 and 601.43, which include failure of an applicant to perform the required postmarketing study with due diligence. Section 505(e) of the act authorizes the agency to withdraw approval of an NDA if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if the applicant has failed to maintain required records or make required reports. In addition, approval may be withdrawn if new information, along with the information considered when the application was approved, shows the labeling to be false or misleading.

For biological products, section 351(d) of the PHS Act authorizes approval of license applications under standards designed to ensure continued safety, purity, and potency. "Potency"

for biological products includes effectiveness (21 CFR 600.3(s)). The PHS Act does not specify license revocation procedures, except to state that licenses may be suspended and revoked "as prescribed by regulations."

For drugs approved under § 314.510, FDA will have determined that reports of postmarketing studies are critical to the risk/benefit balance needed for approval; if those reports are not forthcoming, then, under authority of section 505(d) of the act, the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the act. Therefore, it is important to ensure that the applicant make a good faith effort to complete any required postmarketing studies in a timely manner so that FDA can rapidly determine whether the surrogate endpoint upon which the drug was approved has been confirmed to correlate with clinical benefit. Failure to submit the study results in a timely fashion would also constitute failure to make a required report. Similarly, without submission of the information from required postmarketing studies on biological products approved under these procedures, the biological product is not assured of continued safety and effectiveness. The license application may, therefore, appropriately be revoked as described in § 601.43.

FDA does not find the statements of the grounds for withdrawal of approval under §§ 314.530 and 601.43 of this rule inconsistent with statutory language or ambiguous. The agency notes that, in the event none of the grounds for withdrawal specifically listed in § 314.530 or § 601.43 applies, but another ground for withdrawal under section 505 of the act or section 351 of the PHS Act and implementing regulations at 21 CFR 314.150 or 601.5 does apply, the agency will proceed to withdraw approval under traditional procedures.

38. Two comments expressed concern that it may be difficult for the agency to enforce the requirement that postmarketing studies be pursued with due diligence. The comments asked what would happen if a sponsor using due diligence is unable to recruit enough patients, or if the sponsor questions the validity of the data from the required postmarketing study, and would clumsy data management be seen as sufficient reason to rescind approval for a marketed drug? Another comment stated that once a product is approved and, by definition, provides a "meaningful therapeutic benefit over existing therapies," study accrual may drop off dramatically as patients may refuse to receive the "old" therapy or

placebo, or physicians may consider it unethical not to treat all patients with the approved indication with the new drug or biological product. Under these circumstances, the comment expressed the opinion that neither the sponsor nor the product should be penalized, nor should there be a threat to withdraw approval. Based on FDA's past history in postmarketing studies, which one comment characterized as resulting in poorly done studies; studies conducted much later than agreed upon, or not at all, the comment expressed the opinion that the "due diligence" with which applicants are expected to carry out postmarketing studies may be an overly great expectation. One comment asked FDA to give examples of when it may withdraw approval if "other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use" (proposed §§ 314.530(a)(6) and 601.43(a)(6)).

FDA does not agree that it will be difficult to enforce the "due diligence" provision of this rule. The "due diligence" provision was designed to ensure that the applicant makes a good faith effort to conduct a required postmarketing study in a timely manner to confirm the predictive value of the surrogate marker or other indicator. Any requirement for postmarketing studies will have been agreed to by the applicant at the time of approval, and if the study is not conducted in a timely manner as agreed to by the applicant, approval of the applicant's application will be withdrawn. FDA will expect any required postmarketing study to be conducted in consultation with the agency. Therefore, should the applicant encounter problems with subject enrollment in a study or ethical difficulties about the type of study to conduct, FDA expects the applicant to discuss these problems with the agency and reach agreement on their resolution.

Examples of other evidence demonstrating the drug product is not shown to be safe and effective could include further studies of the effect of the drug and the surrogate endpoint that fail to show the effect seen in previous studies, new evidence casting doubt on the validity of the surrogate endpoint as a predictor of clinical benefit, or new evidence of significant toxicity.

39. Some comments objected to withdrawal of approval of a drug product approved under the accelerated approval process because of perceived misconduct by the applicant, such as failure to perform a required postmarketing study with due diligence or use of promotional materials that are false or misleading. The comments argued that the primary purpose of the

accelerated approval process is to provide improved treatments to desperately ill patients at the earliest possible time, and withdrawal of approval of the new treatments for reasons not directly related to safety or efficacy undermines the purpose of the proposed rule. Two comments suggested that correction of the promotional material without interruption of access to the drug would be a better approach. Another comment suggested that there may be circumstances where continued access to the drug, if accompanied by informed consent, would be appropriate even if substantial questions arise about a product's safety and effectiveness. One comment urged that anticipated withdrawal of approval be preceded by measures to ensure that patients and their physicians will have an uninterrupted supply until alternative treatment arrangements can be made.

The need for "due diligence" in conducting the agreed to postmarketing studies is discussed in paragraph 37. The reasons for concern about misleading promotional materials are discussed under paragraph 16. With respect to promotional materials, FDA expects that, in most cases, any disagreements between the applicant and FDA will be resolved through discussion and modification of the materials, so that the drug or biological product can continue to be marketed. If, however, FDA concludes that the promotional materials adversely affect the risk/benefit conclusion supporting the drug's marketing, the agency intends to minimize the risk to the public health by removing the product from the market through the withdrawal procedures in this rule.

40. One comment expressed concern that the proposed withdrawal procedure may give the appearance of bias or preconceived notions on the part of the agency because the final decision to withdraw approval of a drug would be made by the Commissioner of Food and Drugs and the intention to withdraw approval of the drug will already have been determined by the agency.

Under the withdrawal provisions of this rule, FDA's CDER or CBER, rather than the Commissioner, will initiate the withdrawal proceedings. The withdrawal process will begin with a letter from CDER or CBER notifying the applicant that the Center proposes to withdraw marketing approval and stating the reasons for the proposed action. Although separation of functions will not apply under the provisions of §§ 314.530 or 601.43, the Commissioner's decision regarding withdrawal would not occur until after

the applicant had an opportunity for hearing as described in those sections. The Commissioner would then expect to review the issues with objectivity and fairness having had the benefit of the presentations and discussions at the hearing and of the advisory committee's recommendations.

#### H. Safeguards for Patient Safety

41. One comment asked if drugs approved under the accelerated approval process will be held to the same standards concerning postmarketing safety as drugs approved by the traditional process.

As discussed in the preamble to the proposed rule, applicants gaining approval for new drugs through the accelerated approval procedures will also be expected to adhere to the agency's longstanding requirements for postmarketing recordkeeping and safety reporting (see 21 CFR 314.80 and 314.81). Information that comes to FDA from the applicant or elsewhere that raises potential safety concerns will be evaluated in the same manner that such information is evaluated for drugs approved under the agency's traditional procedures. If the postmarketing information shows that the risk/benefit assessment is no longer favorable, the agency will act accordingly to remove the drug from the market.

42. One comment urged FDA, if the proposed rule were adopted, to require written informed consent so that patients would know that the drugs with which they were being treated had risks and that the benefits had not been adequately established.

The agency does not agree that patients using drug products approved under the accelerated approval regulations should be asked to provide written informed consent. Drugs approved under these provisions are not considered experimental drugs for their approved uses. Like all approved drugs, drugs approved under these provisions will have both risks and benefits. As previously discussed in this preamble, for drugs approved based on studies showing an effect on a surrogate endpoint, the approved labeling will describe that effect. In addition, the labeling will contain information on known and potential safety hazards and precautionary information. As with all prescription drugs, the physician has the responsibility for appropriately advising the patient regarding the drug being prescribed.

43. One comment asked that FDA require manufacturers to maintain an updated list of names, addresses, and phone numbers of physicians prescribing their products approved



under this rule, and in the case of recall or withdrawal of approval, require manufacturers to contact these physicians and encourage them to notify their patients.

FDA does not believe such a procedure is necessary. Furthermore, maintaining such a registry for drugs prescribed through pharmacies would be very difficult. Agency experience with recalls and product withdrawals indicates that the methods of notification that have been developed for such circumstances are adequate.

44. One comment recommended that FDA require patient package inserts (PPI's) for all drugs granted accelerated approval that would state the specific restrictions placed on a drug product and/or the reason for requiring postmarketing studies. In addition, the comment recommended that FDA require the manufacturer to include an adverse drug reaction "hotline" phone number in the PPI along with an FDA phone number. The PPI should inform the patient to report immediately any adverse drug reaction experienced to his or her doctor, the manufacturer, and FDA, and the manufacturer should be required to contact FDA immediately after receiving a report of a serious adverse reaction.

FDA concludes that patient package inserts are not routinely needed for drugs granted accelerated approval, although if circumstances made one appropriate, one would be developed for a particular drug. As with any prescription drug, the approved labeling for a product granted accelerated approval will contain information about the safe and effective use of the product, including all necessary warnings and the extent of clinical exposure. In addition, the conditions of use will be carefully worded to reflect the nature of the data supporting the product's approval. Physicians have the responsibility to inform patients about the safe and effective use of an approved product. Labeling includes suggestions to the physician concerning information to be provided to patients.

The agency notes that in this final rule limited editorial changes have been made to the wording of the proposed rule. The agency has determined that these changes do not affect the intent of the proposed rule.

#### V. Economic Impact

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this final rule and has determined that it is not a major rule as defined by the Order. Indeed, because firms will not be forced to use the accelerated approval mechanism,

applicants will most probably choose to take advantage of the program only where its use is expected to reduce net costs. Similarly, the final rule does not impose a significant economic impact on a substantial number of small entities so as to require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

#### VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VII. Paperwork Reduction Act of 1980

This rule does not contain new collection of information requirements. Section 314.540 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980 (Adverse Drug Experience Reporting, OMB No. 0190-0230).

#### List of Subjects

##### 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

##### 21 CFR Part 601

Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 601 are amended as follows:

#### PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 376).

2. Subpart H consisting of §§ 314.500 through 314.560 is added to read as follows:

#### Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

Sec.  
314.500 Scope.

314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.  
314.520 Approval with restrictions to assure safe use.  
314.530 Withdrawal procedures.  
314.540 Postmarketing safety reporting.  
314.550 Promotional materials.  
314.560 Termination of requirements.

#### Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

##### § 314.500 Scope.

This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

##### § 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

##### § 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

**§ 314.530 Withdrawal procedures.**

(a) For new drugs and antibiotics approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

- (1) A postmarketing clinical study fails to verify clinical benefit;
- (2) The applicant fails to perform the required postmarketing study with due diligence;
- (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
- (4) The applicant fails to adhere to the postmarketing restrictions agreed upon;
- (5) The promotional materials are false or misleading; or
- (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the *Federal Register* in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter

will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

**§ 314.540 Postmarketing safety reporting.**

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

**§ 314.550 Promotional materials.**

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

**§ 314.560 Termination of requirements.**

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product

would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

**PART 601—LICENSING**

3. The authority citation for 21 CFR part 601 continues to read as follows:

*Authority:* Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360b–360j, 371, 374, 376, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

4. Subpart E consisting of §§ 601.40 through 601.46 is added to read as follows:

**Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses**

Sec.

- 601.40 Scope.
- 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- 601.42 Approval with restrictions to assure safe use.
- 601.43 Withdrawal procedures.
- 601.44 Postmarketing safety reporting.
- 601.45 Promotional materials.
- 601.46 Termination of requirements.

**Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses**

**§ 601.40 Scope.**

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

**§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.**

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic,

pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

**§ 601.42 Approval with restrictions to assure safe use.**

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

- (1) Distribution restricted to certain facilities or physicians with special training or experience; or
- (2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

**§ 601.43 Withdrawal procedures.**

(a) For biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

- (1) A postmarketing clinical study fails to verify clinical benefit;
- (2) The applicant fails to perform the required postmarketing study with due diligence;
- (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;
- (4) The applicant fails to adhere to the postmarketing restrictions agreed upon;
- (5) The promotional materials are false or misleading; or
- (6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for

Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the *Federal Register* in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a

petition for a stay of action under § 10.35 of this chapter.

**§ 601.44 Postmarketing safety reporting.**

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

**§ 601.45 Promotional materials.**

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

**§ 601.46 Termination of requirements.**

If FDA determines after approval that the requirements established in § 601.42, § 601.43, or § 601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under § 601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under § 601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Dated: December 7, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 92-30129 Filed 12-9-92; 9:51 am]

BILLING CODE 4190-01-F

# Section 10

## Access to Clinical Trials

## AIDS Clinical Trials Information Service: Providing the Latest Information on HIV and AIDS Treatment Protocols

The AIDS Clinical Trials Information Service is a central resource providing current information on federally- and privately-sponsored clinical trials for AIDS patients and others infected with the human immunodeficiency virus (HIV). This free service is a Public Health Service (PHS) project provided collaboratively by the Centers for Disease Control, the Food and Drug Administration, the National Institute of Allergy and Infectious Diseases, and the National Library of Medicine.

AIDS clinical trials evaluate experimental drugs and other therapies for adults and children at all stages of HIV infection — from patients who are HIV positive with no symptoms to those with various symptoms of AIDS.

### Access Up-To-Date, Accurate Information

The AIDS Clinical Trials Information Service is free and easy to use — one toll-free number puts callers in touch with experienced health specialists who provide information about AIDS clinical trials. These specialists access a database featuring up-to-date, accurate information on AIDS studies currently underway. The database is updated each week.

The Service's health specialists are available to answer questions from individuals infected with HIV and their families, as well as from health professionals. They provide information on:

- Purpose of the study protocol.
- Studies that are open.
- Study locations.
- Eligibility requirements and exclusion criteria.
- Names and telephone numbers of contact persons.

Callers can receive this information immediately over the telephone; on request, they can also obtain a free printout of a customized search of the clinical trials database. The information can also be accessed directly by subscribers through two online databases, AIDSTRIALS and AIDSDRUGS, available through the National Library of Medicine.

