

Appendix K

Federal Programs Dedicated to Pharmaceutical R&D¹

As indicated in the text and summarized in table K-1, the Federal Government maintains 13 targeted drug research and development (R&D) programs. Eleven of these programs focus on drug discovery and testing, and two are devoted solely to clinical R&D. All but one, an antimalarial program run by the U.S. Walter Reed Army Medical Center, are located within the U.S. Department of Health and Human Services in its National Institutes of Health (NIH). This appendix describes the mission and organization of each program.

■ Targeted Drug Discovery Programs

Cancer Development Therapeutics Program

Located within the National Cancer Institute's (NCI) Division of Cancer Treatment, the Developmental Therapeutics Program (DTP) uses both intramural and extramural funding to discover and develop new anticancer and anti-human immunodeficiency virus (HIV) agents. Under its current organization, DTP includes: 1) the Laboratory of Drug Discovery Research and Development for the expeditious development of agents given high priority in the treatment of cancer or HIV infection; 2) the Drug Synthesis and Chemistry Branch which acquires, screens, and evaluates the therapeutic potential of new compounds provided by outside researchers including pharmaceutical firms; and 3) an extramural program that supports preclinical drug discovery and development.

Biological Response Modifiers Programs

Begun in 1972, the Biological Response Modifiers Program supports intramural and extramural research (including some clinical investigation) on agents or

approaches that alter the relationship between a tumor and the "host" patient by modifying the host's biological response to tumor cells in order to realize therapeutic benefits. In recent years, this program has included among the research it supports the development of new approaches to modify the body's response to HIV.

National Sickle Cell Disease Program

This program seeks to develop pharmacological agents that prevent or decrease the "sickling" of red blood cells in order to improve the quality and duration of life for persons afflicted with sickle cell disease. Because sickle cell disease is a hereditary disorder at the molecular level, research supported by this program over the past 20 years has attempted to use the developing tools of "rational drug development." In particular, laboratory investigation has focused on understanding the biochemical actions that underlie the disease and