### Service Is a Cooperative Project of PHS Agencies

The AIDS Clinical Trials Information Service, provided free of charge as a public service, is a cooperative effort by several PHS agencies:

- **Centers for Disease Control (CDC).** The National AIDS Information Clearinghouse, supported by the Centers for Disease Control, operates the toll-free AIDS Clinical Trials Information Service.
- **Food and Drug Administration (FDA).** As the Federal agency responsible for evaluating and approving new therapies, the Food and Drug Administration grants permission to pharmaceutical companies to test experimental drugs and biologic products in humans, monitors the progress of those trials, and reviews the results of the studies. Every experimental treatment undergoing clinical testing for effectiveness in treating AIDS or AIDS-related conditions in FDA-approved trials is included in the database.
- **National Institutes of Health (NIH)**
  - **National Institute of Allergy and Infectious Diseases (NIAID).** NIAID has the major responsibility for funding federally sponsored AIDS clinical trials and supports a nationwide network of AIDS Clinical Trials Units, enrolling thousands of patients. The database includes all NIH-sponsored AIDS clinical trials as well as studies sponsored by other Institutes.

1-800-TRIALS-A

— **National Library of Medicine (NLM).** The National Library of Medicine makes the information in the database available to its worldwide network of users through its online services.

## **What Is an AIDS Clinical Trial?**

An AIDS clinical trial is a study conducted to help find effective therapies to treat people infected with HIV, the virus that causes AIDS.

Patients choose to take part in clinical trials for many reasons. Usually patients hope for benefits for themselves — a cure for the disease, a longer time to live, a way to feel better. Joining a study means taking positive action. Many want to contribute to a research effort that may help others.

AIDS clinical trials for experimental therapies follow strict guidelines to protect participants' privacy and safety.

## **Why Are Clinical Trials Important?**

AIDS clinical trials fill an urgent need to find ways to treat the millions of people who are or who will be infected with HIV. Clinical trials provide important information about new treatments — benefits and risks, effectiveness, and dosages.

Clinical studies also help improve patient care by identifying which treatments and drugs work best. Many new therapies are designed on the basis of what has worked in past trials.

## **Can Anyone with HIV Join a Clinical Trial?**

To be eligible to participate in an AIDS clinical trial, an individual must meet the study's eligibility criteria. Eligibility criteria are different for each study and may include a person's age, symptoms of HIV disease or other illnesses, laboratory test results, and past treatments. Applicants for clinical trials are evaluated on an individual basis by the study's clinical investigator and other health care providers.

# Section 11

## Outside Advisory Panels

# Getting Outside Advice For 'Close Calls'

by Dixie Farley



Ezra Davidson Jr., M.D.

*"Viewpoints vary between concerns of individual clinicians and what may affect the doctor-patient relationship, or how a drug affects a patient circumstance. ... A professional woman on the committee, for instance, takes the position of the woman patient, asking whether medicine is doing something too intrusive, exercising too many prerogatives, or presenting an unreasonable risk for the patient."*

—Ezra Davidson Jr., M.D., professor and chair, Department of Obstetrics and Gynecology, Charles R. Drew University of Medicine and Science, Los Angeles, discussing the Food and Drug Administration's Fertility and Maternal Health Drugs Advisory Committee, which he chairs.

Ezra Davidson Jr., M.D., serves on one of 17 committees that advise FDA about the safety and effectiveness of drugs—particularly on decisions that are "close" calls.

Of the 11 members of his committee, 10 are educators. Seven of the physicians specialize in obstetrics and gynecology—three also in reproductive biology. Two are epidemiologists (specialists in the incidence and prevalence of disease). Other areas represented are nursing and behavioral sciences. Committees meet in the Washington, D.C., area, generally at FDA headquarters in Rockville, Md., and those on Davidson's committee travel from as far away as Hawaii. The executive secretary, an FDA medical officer, connects the committee with the agency.

It may seem unnecessary for FDA to

seek outside advice. After all, the agency employs its own full complement of scientific specialists. But outside experts add a wide spectrum of judgment, outlook, and state-of-the-art experience to drug issues confronting FDA.

"We seek scientists with a broad range of expertise and different backgrounds," says John Treacy, director of the advisors and consultants staff in FDA's Center for Drug Evaluation and Research.

These expert advisers add to FDA's understanding, so that final agency decisions will more likely reflect a balanced evaluation. Committee recommendations are not binding on FDA, but the agency considers them carefully when deciding drug issues.

## Members

Most members of FDA's drug advisory committees are physicians whose specialties involve the drugs under the purview of their committee. Others include registered nurses, statisticians, epidemiologists, and pharmacologists (who study drug effects in the body).

Consumer-nominated members serve on all committees. As voting members, they must possess scientific expertise to participate fully in deliberations. They must have worked with consumer groups so they can assess the impact of decisions on consumers.

The committees range in size from 10 to 15 members, but most have 11. Each committee advises a corresponding FDA drug review group.

All government advisory committees are regulated by the Federal Advisory



***Even at a closed meeting, there must be an open portion at which the public can give presentations, ask questions, and take part in general discussion.***

Committee Act of 1972, although FDA began using panels of outside experts in 1964. Each committee must be renewed by FDA every two years, or its charter automatically expires. Renewals must be approved by the Secretary of Health and Human Services and the Administrator of the General Services Administration.

#### **Committee Independence**

To encourage the committees' independence, FDA recruits members from a broad range of qualified candidates. Sources of nominations—with emphasis on identifying women and minority candidates—include professional, scientific and medical societies; medical and other professional schools; academia; government agencies; industry and trade associations; and consumer and patient groups.

FDA's Office of Consumer Affairs, in particular, seeks suggestions for consumer-nominated representatives through agency field offices, current and former consumer-nominated representatives, and diverse consumer organizations with national and local interests and a widely varied membership, representing women, older people, African Americans, Hispanics, and Asians.

Requests for candidates also appear in the *Federal Register*.

FDA staff members review the nominations (which can exceed 200 candidates) to identify the best mix of expertise for the particular committee. A list of nominees is then sent to the Office of the Commissioner for final selection. Committee chairs are also selected by the commissioner; they are not elected by the committees.

#### **Meetings**

Committees typically meet two to four times a year, but may meet as often as FDA needs them. FDA announces upcoming meetings in the *Federal Register*.

Members receive \$150 a day while attending committee meetings, and reimbursement for costs of travel, food and lodging. This attendance is a public service on the part of many members, who forgo seeing patients or conducting research or teaching activities to serve FDA.

Thanks to the aptly named "Government in the Sunshine Act" of 1977, meetings of drug advisory committees are public, except when a topic's open discussion would be an invasion of privacy or when confidential, commercial, or trade secret information or law enforcement investigations are presented or discussed.

Even at a closed meeting, there must be an open portion at which the public—as time allows—can give presentations, ask questions, and take part in general discussion. Most meetings are entirely open.

FDA almost always sets the agenda and prepares the questions for each meeting. Anyone, however, may ask that a specific drug issue be brought before the appropriate committee. When a committee itself asks to review a matter within its purview, this is granted whenever possible.

#### **Types of Advice**

FDA may especially want a committee's opinion about a new drug, a major new indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling.

The committees may advise FDA on necessary labeling information, and help with guidelines for developing particular kinds of drugs, such as those for anesthesia, heartbeat irregularities, and cancer.

They also may address such questions as whether a proposed study for an experimental drug should be conducted and whether the safety and effectiveness information submitted for a new drug is adequate for marketing approval.

For instance, Cognex (tacrine), the first

drug approved to treat Alzheimer's disease, was the subject of several meetings of the Peripheral and Central Nervous System Drugs Advisory Committee during its clinical testing.

When the committee first met to consider Warner-Lambert Co.'s application for Cognex, in March 1991, it concluded that available evidence did not support approval.

On the basis of additional data submitted in July, the committee still recommended against approval, but advised that studies be conducted with a higher dose, over a longer time. The committee also recommended a Treatment IND (investigational new drug)—an FDA procedure for promising drugs for serious diseases that provides for wider use than is usual during the preapproval stage, provided no satisfactory approved treatment exists and patients won't be exposed to unreasonable risk.

FDA granted the Treatment IND in December 1991, after finding the drug appeared to slightly improve mental function in some patients at low doses and might be more effective at larger doses.

The Treatment IND, begun in February 1992 and involving more than 7,400 patients, showed that Cognex provided a small but clinically meaningful benefit for some patients with mild-to-moderate Alzheimer's disease. Meeting again in March 1993, the committee recommended approval of the marketing application. FDA approved Cognex in September, after reviewing the additional information from studies.

#### **Adverse Reactions**

FDA's advisory committees may also consider reports of adverse reactions to an already marketed drug. If there are severe reactions or deaths and it's not clear what's going on, the agency might call a special meeting.

**To encourage the committee's independence,  
FDA recruits members from a broad range of  
qualified candidates.**

**For More  
Information ...**

For information about FDA advisory committee meetings, call (1-800) 741-8138. In the metropolitan Washington, D.C., area, call (301) 443-0572. This information may also be obtained by accessing the FDA Electronic Bulletin Board Service, via modem, at (1-800) 222-0185 and choosing the topic "meeting." In the D.C. metropolitan area, dial (301) 594-6849 or (301) 594-6857.

For information about how to nominate a consumer representative, write to the Office of Consumer Affairs, FDA, HFE-88, Room 16-85, 5600 Fishers Lane, Rockville, MD 20857. ■

Typical questions include:

- Should the dosage schedule be changed?
- Should certain groups of patients receiving the drug *not* be getting it?
- Should the contraindications (situations when the drug should not be used) be changed?
- Are the reactions to the drug also seen with other drugs in its class?

FDA received some 50 reports of serious reactions, including three deaths, to Omiflox (temafloxacin) in the first three months of marketing. A fluoroquinolone—one of a newer class of anti-

infective drugs—Omiflox had been approved in January 1992.

Side effects included dangerously low blood sugar levels in elderly patients, anemia due to excessive destruction of red blood cells, kidney failure, blood-clotting problems, and abnormal liver function. The manufacturer voluntarily withdrew the drug.

FDA then asked its Anti-Infective Drugs Advisory Committee to discuss the problem and consider implications for quinolones in development.

**Nonprescription Drugs**

Over-the-counter drugs, too, benefit from advisory committee deliberation. From 1972 to 1981, at FDA's request, 16 special panels evaluated the effectiveness and safety of all classes of OTC drugs then on the market.

During hearings before the Advisory Review Panel on OTC Miscellaneous External Drug Products in 1980, New Jersey pharmacist Carmine Varano cited disastrous incidents involving camphorated oil: A 2-year-old died after exposure to camphorated oil on the chest for nearly 80 hours, a 15-month-old became confused and had seizures after crawling through spilled spirits of camphor, and an infant nearly died after camphor ointment was rubbed on its chest. Varano reported he had data from a Detroit hospital about 26 camphorated oil poisonings between 1975 and early 1979. FDA accepted the panel's advice to put camphorated oil in its place—off the U.S. market.

Those OTC panels completed their review tasks and have been disbanded. OTC issues are now brought to the agency's Nonprescription Drugs Advisory Committee, which includes a voting consumer-nominated representative and a non-voting industry representative. On a given issue, the committee will ordinarily meet jointly with another committee with special ex-

pertise in that issue.

There have been a few instances in which FDA has *not* followed a committee's recommendations.

Treacy cites the Rx-to-OTC switch last January of the pain reliever naproxen sodium, previously sold only by prescription under the trade name Anaprox and now also over-the-counter as Aleve.

In June 1993, the combined arthritis and nonprescription committees voted 7 to 4 against the switch.

"They had a lot of reasons," Treacy says. "The dose was too high. The labeling for people over 65 was incorrect because they excrete the drug at a slower rate. The members requested labeling for children because the drug makes the skin more photosensitive, and children already sunburn more easily than adults. Also, the members were uncomfortable with FDA's policy of allowing a manufacturer to mention in the label any of a list of several types of pain on the basis of studies of just any two types on the list. Although this policy had been suggested by an advisory panel before being accepted by the agency, members suggested that our scientific knowledge has increased to the point where we can be more specific."

The manufacturer, Syntex Laboratories, listened to all the objections, Treacy says, and, working with FDA, immediately altered the dose interval and the dose, and changed the labeling for people over 65 and for children.

FDA had a follow-up meeting to brief the committees on the changes and its decision to approve the switch.

"The bottom line is FDA's," Treacy says. "The committees are advisory only. In approving the switch, we took into account the objections of the members. However, we treated it just like all the other OTC painkillers in terms of the labeling in order to give it parity with other OTC analgesics."

# *Recommendations supplement FDA expertise and add to the quality of the agency's decisions.*

## *Managing Conflicts*

The National Academy of Sciences' Institute of Medicine published findings in December 1992 of a study it did—at FDA's request—of the agency's advisory committees. FDA had been having increasing difficulty identifying potential members with needed expertise, but without financial or professional interests that could lead to conflicts of interest or the appearance of conflicts.

The institute confirmed that the system was fundamentally sound and did not need major changes. But it recommended a number of administrative and procedural changes regarding committee membership, committee operations, integrity of the committee system, and FDA organization and management of the system.

While the institute's study was going on, FDA conducted its own analysis of its advisory committee system. The outcome of the two reviews led the agency to concur with nearly all the institute's recommendations, which are reflected in how members are recruited and meet-

ings are managed today.

"We did a lot of work to strengthen the integrity of the system by resolving conflicts of interest up front," says John Treacy, director of the advisors and consultants staff for FDA's Center for Drug Evaluation and Research.

Throughout the government, advisory committee members are subject to federal laws and regulations prohibiting participation in any official action in which they have financial interests—which the law says include those of their regular employing organization. If a member is on the faculty of a university that has a grant from the pharmaceutical firm to study the drug to be reviewed by that committee, the member can't act on that issue, Treacy says.

The law does allow waiver of the interest.

"Before every meeting," Treacy says, "we send members a questionnaire, stating the issues coming up and the companies with financial interests. We ask, 'Do you own stock or have grants or contracts involving these issues or firms?' If there is a conflict, we exclude the per-

son, or, if our need outweighs the conflict, a waiver may be granted."

In a typical meeting with 11 members, there are usually two or three who have waivers, he says. (Sometimes there are none; other times, more than three.)

Criteria for granting a waiver are based on many factors, such as the amount of the financial interest, what percentage of a person's net worth that interest is, and the impact on the firm if a given product is approved or disapproved.

For example, a waiver would not be granted, Treacy says, if a member owned more than \$100,000 in stock in a firm whose drug was coming before the committee, and this was more than 5 percent of the person's net worth.

"On the other hand," he says, "if the member's university had a grant of less than \$15,000 to study a drug to be discussed, and the member was not involved with the grant, we'd generally grant the waiver." ■

—D.F.

Nevertheless, Treacy emphasizes that FDA carefully considers committee recommendations, "so we're reevaluating what is appropriate labeling for all OTC painkiller products. In fact, at another advisory committee meeting on Sept. 8 and 9, 1994, the members discussed what indications for the products must be studied."

As these many examples show, recom-

mendations from advisory committees supplement FDA expertise and add to the quality and credibility of the agency's decisions.

Advisory committee members benefit, too. Says Fertility and Maternal Health Drugs Advisory Committee chair Davidson:

"It's a great educational opportunity,

whatever the issue. As an ob-gyn, academician, and otherwise inquisitive person, I find this advisory panel to be a mixture of science and policy that attracts my interest." ■

*Dixie Farley is a staff writer for FDA Consumer.*

## FDA Advisory Committee Information Line

In order to serve the public better, the FDA has implemented a telephone bulletin board to provide information about FDA advisory committees as soon as it becomes available. Many people who do not have immediate access to the Federal Register may find the Information Line a more convenient source for up-to-date information about FDA advisory committees. Please feel free to give us your comments on this service at (301) 443-4695 so we can make it as convenient for the public as possible.

**For long distance callers only: 1-800-741-8138**

**Local callers, please use: 301-443-0572**

When you call the FDA Advisory Committee Information Line, you will be able to hear general information about FDA advisory committees, and specific information about the committees associated with any of the eight centers with advisory committees in FDA. If you are only interested in committees associated with the Center for Drug Evaluation and Research (CDER) you can press 3 immediately. If you are only interested in a particular committee, you can immediately press the number for that committee and by-pass all the general information.

***NOTE:** you must be at the FDA main menu to use the five digit direct numbers. If you wish to check several committees, press the five digit number for one committee when the line is answered, listen to it, then press 9 for the FDA main menu, then press the five digit number for the next committee of interest.*

The CDER advisory committees and their five digit numbers are:

| <u>Advisory Committee</u>                   | <u>Number</u> |
|---|---------------|
| Anesthetic and Life Support Drugs           | 12529         |
| Anti-Infective Drugs                        | 12530         |
| Antiviral Drugs                             | 12531         |
| Arthritis                                   | 12532         |
| Cardiovascular and Renal Drugs              | 12533         |
| Dermatologic Drugs                          | 12534         |
| Drug Abuse                                  | 12535         |
| Endocrinologic and Metabolic Drugs          | 12536         |
| Fertility and Maternal Health Drugs         | 12537         |
| Gastrointestinal Drugs                      | 12538         |
| Generic Drugs                               | 12539         |
| Medical Imaging Drugs                       | 12540         |
| Nonprescription Drugs                       | 12541         |
| Oncologic Drugs                             | 12542         |
| Peripheral and Central Nervous System Drugs | 12543         |
| Psychopharmacologic Drugs                   | 12544         |
| Pulmonary and Allergy Drugs                 | 12545         |

# Section 12

## Post Marketing Monitoring

# Watching for Problems That Testing May Have Missed

by Stephen J. Ackerman

“Jane” is 71 years old; she weighs just 100 pounds. She works mornings in a Washington, D.C., office, then travels to a Virginia nursing home to care for her husband, a victim of Alzheimer’s disease. When she came down with shingles (herpes zoster, a viral irritation of the nerve endings), her doctor prescribed a painkiller he had used successfully in patients for 20 years so she could keep up her routine.

When Jane took the prescribed dose at work, something went wrong. So violent were her dizziness and nausea that her colleagues rushed her to a nearby emergency room. She was given an electrocardiogram, intravenous fluids, and a sedative injection. After five hours, she still needed help in getting home, and she was still groggy a week later.

Now recovered, Jane blames herself for not being more careful. With her small frame, she’d had milder reactions to adult doses of both prescription and nonprescription drugs in the past. She feels she should have reminded her long-time physician of this when he wrote the prescription. She wonders whether adult drug dosages shouldn’t be modified to take into account the patient’s health, weight and age.

Jane isn’t alone. In 1986 FDA received over 53,000 reports of adverse reactions to drugs. While many reactions are mild, some are serious indeed: more than 12,000 deaths or hospitalizations suspected of being related to reactions to drugs are reported yearly. (Not all of these suspected reactions are confirmed.)

---

## NO ABSOLUTE SAFETY

---

Do these reports mean that the drug approval process is flawed? Do drug manufacturers put products on the market and then hold their breath to see if they really work? Doesn’t a drug’s approval mean that it’s absolutely safe? The answer to all these questions is no. A closer look at the numbers shows that adverse drug reactions occur in just a small percentage of the 2.3 billion inpatient and outpatient prescriptions filled annually. Moreover, a drug’s development

process doesn’t end when it is marketed; in a sense, it never really ends at all.

Let’s look at what happens when—after perhaps a decade of development costing millions of dollars, testing on thousands of volunteers, and rigorous evaluation of the results by FDA—a new drug is finally approved for general use.

Even the most extensive pre-market testing can never cover all possible circumstances. Testing perhaps 3,000 people over a period of months or even a few years won’t always identify a rare reaction unfolding over a long time, or affecting perhaps just one person in 10,000. Furthermore, drugs are rarely tested in such potentially vulnerable groups as the elderly, and never among pregnant women. Consequently, not every reaction can be foreseen for the entire population; groups in whom a drug has not been tested must be particularly cautious in using it.

A case in point is diethylstilbestrol (DES), widely prescribed in the 1950s and 1960s to prevent miscarriages. The vaginal tumors caused by this drug only began to show up in the daughters of DES users more than 15 years later. Mercifully, such cases are uncommon.

Side effects and adverse reactions that show up in testing before a drug goes on the market are noted in the instructions that physicians (and, in some cases, patients) receive. But in some circumstances, FDA approves drugs with the condition that continuing studies of their safety be carried on to uncover rare or long-term reactions. The anti-cholesterol drug lopid and the Copper-7 intrauterine contraceptive first reached the market in that way.

For all drugs, to minimize the chances of unforeseen disaster, and to take advantage of any new benefits a product may reveal, the drug development process continues after FDA approval in the form of “Post-Marketing Surveillance.”

---

## POST-MARKETING SURVEILLANCE

---

FDA and the pharmaceutical industry closely monitor drug products on the market. On the most basic level, FDA agents around the country inspect factories regularly to ensure good manufacturing and laboratory practices which

guarantee that the drugs we buy are pure, properly compounded, and accurately labeled. In addition, both FDA and manufacturers collect reports of adverse drug reactions. Drug firms must report all reactions they learn of to FDA. Serious ones must be reported quickly; others may be sent in quarterly or annually. A serious reaction is one that causes hospitalization (or which prolongs a hospital stay), or results in permanent disability or death. Reactions involving deliberate or accidental overdose, cancer, or birth defects are always regarded as serious. If a manufacturer notes an increased frequency of reactions—that is, more than anticipated from earlier testing—this increase also must be reported within 15 days.

FDA quickly puts all reports into a computer and then searches for any significant patterns. Should an important new toxicity problem emerge and be confirmed, FDA and the industry have several options. One is to change the directions for the product to reduce the dose or warn certain vulnerable groups of people.

In urgent and unusual circumstances, products may be withdrawn from the market, either voluntarily by the manufacturer or by FDA order. The example of one product illustrates how FDA and industry can use information gained from reaction reports to speed protection of the public. In January 1986, the anti-inflammatory drug suprofen, newly approved to treat arthritis, reached the U.S. market. By mid-March, half a dozen adverse reaction reports alerted FDA and the manufacturer to a possible connection with “flank pain syndrome,” a serious side effect involving severe pain and kidney problems. By April, a “Dear Doctor” letter notified 170,000 physicians of the situation. Three other “Dear Doctor” letters and two *FDA Drug Bulletin* articles followed. The product’s instructions were changed to reduce suprofen to a drug of second choice. The consequent drop-off in its use was steep and sudden, resulting in its virtual disuse by the time it was formally taken off the market by its manufacturer some months later. Although the product had been on the market in Europe for four years, prompt reaction reporting enabled FDA

to determine the seriousness of a previously unnoticed side effect in just four months.

### REPORTING DRUG REACTIONS

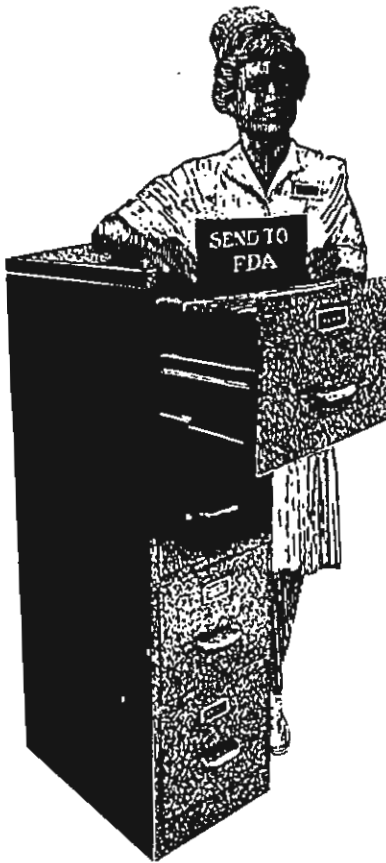
To help track the performance of their products, many drug firms rely on their sales personnel. These "detail" men and women not only sell products, but also elicit information from the health-care providers they visit. They must report back to their firms the product information they glean in their travels. "We get about half of our ADR [adverse drug reaction] reports from our own representatives," says Merck, Sharp & Dohme's director of epidemiology, Dr. Robert E. Damiano, as he leafs through a two-inch thick computer printout mapping the performance of one product. "They're very thorough and professional."

The other principal source of reports, both for FDA and for industry, is physicians who report directly. In the United States, their cooperation is entirely voluntary; no law requires them to report the reactions they observe. Few believe that imposing a reporting requirement would be effective; in Sweden, even though required to do so by law, doctors report only about a third of the adverse reactions they observe.

Since it means faster, more effective response to unforeseen reactions, industry and government encourage more adverse reaction reporting by doctors and other health professionals. "We like to give them something in return for contacting us," says Hoffmann-La Roche's director of drug safety, Dr. James Labraico. His firm offers doctors who report reactions up-to-date information about other reports, treatments, and statistical patterns on drug problems.

Like FDA, manufacturers want to analyze reaction reports promptly to detect any problems and gain new information about the effects of products in various patient populations. Merck, Sharp & Dohme employs three teams headed by physicians to oversee drug reports, with an internal alert system and an in-house quarterly report. In what it calls a "major serious event," the firm might notify practitioners by letter, contact them through the sales staff, or both.

Such monitoring isn't just "damage control," since the reports aren't always bad. Sometimes the wider use of drugs



on the market reveals beneficial uses that were not evident during testing. For instance, minoxidil, approved to treat high blood pressure, turned out to stimulate hair growth in some users; now it is being tested as a hair restorer. Beta blockers developed for use against angina are now being used against hypertension.

Likewise, news reports indicate that Naltrexone, a drug approved for treatment of heroin addicts, may be effective against Kaposi's sarcoma, a cancer associated with AIDS (acquired immune deficiency syndrome). In this case, the drug seems to have been used without formal testing or notifying FDA. Apparently, physicians who noted the drug's effects on the immune system used it, with their patients' consent, to treat this AIDS-related condition. This is possible—and legal—because once FDA has released a drug into the marketplace, there is no law requiring that physicians dispense it only for approved uses.

### BALANCING RISKS AND BENEFITS

Does a system that expects marketed drugs to have unforeseen problems make consumers of these drugs "guinea

pigs"? Hardly. Unlike controlled experiments, public use of a drug necessarily brings it into contact with a greater variety of patients. Our specific age, sex, diet, habits, overall health, and even genetic background are just a few of the conditions the drug may not have encountered in testing.

There is an element of risk involved in taking any drug, no matter how common. Although it has passed through a rigorous approval process, a drug strong enough to require a prescription—especially a new product—obviously must be approached with caution. In most cases, a product appropriately prescribed and taken according to instructions will be quite safe. That a drug is approved for marketing, however, does not guarantee that it is absolutely risk-free.

Indeed, widespread public expectation of a 100 percent risk-free drug could ultimately chill new drug development. "We're concerned that the demand for absolute certainty about all properties of a drug prior to approval could stifle drug development throughout the industry," one pharmaceutical official confides. He notes that the threat of lawsuits could cause many firms to shun work on drugs that are needed, but have a high potential for side effects, such as antihypertensive products. "The temptation could be for firms to restrict their research and development to relatively low-risk areas," adds a consumer advocate.

### IMPROVING THE PROCESS

Many observers in government, industry, and the consumer movement believe that the United States enjoys the best drug development and surveillance in the world. A number of nations simply adopt stringent American drug decisions as their own policies. Yet the same observers concede that there is room for improvement.

Although basically sound, the adverse reaction reporting system can be circumvented. Of course, it would be suicidal for a firm to suppress reports, since in time a drug's shortcomings will inevitably come out. Nonetheless, such cases have occurred. Pharmaceutical officials who failed to report adverse reactions caused by the blood pressure drug Selaeryn, marketed in the early 1980s, were sent to prison. Although the incidents of deliberate deception of FDA

tend to draw headlines, they are uncommon.

In fact, many believe that current FDA reporting requirements yield too much data, mixing significant information in a mountain of trivia. Some suggest that after a drug's first few years on the market, the requirement to report a drug's routine, expected reactions could be dropped, leaving changes in frequency or seriousness of reactions to stand out.

Nonetheless, the major weakness of the post-marketing surveillance system is the under-reporting of adverse drug reactions by physicians. Fewer than 10 percent of doctors report reactions they have observed, and even these report only a fraction of what they see. "Reporting a problem with a drug is as important as reporting a fire," insists Victoria Leonard of the Women's Health Network. Yet pilot projects by Rhode Island, Maryland, Massachusetts, Mississippi and Colorado under the aus-

pices of FDA reveal widespread unawareness and disuse of FDA's reporting system. Only 55 percent of doctors were aware of the system—despite regular reminders from the *FDA Drug Bulletin*, which is mailed to virtually every U.S. physician—and only 40 percent knew how to use it.

Dr. Gerald Faich, director of post-marketing drug surveillance in FDA, believes that better reporting by doctors is long overdue. The state pilot projects show that by making drug reaction reporting better understood (through meetings and bulletins for doctors), easier (by means of hot lines and third-party reporting), and more rewarding (by returning useful information), significant increases in reporting are possible. More reporting by other health professionals like nurses and pharmacists can also help speed vital feedback about drug reactions.

In fact, steps are being taken along these lines, and the results are encourag-

ing. Maryland and Rhode Island achieved fourfold increases in adverse drug reaction reporting in the first year of their promotional efforts. In its first three weeks, the Mississippi project yielded more than half the number of reports FDA received from that state during the entire previous year. A 10 percent increase in reports nationwide in 1986 seems to reflect not an increased number of adverse reactions, but increased reporting. Better still, industry is finding a gradual long-term increase in reports it receives. Such steps can only improve what FDA Commissioner Frank E. Young, M.D., Ph.D., calls "the best post-marketing surveillance system in the world." And that's the bottom line: Better reporting ultimately helps the patients who experience adverse drug reactions. ■

*Stephen J. Ackerman is a free-lance writer in Washington, D.C.*

## Avoiding Problems With Your Medications



You can help avoid problems with your medications by following these suggestions:

- Properly taken, most medicines are remarkably safe. When you get a prescription, make sure your doctor is aware of any other drugs you are taking. If you have more than one doctor and, perhaps, a dentist prescribing for you, let each know what the others have prescribed. A drug safe when taken alone might interact badly in combination with another. Mention any nonprescription medicines and whether you drink alcoholic beverages, too. Your doctor may have to be

reminded of allergies, other medical conditions, or a history of problems tolerating drugs.

- Ask your doctor how long the drug has been on the market and what side effects it can produce. Some physicians simply won't prescribe a drug until it has been in use for a couple of years, long enough to reveal unsuspected problems.

- When you take a drug, follow instructions exactly. Many over-the-counter and some prescription drugs come with a package insert you should save, since it can help you deal with possible reactions you could have to the medication.

- Never share prescription drugs with others for whom they were not prescribed.

- If you suspect you are having an adverse reaction to a drug, call your doctor or pharmacist at once and stop taking the drug immediately. A serious reaction demands immediate medical attention. Don't be shy in seeking it.

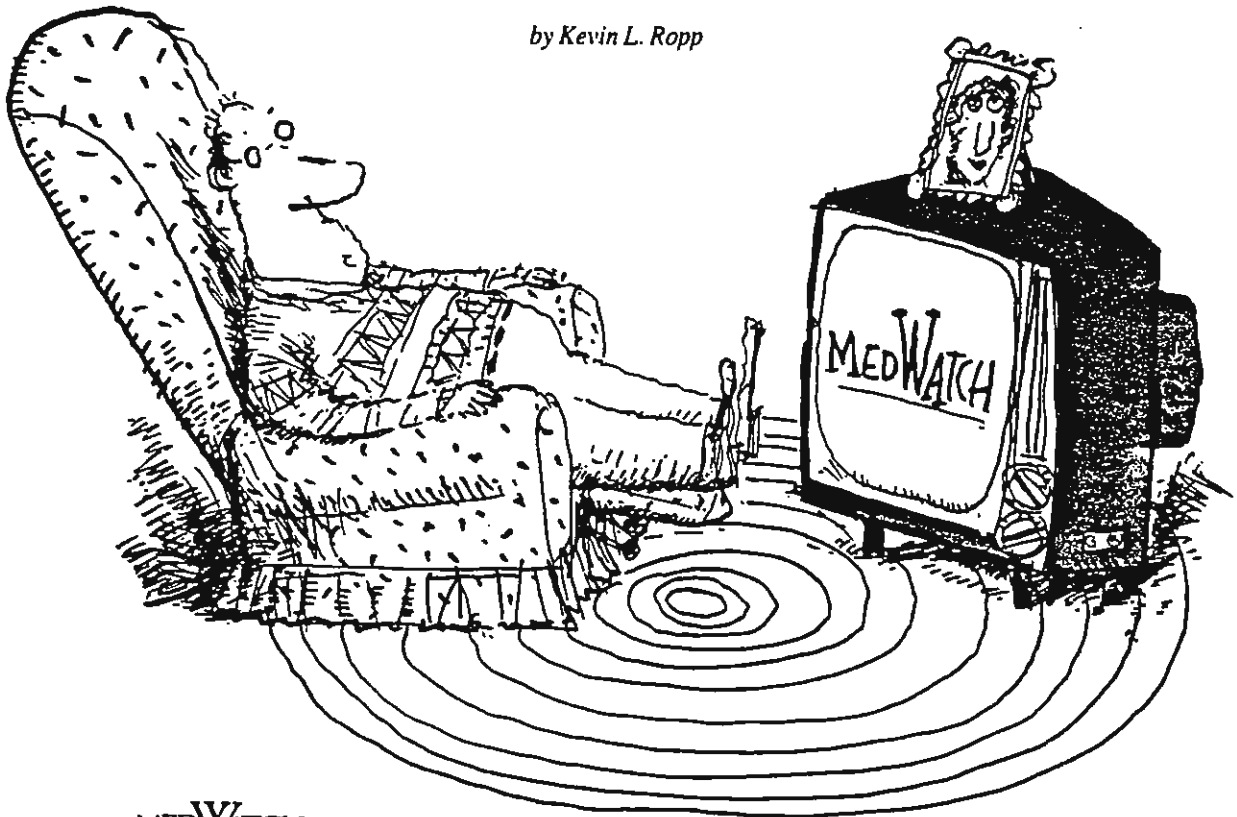
- Ask your doctor or pharmacist to report any adverse reaction to the drug's manufacturer or to FDA directly. The quicker FDA receives a report of a drug reaction from a health professional, the sooner it can respond. ■



# MEDWATCH

## On Lookout for Medical Product Problems

by Kevin L. Ropp



### MEDWATCH

No, it's not some new doctor show in this fall's TV line-up.

Unveiled last June 3, MEDWATCH is the Food and Drug Administration's new voluntary Medical Products Reporting Program for quickly identifying unsafe medical products on the market.

"Post-market surveillance is critical to our job of ensuring the safety of drugs, devices, and other FDA-regulated products," FDA Commissioner David A. Kessler, M.D., said in a May 4, 1993, address to health professional organizations.

"There is simply no way that we can anticipate all possible effects of a drug or device during the clinical trials that precede approval," he said. "A new drug application, for example, typically includes safety data on several hundred to several thousand patients. If an adverse event occurs in 1 in 5,000 or even 1 in 1,000 users, it could be missed in clinical trials. But it could pose a serious safety problem when the drug is used by many times that number of patients."

A recent example is Omnidox (temafloxacin), an antibiotic drug first marketed in the United States in February 1992. Less than four months after its introduction into the marketplace, Omnidox was withdrawn after FDA received about 50 reports of serious adverse events, including three deaths. These occurred during the first three months of the drug's use in this country. Side effects included dangerously low blood-sugar levels in older patients; excessive destruction of red blood cells that was frequently associated with renal failure; ab-

# FDA had set up its own surveillance program to monitor adverse drug reactions in 1961 following another drug-related tragedy, birth defects caused by thalidomide.

normal liver function tests; and impaired blood clotting.

Before FDA approval, slightly more than 4,000 patients had received the drug in clinical trials, but in its first three months of marketing many more thousands of patients used it and the serious side effects became apparent.

"That is why it is so crucial to keep an eye on a product once it is in general use," Kessler said in his address. "And the health professionals who use the products are indispensable to that process."

## Avoidable Tragedies?

The first post-marketing surveillance program was established in 1954 by the American Medical Association following reports of aplastic anemia (a blood disorder) associated with the use of chloramphenicol, an antibiotic, according to Charles Anello, Sc.D., acting director of the Office of Epidemiology and Biostatistics in FDA's Center for Drug Evaluation and Research.

AMA's program, run by its Committee on Blood Dyscrasias, was expanded in 1961 to monitor all adverse drug events. The program was discontinued because of parallel efforts by FDA.

FDA had set up its own surveillance program to monitor adverse drug reactions in 1961 following another drug-related tragedy, birth defects caused by thalidomide, a sedative and hypnotic drug marketed in Europe for nausea during pregnancy.

"It turns out, that drug caused a condition called phocomelia—a congenital malformation where arms and legs are shortened or not developed," Anello explains. "By the time the problem was recognized, there were 10,000 cases of phocomelia worldwide. In the United States, the drug was under investigation but had not been marketed."

In an effort to avoid future tragedies, the

World Health Organization and most industrialized countries, including the United States, implemented adverse reaction reporting systems.

The U.S. Congress passed the 1962 Drug Amendments to the Food, Drug, and Cosmetic Act, which required drug manufacturers to report to FDA all adverse drug events they became aware of that were associated with their products.

Reporting requirements, including biologics reporting, were further strengthened by regulations passed by FDA in 1985. These activities were focused in FDA's Bureau of Drugs (now the Center for Drug Evaluation and Research). The center also started in the late 1960s a voluntary marketplace surveillance program to monitor the quality of prescription and nonprescription products.

In 1973, the agency's Bureau of Medical Devices (now the Center for Devices and Radiological Health) established its surveillance system to monitor medical product quality problems and adverse events.

In all, by 1991, there were five different forms for manufacturers and health professionals to report medical product problems to the agency—a somewhat confusing system.

## Enter MEDWATCH

MEDWATCH is designed to make it easier for health professionals to report serious adverse events.

A significant change to help simplify the procedure is use of a single form to report problems with any FDA-regulated medical product.

"Over a year-and-a-half, we worked closely with four FDA centers to consolidate five different reporting forms," says Dianne Kennedy, MEDWATCH director. "We also had input from several health professional organizations, including the American Medical Association and

American Nurses Association.

"Now, all the health professional needs to do is pick up one form and send it in to us. Once it comes in here to our central triage unit we review it and deliver it to the program it belongs to."

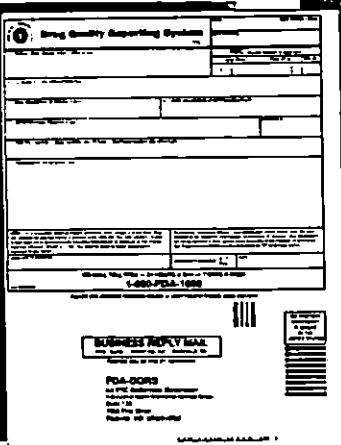
Post-marketing surveillance and reporting can often signal potentially serious safety problems with marketed products—especially newly marketed products—and serve to prevent widespread tragedies such as occurred with thalidomide, according to Anello.

Through MEDWATCH, FDA officials hope to improve the safety of drugs, biologics, medical devices, dietary supplements, medical foods, infant formulas, and other regulated products by encouraging health professionals to report serious adverse events and product defects.

FDA does not want reported to MEDWATCH problems with other types of food items, veterinary products, or vaccines. Adverse events with veterinary products are reported to the agency's Center for Veterinary Medicine on a separate form. Vaccine adverse event reports are already required by law and are to be sent to the Vaccine Adverse Event Reporting System (VAERS) program. (See "Vaccine Reporting.")

An adverse event is any undesirable experience a patient has using a medical product. Serious adverse events—the ones FDA is primarily interested in—include death, life-threatening situations, initial or prolonged hospitalization, and situations requiring medical intervention to prevent

Patients who suspect they've had a serious adverse event after using a medical product should ask their physicians to call the MEDWATCH hot line at (1-800) FDA-1088. ■



**MEDWATCH**  
THE FDA MEDICAL DEVICE ISOPROBOLIN, NOV 1998

For VOLUNTARY reporting  
by health professionals of adverse  
events and product problems

This form may be obtained from:  
FDA Form 3500  
2000  
3-98

Page 1 of 1

|  |  |   |  |
|--|--|---|--|
| <b>A. Patient information</b><br>1. Patient identifier: <input type="checkbox"/> Name of patient or <input type="checkbox"/> Age in years of child<br>2. Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female<br>3. Weight: <input type="checkbox"/> Normal <input type="checkbox"/> Overweight<br>4. Race: <input type="checkbox"/> White <input type="checkbox"/> Black <input type="checkbox"/> Other   |  | <b>C. Suspect medication(s)</b><br>1. Name (agent, strength, & pH label, if known)<br>2. Quantity (number of tablets, capsules, etc.)<br>3. History (date of collection, give duration, amount, etc.)<br>4. Disposition (see instructions)<br>5. Date of onset<br>6. Date of report<br>7. Exp. date of report<br>8. Best response after discontinuation<br>9. NDC # (for product packaging only)  |  |
| <b>B. Adverse event or product problem</b><br>1. Adverse event: <input type="checkbox"/> Injury <input type="checkbox"/> Product problem (e.g., device, packaging)<br>2. Describe nature of adverse event (check all that apply):<br><input type="checkbox"/> Death <input type="checkbox"/> Disability <input type="checkbox"/> Hospitalization <input type="checkbox"/> Other<br><input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Convulsion <input type="checkbox"/> Hemorrhage <input type="checkbox"/> Hypertension <input type="checkbox"/> Hypotension <input type="checkbox"/> Infection <input type="checkbox"/> Irritation <input type="checkbox"/> Rash <input type="checkbox"/> Stomatitis <input type="checkbox"/> Tachycardia <input type="checkbox"/> Tachypnea <input type="checkbox"/> Urinary retention <input type="checkbox"/> Vomiting <input type="checkbox"/> Xeroderma <input type="checkbox"/> Other |  | 10. Equipment (model, product and therapy date) (include treatment of event)<br><b>D. Suspect medical device</b><br>1. Device name<br>2. Type of device<br>3. Manufacturer name & address<br>4. Operator of device:<br><input type="checkbox"/> Health professional<br><input type="checkbox"/> Manufacturer<br><input type="checkbox"/> Other<br>5. Equipment date (month/year)<br>6. If equipment, give date (month/year)<br>7. If equipment, give date (month/year)<br>8. If equipment, give date (month/year)<br>9. Device available for evaluation? (Do not send to FDA)<br><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Return to manufacturer on: _____<br>10. Comment (model, product and therapy date) (include treatment of event) |  |
| 5. Date of onset<br>6. Date of this report<br>7. Describe nature of problem<br>8. Repeat (manufacturer, date, military time)<br>9. Other relevant history, including pregnancy, menstrual conditions in females, diet, pregnancy, smoking and alcohol use, behavioral dysfunction, etc.  |  | <b>E. Reporter (see confidentiality section on back)</b><br>1. Name, address & phone #<br>2. Health professional? <input type="checkbox"/> Yes <input type="checkbox"/> No<br>3. Occupation<br>4. Date reported to:<br><input type="checkbox"/> Manufacturer <input type="checkbox"/> Local health authority <input type="checkbox"/> Distributor<br>5. If you do NOT send your identity disclosed to the manufacturer, please check "X" in this box.   |  |

Mail to: MEDWATCH, 2020 Parkers Lane, Rockville, MD 20852-0797  
 or FAX to: 1-800-FDA-6171

FDA Form 3500 (9/98) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

permanent damage, disability, and congenital anomaly. Congenital anomalies include birth defects, miscarriage and still-birth, or birth with cancer or some other serious disease.

The identity of patients involved in MEDWATCH reports is confidential and legally protected. The identity of the reporter may be shared with the manufacturer unless the reporter requests otherwise.

"Physicians should report when there is a suspicion that the drug or device may be related to a serious adverse effect; they are not expected to establish the connection or even wait until evidence seems compelling," Kessler wrote in a recent *Journal of the American Medical Association* article.

"On the other hand, the FDA does not want providers to report every adverse reaction observed; this would not be practical for the practitioner or useful to FDA," Kessler continued.

Problems should also be reported when there is concern about the quality, performance or safety of any medication or device. Product quality problems may occur during manufacturing, shipping or storage. These problems include contamination, defective components, poor packaging or product mix-up, questionable stability, and labeling concerns.

The agency's MEDWATCH central unit receives all the reports initially. From there, it is determined what type of product is involved. Within one working day of receipt

of a report, it is in the hands of the appropriate program in the center responsible for the particular product.

"We're currently receiving about 100,000 reports each year of adverse events with drugs," Anello says. "Several thousand of those are serious and unlabeled [not listed in the product labeling] reactions. Not every one of those reports establishes cause-and-effect relationships. We have a staff of epidemiologists who assess the causes [of the reaction] and also the public health importance of these reported adverse events."

Once an adverse event or product problem is identified, FDA can take any of the following actions:

- **Labeling Changes**—Adverse events of

# Vaccine Reporting

MEDWATCH doesn't include vaccines.

In 1986, Congress passed the National Childhood Vaccine Injury Act, requiring health-care practitioners and vaccine manufacturers to report serious adverse events with certain vaccines.

The Vaccine Adverse Event Reporting System (VAERS) began Nov. 1, 1990, collecting all vaccine reports for FDA and the national Centers for Disease Control and Prevention.

"In 1992, VAERS received 11,015 reports," says John Nazario, FDA's VAERS project officer. "Of those, 1,510 were serious."

Congress passed the act after realizing litigation against manufacturers was driving up vaccine costs and motivating some companies to stop vaccine production, Nazario explained.

Anyone—consumers, parents, manufacturers, and health-care providers—can submit a VAERS form, but patients or their representatives are encouraged to also consult their doctors, Nazario says.

For a VAERS form or more information on reporting vaccine adverse events, call the 24-hour VAERS hot line at (1-800) 822-7967. ■

—K.L.R.

ten prompt FDA to require the manufacturer to add new information to the product's package insert.

- **Boxed Warnings**—are reserved for the most serious adverse events. FDA can require that warnings be placed in a prominent position on the product's packaging to ensure its continued safe use.

- **Product Recalls and Withdrawals**—are among the most serious actions FDA can advise a company to take. Recalls involve the firm's removal of a product from the market and may require taking the product off the market permanently.

- **Medical and Safety Alerts**—are used to provide important safety information about a product to health professionals, trade, and media organizations.

## Sharing Information

Communicating FDA actions that resulted from MEDWATCH reports to health professionals is another primary goal of the new program.

"Already we have about 70 health-care organizations that have signed up to be our partners," Kennedy says. "They're doing news and journal articles, distributing forms, publishing print ads, public service announcements—we're really just getting into the phase where we would expect to see a real surge of reporting."

These organizations have also agreed to help disseminate information about the safety actions the agency has taken.

FDA also reports back to health-care professionals through "Dear Doctor" and

"Dear Health Professional" letters, *FDA Medical Bulletin*, and through press releases and journal articles.

"The plans are for us to provide whatever information comes out back to the health professional," Kennedy says. "We're certainly not able to individualize responses, although if a significant problem is discovered, we might look back at the reports used in discovering the problem and write back to those who reported it."

## What Does MEDWATCH Mean to You?

The MEDWATCH program will provide different benefits to different people.

For health professionals, the MEDWATCH program will help educate and inform practitioners of the need for adverse event reporting. It will also quickly correct product problems and remove defective or dangerous products from distribution.

But the greatest beneficiary will be the general public. "MEDWATCH will help identify problems earlier so that we [FDA] can prevent the continued occurrence of that problem," Kennedy says.

Simply put, MEDWATCH is expected to make medical products safer for consumers by ensuring the safety of products on the market and enabling faster removal from the market of those that cause problems.

As Kessler told the health professionals, "What MEDWATCH is all about is preventing illness and death. It is about someone in my family, in your family, someone anywhere in this country who will escape illness or even death because a health professional filed a report. And it is about every patient who will suffer because a report was not filed." ■

*Kevin L. Ropp is a staff writer for FDA Consumer.*

# Section 13

## Establishment Inspections

# AN INSIDE LOOK AT

## FDA ON-SITE

There are nearly 15,000 establishments in the United States that manufacture, test, pack, and label drug products for humans. The Federal Food, Drug, and Cosmetic Act requires FDA to inspect each of these facilities at least once every two years. In addition, 800 to 1,000 foreign facilities are periodically inspected.

Agency investigators, working from field offices in some 160 locations throughout the country, completed 3,142 domestic inspections in 2,618 human drug establishments in the fiscal year that ended Sept. 30, 1993. Another 223 inspections were done at 213 foreign establishments.

During that year, the agency took a number of legal actions to correct deficiencies for failure to meet drug manufacturing and product standards. These included one prosecution, two injunctions, 15 seizures, and 408 warning letters. FDA also monitored recalls involving 406 drug products in various dosage forms.

An inspection can last from one or two days to several weeks, depending on its purpose and scope. There are three primary types of inspections: preapproval, postapproval, and surveillance good manufacturing practice (GMP) inspections.

Preapproval inspections are often initiated by the Center for Drug Evaluation and Research at FDA headquarters. While the center is reviewing a new drug application or abbreviated new drug application, it requests that the field office inspect the drug manufacturing facilities.

This inspection represents a significant step in the drug review process. The investigators must determine if the data submitted in the firm's application are authentic and accurate and if the plant is in compliance with current good manufacturing practice regulations. The district office recommends approval or disapproval of the application, based on its findings.

After the center approves an application and the firm is ready to start marketing the drug, FDA conducts a postapproval inspection, intended to evaluate the firm's validation studies. Validation refers to FDA's requirement that the firm show it can consistently manufacture a drug product within tight parameters from batch to batch, day to day, year to year. The investigators also verify that the firm has not changed its manufacturing, labeling, or quality control testing for that drug without filing a supplement to its application, and that the firm has not exceeded a ten-fold "scale-up" in production.

"Scaling up" is the process of increasing the batch size for commercial manufacture. "For commercial production, FDA lets firms manufacture their product in batches ten times larger than those produced for clinical or bioequivalency testing," Kirk Sooter, investigator with the agency's Morgantown, W.Va., resident post, says. "For example, if tablets were produced in batches of 100,000 during clinical testing, the commercial production batch cannot exceed 1 million tablets."

The investigators collect samples at both preapproval and postapproval inspections for analyses that will compare the composition of the product against known standards. The drug's chemical "fingerprint" must match the standard pattern for the compound. Samples are also collected to verify that the firm's laboratory methods are proper and consistent with the drug application.

Finally, a GMP, or "routine," inspection evaluates the firm's entire operations. Although pre- and postapproval inspections include examination of the firm's manufacturing practices, they are product-specific. GMP inspections, on the other hand, involve a comprehensive review of the firm's manufacturing operations. ■

*by Marian Segal*



**W**hen FDA's Sarah Brown (left) and Kirk Sooter (middle) arrive to inspect Barre-National Inc., a Baltimore drug manufacturer, they show their credentials and issue a written "Notice of Inspection" to the firm's quality assurance manager. A full inspection may take weeks, while a visit to look at one or two specific things may take only an afternoon. An inspection team may comprise several people, including analysts, chemists, microbiologists, and investigators.

Before coming to the plant, Brown, a chemist with the Baltimore district office, and Sooter reviewed the plant's inspection history.



**I**n the plant's receiving section, the investigators make sure the firm is following its written procedures for receiving and handling incoming raw materials. They also evaluate the procedures to make sure they are adequate.

Early in the inspection, Sooter and Brown look over the company's complaint files. These files not only reveal how the firm conducts its complaint investigations, but may help the investigators determine what areas they want to focus on in their inspection.

"If there are substantial problems or complaints about a product, we look at what kind of effort the firm puts into resolving the complaints," Sooter says. "If the firm is responsible for the problem, what sort of corrective action did it take? Did they look at manufacturing batch records? Did they review the laboratory analyses?"

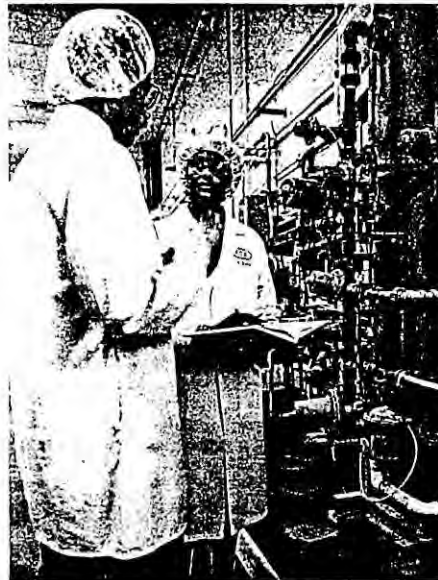
"If there are excessive complaints about a particular product," Brown adds, "the investigator may collect a sample from a store shelf and have it analyzed at FDA's laboratory. A product that doesn't meet standards may be removed from the marketplace."



*In the weighing station, precise amounts of raw materials are weighed for compounding when formulating products. A technician hands Sooter a weighing slip showing the weight of the material on the scale. Sooter will check to see that the scales are calibrated, start at zero, and are steady at the registered weight.*

*"It's also important to make sure that proper procedures are followed to prevent cross-contamination of chemicals in production areas," Sooter says. "For example, in the weighing station, do they use the same scoop for two materials? Is one chemical container open while another chemical is being weighed out, leaving the potential for cross-contamination?"*

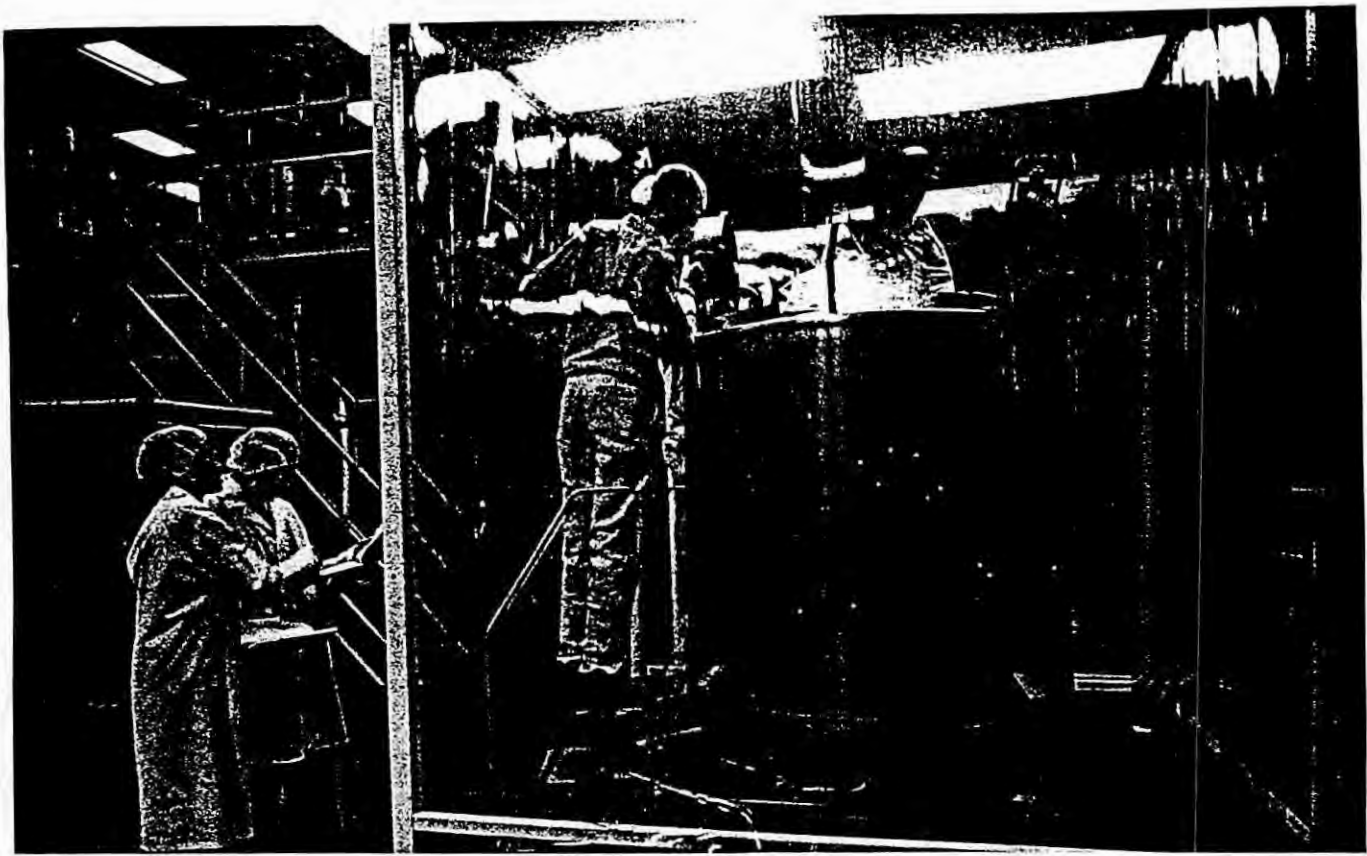
*In production areas, hair must be covered to prevent product contamination. Men must also cover beards and mustaches. Here, the two wear masks also to prevent inhalation of fine particles of the powdery material.*



*Brown discusses with a quality control officer how the firm's water purification system works, how it's monitored, and how frequently the water is tested. Water used as an ingredient in any drug product must meet chemical and microbial standards.*

*"They need to test not only for microbial contaminants," Brown says, "but for pH levels and levels of chemicals that can cause production problems down the road."*

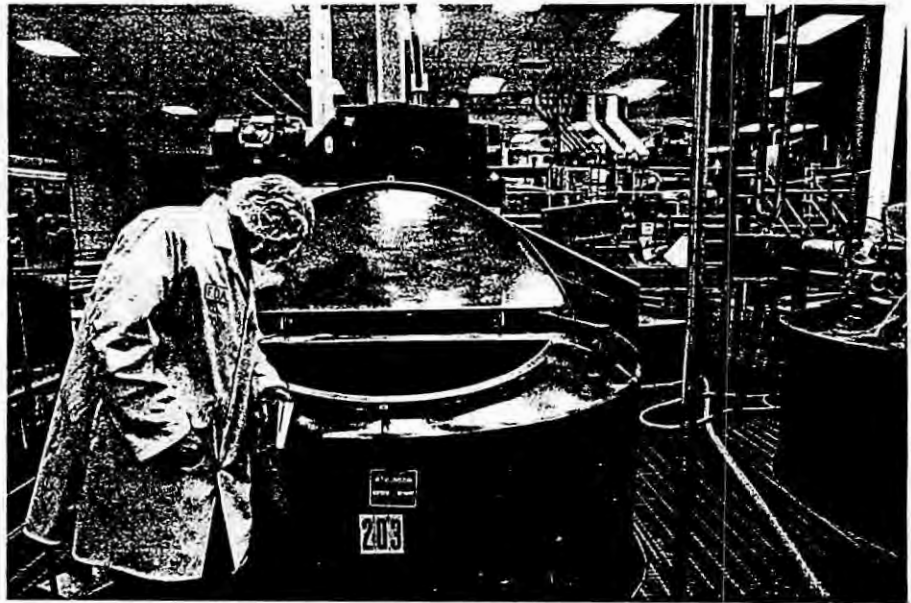




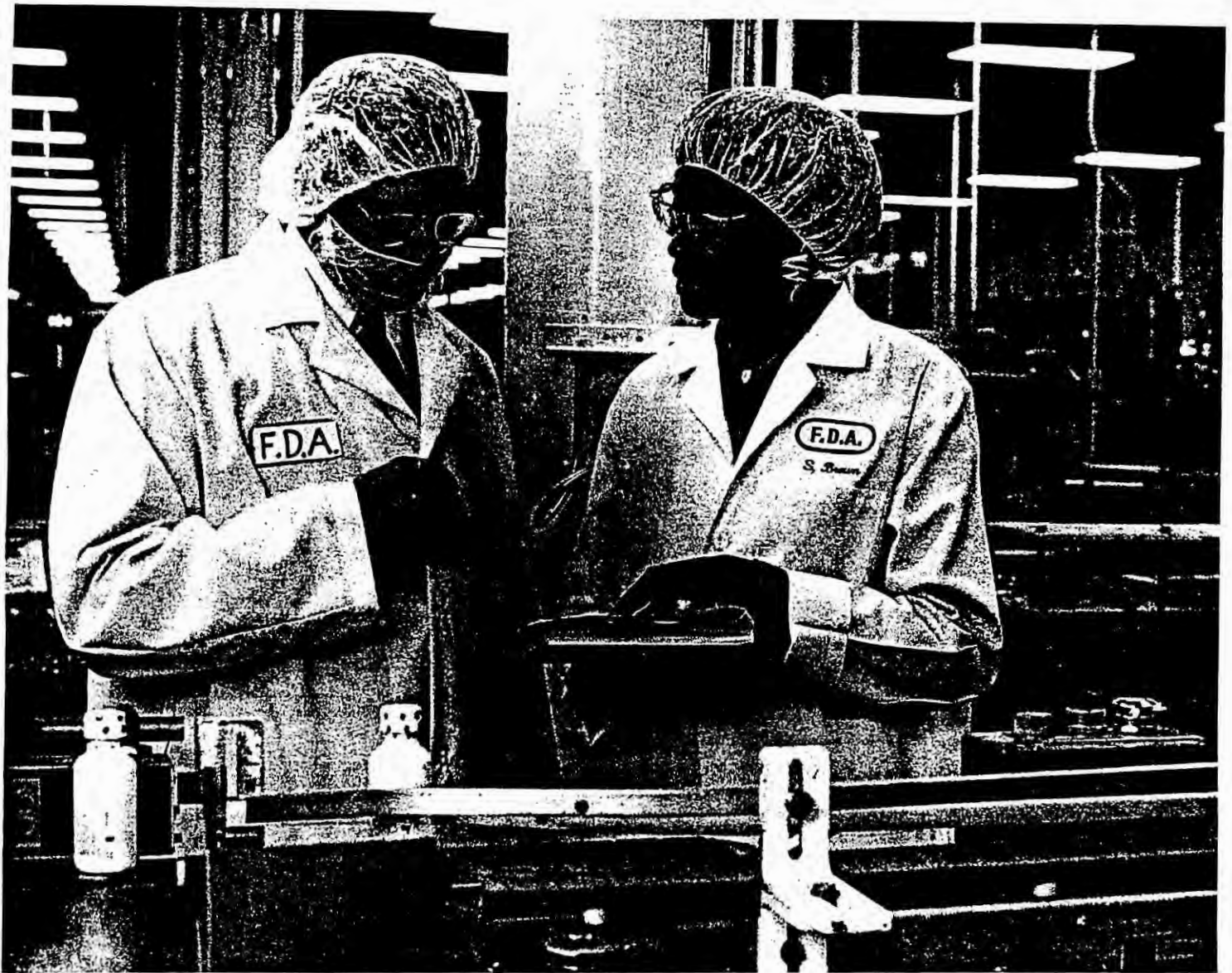
*While a technician adds an ingredient to a product in a compounding tank, Brown consults the batch production and control record and Sooter checks employee signatures to see that ingredients have been added and mixed as prescribed.*

*“Certain ingredients should be added slowly because of chemical reactions; others need to be added quickly, but cooled to a certain temperature, or the mixing needs to be stopped or speeded up,” Sooter explains.*

*The curtain around the tank defines a “controlled” area. The curtain helps keep foreign substances out of the area and keeps other substances, such as dust rising from powders dumped in the tank, from escaping and getting into other equipment.*



*Sooter inspects one of the large compounding tanks for cleanliness and will check to see that the equipment log accurately reflects the usage and cleaning of that particular vessel. Proper cleaning between uses is important to avoid contamination of products.*



*Sooter and Brown review batch records for products that have reached the filling line where labels are affixed.*

*"A batch record is one of the most important documents in drug production because it tells the whole history of that batch," says Peter Smith of FDA's division of field investigations at agency headquarters. "It's a copy of the master record, the approved way to manufacture a particular product in a particular batch size. The record literally follows the batch production from one processing area to the next and records every step from beginning to end. Employee signatures document that the steps in manu-*

*facture, processing, packaging, or holding were completed."*

*The record contains everything that happened concerning production of that batch—what went into it, where samples were taken, problems during manufacturing (such as equipment failure or power failure or a broken hose)—down to the exact batch yield.*

*If there is a problem with a product after it's on the market, Smith says, one of the first things investigators do is examine the batch record for any problems—even those seemingly unimportant at the time—that may have occurred during manufacture.*



*In the laboratory, a technician shows Brown the results of a high performance liquid chromatography (HPLC) assay she's doing on a finished product sample. The test is done to ensure the product conforms to standards and contains no impurities.*

*HPLC detects the active ingredients of a formulation. "Every formulation has its own 'chemical fingerprint' that appears on the chromatogram as a distinct pattern of peaks," Brown says. "If the pattern does not match the known standard, then a problem is apparent. Further tests can determine what the abnormal peaks represent."*

*"When we go into the laboratory," Brown says, "we make sure the HPLC and other instruments are working properly, check the quality of chromatograms, review what analytical methods are used for what purposes, and if they are appropriate and calculated correctly."*

*Marian Segal is a member of FDA's public affairs staff.*

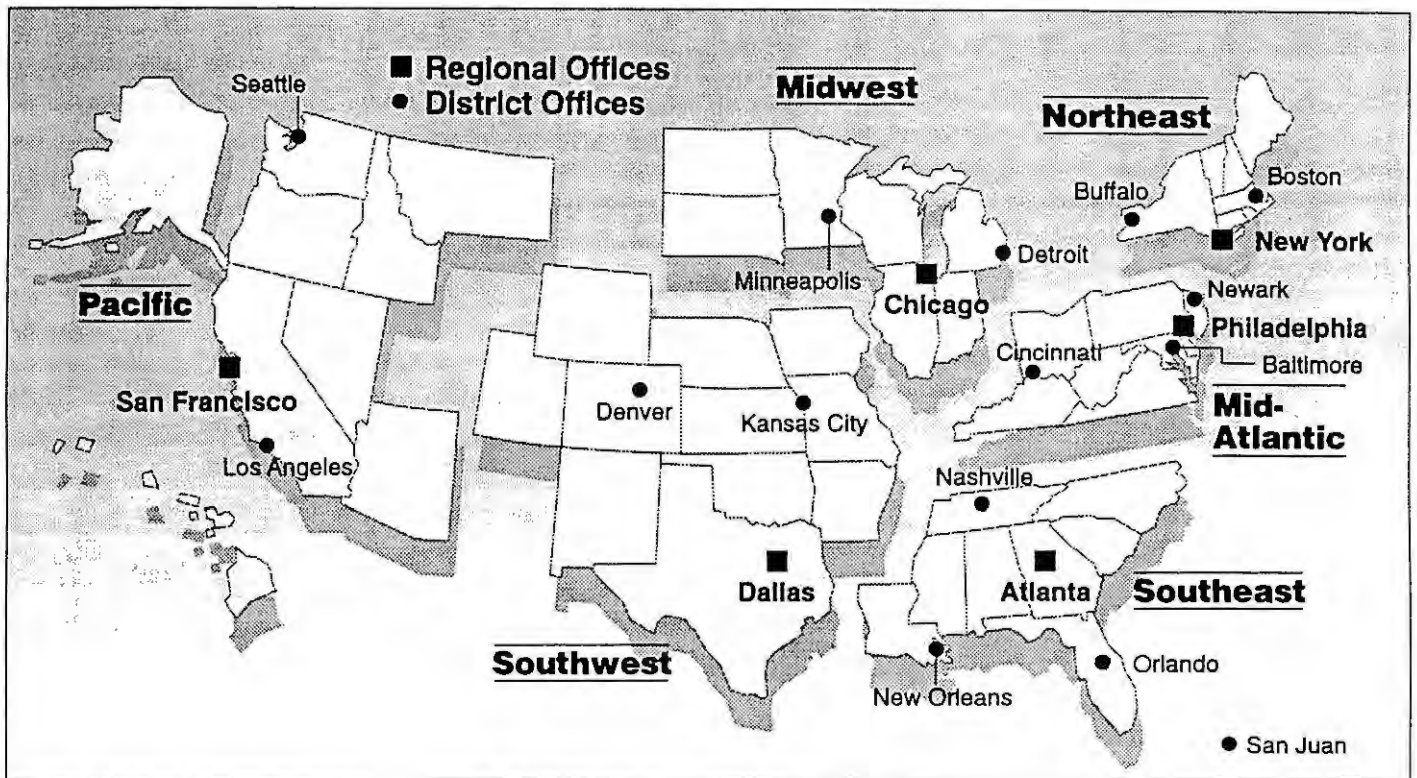


*Sooter waits while some boxes stored in the high bay warehouse area are brought down for him to check. Here, the firm may store products not yet distributed or failed products that haven't yet been destroyed.*

*"An investigator may want to look at the 'morgue'—the area where failed product is kept—early on in the inspection for clues about what to key in on," says Sooter. For example, he says, if batches of a particular product have failed or been rejected, that product will warrant a closer look.*

# FDA's Field Operations

Six regions, each responsible for a distinct part of the country, make up FDA's field operations. In addition to the six regional offices and 15 district offices shown below, there are 130 resident inspection posts located throughout the United States.



# FDA's Field Operations

## NORTHEAST REGION

One Montvale Ave.  
Stoneham, MA 02180  
(617) 279-1675 (ext. 184)  
FAX (617) 279-1687

850 Third Ave.  
Brooklyn, NY 11232  
(718) 965-5300 (ext. 5043)  
FAX (718) 965-5117

599 Delaware Ave.  
Buffalo, NY 14202  
(716) 846-4461  
FAX (716) 846-4470

## MID-ATLANTIC REGION

61 Main St.  
West Orange, NJ 07052  
(201) 645-6365  
FAX (201) 645-3848

2nd and Chestnut Streets  
Room 900, U.S. Customhouse  
Philadelphia, PA 19106  
(215) 597-0837  
FAX (215) 597-6649

900 Madison Ave.  
Baltimore, MD 21201  
(410) 962-3731  
FAX (410) 962-2307

Resident Inspection Post  
1110 N. Glebe Road, Room 250  
Arlington, VA 22201  
(703) 285-2578  
FAX (703) 235-4330

1141 Central Parkway  
Cincinnati, OH 45202-1097  
(513) 684-3501  
FAX (513) 684-2905

Resident Inspection Post  
3820 Center Road  
P.O. Box 838  
Brunswick, OH 44212  
(216) 273-1038 (ext. 114)  
FAX (216) 225-7477

## SOUTHEAST REGION

Puerta de Tierra Station  
P.O. Box 5719  
Stop 8 1/2 Fernandez Juncos Ave.  
San Juan, Puerto Rico 00906-5719  
(809) 729-6852  
FAX (809) 729-6809

60-8th St. N.E.  
Atlanta, GA 30309  
(404) 347-7355  
FAX (404) 347-1912

7200 Lake Ellenor Dr.  
Suite 120  
Orlando, FL 32809  
(407) 648-6922  
FAX (407) 648-6881

6601 N.W. 25th St.  
P.O. Box 59-2256  
Miami, FL 33159-2256  
(305) 526-2800  
FAX (305) 526-2693

297 Plus Park Blvd.  
Nashville, TN 37217  
(615) 781-5372  
FAX (615) 781-5383

4298 Elysian Fields Ave.  
New Orleans, LA 70122  
(504) 589-2420 (ext. 121)  
FAX (504) 589-6360

## MIDWEST REGION

300 S. Riverside Plaza  
Suite 550 - South  
Chicago, IL 60606  
(312) 353-5863 (ext. 188)  
FAX (312) 886-3280

1560 East Jefferson Ave.  
Detroit, MI 48207  
(313) 226-6260 (ext. 149)  
FAX (313) 226-3076

Resident Inspection Post  
101 W. Ohio St.  
Indianapolis, IN 46204  
(317) 226-6500 (ext. 13)  
FAX (317) 226-6506

240 Hennepin Ave.  
Minneapolis, MN 55401  
(612) 334-4100 (ext. 129)  
FAX (612) 334-4134

Resident Inspection Post  
2675 North Mayfair Road  
Suite 200  
Milwaukee, WI 53226-1305  
(414) 771-7167  
FAX (414) 771-7512

## SOUTHWEST REGION

3310 Live Oak St.  
Dallas, TX 75204  
(214) 655-5315 (ext. 303)  
FAX (214) 655-5331

Resident Inspection Post  
1445 N. Loop West  
Suite 420  
Houston, TX 77008  
(713) 802-9095 (ext. 15)  
FAX (713) 802-0906

Resident Inspection Post  
10127 Morocco  
Suite 119  
San Antonio, TX 78216  
(210) 229-4531  
FAX (210) 229-4548

11630 West 80th St.  
Lenexa, KS 66214  
(913) 752-2141  
FAX (913) 752-2111

808 North Collins Alley  
St. Louis, MO 63101  
(314) 425-5021 (ext. 23)  
FAX (314) 425-4896

Denver Federal Center  
Building 20, Room B-1121  
P.O. Box 25087  
6th Ave. and Kipling  
Denver, CO 80225-0087  
(303) 236-3000 (ext. 318)  
FAX (303) 236-3099

## PACIFIC REGION

1431 Harbor Bay Parkway  
Alameda, CA 94502-7070  
(510) 769-3012 (ext. 1089)  
FAX (510) 769-3008

1521 W. Pico Blvd.  
Los Angeles, CA 90015-2486  
(213) 252-7597  
FAX (213) 252-7701

Resident Inspection Post  
4615 East Elmwood St.  
Suite 200  
Phoenix, AZ 85040  
(602) 379-4595 (ext. 225)  
FAX (602) 379-4646

22201 23rd Dr. S.E.  
Bothell, WA 98021-4421  
(206) 483-4953  
FAX (206) 483-4996

Resident Inspection Post  
511 N.W. Broadway  
Federal Building, Room 694  
Portland, OR 97209  
(503) 326-5824 (ext. 22)  
FAX (503) 326-5690

# Section 14

## Personal Importation Guidelines

---

# REGULATORY PROCEDURES MANUAL

## Part 9, IMPORT PROCEDURES

### CHAPTER 9-71 COVERAGE OF PERSONAL IMPORTATIONS

---

|         |                  |
|---------|------------------|
| 9-71-00 | Purpose          |
| 10      | Background       |
| 20      | Personal Baggage |
| 25      | Mail Shipments   |
| 30      | General Guidance |
| 40      | Import Alerts    |

#### 9-71-00 PURPOSE

To provide guidelines for the coverage of personal-use quantities of FDA-regulated imported products in baggage and mail and to gain the greatest degree of public protection with allotted resources.

#### 9-71-10 BACKGROUND

This new chapter consolidates policy and procedures that previously existed in RPM Chapter 9-71, Mail Importations; RPM Chapter 9-72, Coverage of Importations Contained in Personal Baggage; and, Pilot Guidance for Release of Mail Importations.

Because the amount of merchandise imported into the United States in personal shipments is normally small, both in size and value, comprehensive coverage of these imports is normally not justified. Small shipments, however, are occasionally entered in baggage or mail as a way of avoiding formal entry review. This guidance clarifies how FDA may best protect consumers with a reasonable expenditure of resources.

There has always been a market in the United States for some foreign made products that are not available domestically. For example, individuals of differing ethnic backgrounds sometimes prefer products from their homeland or products labeled in their native language to products available in the United States. Other individuals seek medical treatments that are not available in this country. Drugs are sometimes mailed to this country in response to a prescription-like order to allow continuation of a therapy initiated abroad. With increasing international travel and world trade, we can anticipate that more people will purchase products abroad that may not be approved, may be health frauds, or may be otherwise not legal for sale in the United States.

In addition, FDA must be alert to foreign and domestic businesses that ship unapproved, fraudulent, or otherwise illegal medical treatments into the United States or who encourage persons to order these



products. Such treatments may be promoted to individuals who believe that treatments available abroad will be effective in the treatment of serious conditions such as AIDS or cancer. Because some countries do not regulate or restrict the commercial exportation of unapproved products, people who mail order from these businesses may not be afforded the protection of either foreign or U.S. laws. In view of the potential scale of such commercial operations, FDA has focused its enforcement resources more on products that are shipped commercially, including small shipments solicited by traditional mail-order promotions, and less on those products that are personally carried, shipped by a personal non-commercial representative of a consignee, or shipped from a foreign medical facility where a person has undergone treatment.

9-71-20 PERSONAL BAGGAGE

FDA personnel are not to examine personal baggage. This responsibility rests with the U.S. Customs Service. It is expected that a Customs officer will notify the local FDA district office by telephone when he or she has detected a promotional shipment or a shipment of an FDA-regulated article intended for commercial distribution (see 9-71-30), an article that FDA has specifically requested be detained, or an FDA-regulated article that represents a health fraud or an unknown risk to health.

When items in personal baggage are brought to FDA's attention, the district office should use its discretion, on a case-by-case basis, in accordance with the guidance provided in 9-71-30 in deciding whether to request a sample, detain the article, or take other appropriate action.

9-71-25 MAIL SHIPMENTS

Generally, FDA personnel only monitor mail importations. It is expected that a Customs officer from the Customs Mail Division will examine a parcel and will set it aside if it appears to contain a drug, biologic, or device, an article that FDA has specifically requested be detained, or an FDA-regulated article that represents a health fraud or unknown risk to health.

FDA should audit those parcels set aside by Customs in accordance with the guidance provided in 9-71-30 using the following procedures:

Complete the form FD-725 "Mail Collection Report" for each parcel collected for sampling. Generally, a physical sample is not required on mail importations because a documentary sample, e.g.,

labels, inserts, etc., will be sufficient for most regulatory purposes. If a physical sample is needed, collect only the minimum necessary for analysis by the laboratory. The remaining portion should not be removed from the custody of the Customs Mail Division.

Importations detained in accordance with this guidance should be held by Customs until they are either released or refused entry. Attached as guides are two specimen letters that may be sent with the Notice of Detention and Hearing when a parcel is detained: Exhibit X9-71-1 for use in general mail importations, and Exhibit X9-71-2 for use in unapproved drug or device mail importations.

On occasion, products detained by FDA will be mixed with non-FDA-regulated products. When we refuse admission of the FDA-regulated portion, any request for the release of the non-FDA-regulated portion should be referred to the Customs Mail Division with a Notice of Refusal of Admission covering the detained article. Final disposition of all merchandise, including the destruction of detained merchandise, is the responsibility of Customs.

9-71-30 GENERAL GUIDANCE

Even though all products that appear to be in violation of statutes administered by FDA are subject to refusal, FDA personnel may use their discretion to examine the background, risk, and purpose of the products before making a final decision. Although FDA may use its enforcement discretion to allow admission of certain violative items, this should not be interpreted as a license to individuals to bring in such shipments.

A. Commercial or Promotional Shipments

Commercial and promotional shipments are not subject to this guidance. Whether or not a shipment is commercial or promotional should be determined by a number of factors including the type of product, the accompanying literature, the size, value, and the destination of the shipment. FDA personnel should also consider whether an importation of drugs or medical devices is a commercial shipment by evaluating whether the article appears to have been purchased for personal use or whether the quantity suggests commercial distribution (i.e., the supply exceeds what one person might take in approximately three months). Commercial shipments include most shipments other than those products that are personally carried, shipped by a personal non-commercial

representative of a consignee, or shipped from a foreign medical facility where a person has undergone treatment.

B. Products Other than Drugs and Devices

Many products other than drugs, biologics, and devices that individuals seek to import in personal quantities do not pose a significant health risk, although they appear to be violative and may already be the subject of an import alert or automatic detention on the basis of filth or labeling problems. When such items are brought to FDA's attention by Customs, it may be appropriate for FDA personnel to use their discretion to "Release with Comment" and advise the importer of the agency's concerns. FDA personnel should be alert to, and should detain, however, those products that do pose a significant health risk, such as ackee or betel nuts.

C. Drugs, Biologics, and Devices

When personal shipments of drugs and devices that appear violative are brought to FDA's attention by Customs, FDA personnel will have to use their discretion to decide on a case by case basis whether to sample or detain. Generally, drugs and devices subject to Import Alerts are not amenable to this guidance. Devices to be used by practitioners for treating patients should not be viewed as personal importations subject to this chapter. Drugs subject to Drug Enforcement (DEA) jurisdiction should be returned to Customs for handling.

In deciding whether to exercise discretion to allow personal shipments of drug or devices, FDA personnel should consider a more permissive policy in the following situations:

- o when the intended use is appropriately identified, such use is not for treatment of a serious condition, and the product is not known to represent a significant health risk; or
- o when 1) the intended use is unapproved and for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means; 2) there is no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue; 3) the product is considered not to represent an unreasonable risk; and 4) the individual seeking to import the product affirms in writing that it is for the patient's own use (generally not more than 3 month supply)

---

TN 90-02 (12/11/89)

FORM FDA 3251 (9/88)

and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product or provides evidence that the product is for the continuation of a treatment begun in a foreign country.

Where there are any questions about the application of these factors to any product, the product should be detained and FDA personnel should consult with the appropriate headquarters office.

Where a shipment is not detained or refused, FDA personnel should "Release with Comment" and, as appropriate, advise the recipient that 1) the drug (or device) that has been obtained for personal use appears to be unapproved in the United States; 2) the drug (or device) should be used under medical supervision; 3) FDA may detain future shipments of this product; and 4) the patient's physician should consider enrolling the patient in an Investigational study or applying for an Investigational New Drug (IND) exemption.

9-71-40 IMPORT ALERTS

FDA personnel should recommend to HFC-131 the issuance of an import alert if they encounter:

- o personal importation of products that represent either a direct or indirect risk;
- o the promotion of unapproved foreign products for mail-order shipment; or
- o repeated importation of products that represent a health fraud.

# Section 15

## Medical Treatment

# AN FDA GUIDE TO CHOOSING

# MEDICAL TREATMENTS

by Isadora B. Stehlin

Medical treatments come in many shapes and sizes. There are "home remedies" shared among families and friends. There are prescription medicines, available only from a pharmacist, and only when ordered by a physician. There are over-the-counter drugs that you can buy—almost anywhere—without a doctor's order. Of growing interest and attention in recent years are so-called alternative treatments, not yet approved for sale because they are still undergoing scientific research to see if they really are safe and effective. And, of course, there are those "miracle" products sold through "back-of-the-magazine" ads and TV infomercials.

How can you tell which of these may really help treat your medical condition, and which will only make you worse off—financially, physically, or both?

Many advocates of unproven treatments and cures contend that people have the right to try whatever may offer them hope, even if others believe the remedy is worthless. This argument is especially compelling for people with AIDS or other life-threatening diseases with no known cure.

## Clinical Trials

Before gaining Food and Drug Administration marketing approval, new drugs, biologics, and medical devices must be proven safe and effective by controlled clinical trials.

In a clinical trial, results observed in patients getting the treatment are compared with the results in similar patients receiving a different treatment or pla-

cebo (inactive) treatment. Preferably, neither patients nor researchers know who is receiving the therapy under study.

To FDA, it doesn't matter whether the product or treatment is labeled alternative or falls under the auspices of mainstream American medical practice. (Mainstream American medicine essentially includes the practices and products the majority of medical doctors in this country follow and use.) It must meet the agency's safety and effectiveness criteria before being allowed on the market.

In addition, just because something is undergoing a clinical trial doesn't mean it works or FDA considers it to be a proven therapy, says Donald Pohl, of FDA's Office of AIDS and Special Health Issues. "You can't jump to that conclusion," he says. A trial can fail to prove that the product is effective, he explains. And that's not just true for alternative products. Even when the major drug companies sponsor clinical trials for mainstream products, only a small fraction are proven safe and effective.

Many people with serious illnesses are unable to find a cure, or even temporary relief, from the available mainstream treatments that have been rigorously studied and proven safe and effective. For many conditions, such as arthritis or even cancer, what's effective for one patient may not help another.

## Real Alternatives

"It is best not to abandon conventional therapy when there is a known response

[in the effectiveness of that therapy]," says Joseph Jacobs, M.D., former director of the National Institutes of Health's Office of Alternative Medicine, which was established in October 1992. As an example he cites childhood leukemia, which has an 80 percent cure rate with conventional therapy.

But what if conventional therapy holds little promise?

Many physicians believe it is not unreasonable for someone in the last stages of an incurable cancer to try something unproven. But, for example, if a woman with an early stage of breast cancer wanted to try shark cartilage (an unproven treatment that may inhibit the growth of cancer tumors, currently undergoing clinical trials), those same doctors would probably say, "Don't do it," because there are so many effective conventional treatments.

Jacobs warns that, "If an alternative practitioner does not want to work with a regular doctor, then he's suspect."

Alternative medicine is often described as any medical practice or intervention that:

- lacks sufficient documentation of its safety and effectiveness against specific diseases and conditions
- is not generally taught in U.S. medical schools
- is not generally reimbursable by health insurance providers.

According to a study in the Jan. 28, 1993, *New England Journal of Medicine*, 1 in 3 patients used alternative therapy in 1990. More than 80 percent of those who use alternative therapies

used conventional medicine at the same time, but did not tell their doctors about the alternative treatments. The study's authors concluded this lack of communication between doctors and patients "is not in the best interest of the patients, since the use of unconventional therapy, especially if it is totally unsupervised, may be harmful." The study concluded that medical doctors should ask their patients about any use of unconventional treatment as part of a medical history.

Many doctors are interested in learning more about alternative therapies, according to Brian Berman, M.D., a family practitioner with the University of Maryland School of Medicine in Baltimore. Berman says his own interest began when "I found that I wasn't getting all the results that I would have liked with conventional medicine, especially in patients with chronic diseases.

"What I've found at the University of Maryland is a healthy skepticism among my colleagues, but a real willingness to collaborate. We have a lot of people from different departments who are saying, let's see how we can develop scientifically rigorous studies that are also sensitive to the particular therapies that we're working with."

Anyone who wants to be treated with an alternative therapy should try to do so through participation in a clinical trial. Clinical trials are regulated by FDA and provide safeguards to protect patients, such as monitoring of adverse reactions. In fact, FDA is interested in assisting investigators who want to study alternative therapies under carefully controlled clinical trials.

Some of the alternative therapies currently under study with grants from NIH include:

- acupuncture to treat depression, attention-deficit hyperactivity disorder, osteoarthritis, and postoperative dental pain
- hypnosis for chronic low back pain and accelerated fracture healing
- Ayurvedic herbals for Parkinson's disease. (Ayurvedic medicine is a holistic system based on the belief that herbals, massage, and other stress relievers help the body make its own natural drugs.)
- biofeedback for diabetes, low back pain, and face and mouth pain caused by jaw disorders. (Biofeedback is the con-

## *Anyone who wants to be treated with an alternative therapy should try to do so through participation in a clinical trial*

scious control of biological functions, such as those of the heart and blood vessels, normally controlled involuntarily.)

- electric currents to treat tumors
- imagery for asthma and breast cancer. (With imagery, patients are guided to see themselves in a different physical, emotional or spiritual state. For example, patients might be guided to imagine themselves in a state of vibrant health and the disease organisms as weak and destructible.)

While these alternative therapies are the subject of scientifically valid research, it's important to remember that at this time their safety and effectiveness are still unproven.

### **Avoiding Fraud**

FDA defines health fraud as the promotion, advertisement, distribution, or sale of articles, intended for human or animal use, that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberately deceptive, or done without adequate knowledge or understanding of the article.

Health fraud costs Americans an estimated \$30 billion a year. However, the costs are not just economic, according to



*Acupuncture is one "alternative" therapy currently under study with grants from the National Institutes of Health.*

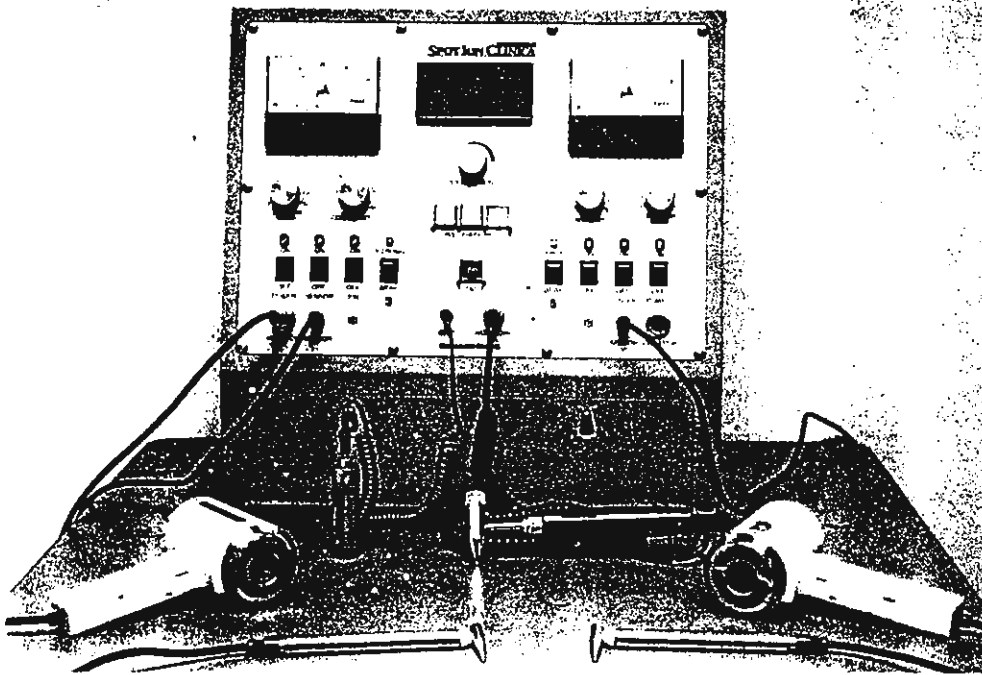
Images provided by © 1994 PhotoDisc, Inc.

## Tip-Offs to Rip-Offs

New health frauds pop up all the time, but the promoters usually fall back on the same old clichés and tricks to gain your trust and get your money. According to FDA, some red flags to watch out for include:

- claims the product works by a secret formula. (Legitimate scientists share their knowledge so their peers can review their data.)
- publicity only in the back pages of magazines, over the phone, by direct mail, in newspaper ads in the format of news stories, or 30-minute commercials in talk show format. (Results of studies on bona fide treatments are generally reported first in medical journals.)

- claims the product is an amazing or miraculous breakthrough. (Real medical breakthroughs are few and far between, and when they happen, they're not touted as "amazing" or "miraculous" by any responsible scientist or journalist.)
- promises of easy weight loss. (For most people, the only way to lose weight is to eat less and exercise more.)
- promises of a quick, painless, guaranteed cure
- testimonials from satisfied customers. (These people may never have had the disease the product is supposed to cure, may be paid representatives, or may simply not exist. Often they're identified only by initials or first names.) ■



*Promoters promised that this "High Genki" machine could treat diabetes, high blood pressure, muscular pain, and arthritis. FDA said it was an unapproved medical device, and on Nov. 9, 1993, the government seized this machine and several similar devices in Hawaii. "It beeped, buzzed, gave a mild electric shock, and that was about all," said Cindy Wolodkin, a public affairs specialist in FDA's San Francisco office.*

John Renner, M.D., a Kansas City-based champion of quality health care for the elderly. "The hidden costs—death, disability—are unbelievable," he says.

To combat health fraud, FDA established its National Health Fraud Unit in 1988. The unit works with the National Association of Attorneys General and the Association of Food and Drug Officials to coordinate federal, state and local regulatory actions against specific health frauds.

Regulatory actions may be necessary in many cases because products that have not been shown to be safe and effective pose potential hazards for consumers both directly and indirectly. The agency's priorities for regulatory action depend on the situation; direct risks to health come first.

Unproven products cause direct health hazards when their use results in injuries or adverse reactions. For example, a medical device called the InnerQuest Brain Wave Synchronizer was promoted to alter brain waves and relieve stress. It consisted of an audio cassette and eyeglasses that emitted sounds and flashing lights. It caused epileptic seizures in some users. As a result of a court order requested by FDA, 78 cartons of the devices, valued at \$200,000, were seized by U.S. marshals and destroyed in June 1993.

Indirectly harmful products are those that do not themselves cause injury, but may lead people to delay or reject proven remedies, possibly worsening their condition. For example, if cancer patients reject proven drug therapies in favor of unproven ones and the unproven ones turn out not to work, their disease may advance beyond the point where proven therapies can help.

"What you see out there is the promotion of products claiming to cure or prevent AIDS, multiple sclerosis, cancer, and a list of other diseases that goes on and on," says Joel Aronson, director of FDA's Health Fraud Staff, in the agency's Center for Drug Evaluation and Research. For example, he says, several skin cream products promise to prevent transmission of HIV (the virus that causes AIDS) and herpes viruses. They are promoted especially to health-care workers. Many of the creams con-





tain antibacterial ingredients but, "there is no substantiation at all on whether or not [the skin creams] work" against HIV, says Aronson. FDA has warned the manufacturers of these creams to stop the misleading promotions.

#### **People at Risk**

Teenagers and the elderly are two prime targets for health fraud promoters.

Teenagers concerned about their appearance and susceptible to peer pressure may fall for such products as fraudulent diet pills, breast developers, and muscle-building pills.

Older Americans may be especially vulnerable to health fraud because approximately 80 percent of them have at least one chronic health problem, according to Renner. Many of these problems, such as arthritis, have no cure and, for some people, no effective treatment. He says their pain and disability lead to

despair, making them excellent targets for deception.

#### **Arthritis**

Although there is no cure for arthritis, the symptoms may come and go with no explanation. According to the Arthritis Foundation, "You may think a new remedy worked because you took it when your symptoms were going away."

Some commonly touted unproven treatments for arthritis are harmful, according to the foundation, including snake venom and DMSO (dimethyl sulfoxide), an industrial solvent similar to turpentine. FDA has approved a sterile form of DMSO called Rimso-50, which is administered directly into the bladder for treatment of a rare bladder condition called interstitial cystitis. However, the DMSO sold to arthritis sufferers may contain bacterial toxins. DMSO is readily absorbed through the skin into

## *Approaching Alternative Therapies*

The NIH Office of Alternative Medicine recommends the following before getting involved in any alternative therapy:

- Obtain objective information about the therapy. Besides talking with the person promoting the approach, speak with people who have gone through the treatment—preferably both those who were treated recently and those treated in the past. Ask about the advantages and disadvantages, risks, side effects, costs, results, and over what time span results can be expected.
- Inquire about the training and expertise of the person administering the treatment (for example, certification).
- Consider the costs. Alternative treatments may not be reimbursable by health insurance.
- Discuss all treatments with your primary care provider, who needs this information in order to have a complete picture of your treatment plan.

For everyone—consumers, physicians and other health-care providers, and government regulators—FDA has the same advice when it comes to weeding out the hopeless from the hopeful: Be open-minded, but don't fall into the abyss of accepting anything at all. For there are—as there have been for centuries—countless products that are nothing more than fraud. ■

## Medical Guides

Whether looking for an alternative therapy or checking the legitimacy of something you've heard about, some of the best sources are advocacy groups, including local patient support groups. Those groups include:

American Cancer Society  
1599 Clifton Road, N.E.  
Atlanta, GA 30329  
(404) 320-3333, (1-800) ACS-2345

Arthritis Foundation  
P.O. Box 19000  
Atlanta, GA 30326  
(1-800) 283-7800

National Multiple Sclerosis Society  
733 Third Ave.  
New York, NY 10017-3288  
(212) 986-3240, (1-800) 344-4867

HIV/AIDS Treatment Information Service  
P.O. Box 6303  
Rockville, MD 20849-6303.  
(1-800) 448-0440, TDD/Deaf Access: (1-800) 243-7012

Federal government resources on health fraud and alternative medicine are:

FDA (HFE-88)  
Rockville, MD 20857  
(301) 443-3170

Office of Alternative Medicine/NIH Information Center  
6120 Executive Blvd., EPS  
Suite 450  
Rockville, MD 20852  
(301) 402-2466

U.S. Postal Inspection Service  
(monitors products purchased by mail)  
Office of Criminal Investigation  
Washington, DC 20260-2166  
(202) 268-4272

Federal Trade Commission  
(regarding false advertising)  
Room 421  
6th St. and Pennsylvania Ave., N.W.  
Washington, DC 20580  
(202) 326-2222

Other agencies that may have information and offer assistance include local Better Business Bureaus, state and municipal consumer affairs offices, and state attorneys general offices. ■

the bloodstream, and these toxins enter the bloodstream along with it. It can be especially dangerous if used as an enema, as some of its promoters recommend.

Treatments the foundation considers harmless but ineffective include copper bracelets, mineral springs, and spas.

### Cancer and AIDS

Cancer treatment is complicated because in some types of cancer there are no symptoms, and in other types symptoms may disappear by themselves, at least temporarily. Use of an unconventional treatment coinciding with remission (lessening of symptoms) could be simply coincidental. There's no way of knowing, without a controlled clinical trial, what effect the treatment had on the outcome. The danger comes when this false security causes patients to forgo approved treatment that has shown real benefit.

Some unapproved cancer treatments not only have no proven benefits, they have actually been proven dangerous. These include Laetrile, which may cause cyanide poisoning and has been found ineffective in clinical trials, and coffee enemas, which, when used excessively, have killed patients. (See "Hope or Hoax? Unproven Cancer Treatments" in the March 1992 *FDA Consumer*.)

Ozone generators, which produce a toxic form of oxygen gas, have been touted as being able to cure AIDS. To date this is still unproven, and FDA considers ozone to be an unapproved drug and these generators to be unapproved medical devices. At least three deaths have been connected to the use of these generators. Four British citizens were indicted in 1991 for selling fraudulent ozone generators in the United States. Two of the defendants fled to Great Britain, but the other two pleaded guilty and served time in U.S. federal prisons.

The bottom line in deciding whether a certain treatment you've read or heard about might be right for you: Talk to your doctor. And keep in mind the old adage: If it sounds too good to be true, it probably is. ■

*Isadora B. Stehlin is a staff writer for FDA Consumer.*

# Questions about treatment for HIV disease?

**Call the *HIV/AIDS Treatment Information Service* for federally approved treatment guidelines and information. (All calls are completely confidential)**

The HIV/AIDS Treatment Information Service provides timely, accurate treatment information on HIV and AIDS. The service was developed through a coordinated Public Health Service\* effort and is offered through the CDC National AIDS Clearinghouse.

The HIV/AIDS Treatment Information Service is a free telephone reference service for:

- ◆ People with HIV disease, their families and friends
- ◆ Health care providers

The service is staffed by information specialists who answer questions using the National Library of Medicine database of HIV/AIDS treatment information. This database is also available to the public— free of charge—by computer link.

## Services

- ◆ Answers to questions about treatment of HIV disease
- ◆ Copies of federally approved HIV/AIDS treatment guidelines and information
- ◆ Bilingual reference specialists, Spanish and English

## A link to HIV/AIDS treatment information resources

The staff is working with many different HIV/AIDS information services to build a comprehensive treatment information referral network. This network will be used to link callers to appropriate information resources.

**HIV/AIDS** TREATMENT  
INFORMATION  
SERVICE  
**1-800-HIV-0440**

### Call:

**800-HIV-0440**  
**(800-448-0440)**

TDD/Deaf Access:  
800-243-7012

Monday - Friday  
9:00 am to 7:00 pm, EST

All calls are completely  
confidential.

### Write:

P.O. Box 6303,  
Rockville, MD 20849-6303  
Fax: 301-738-6616

\*Public Health Service Coordinating Group: Agency for Health Care Policy and Research, Centers for Disease Control and Prevention, Health Resources and Services Administration, Indian Health Service, National Institutes of Health, Substance Abuse and Mental Health Services Administration.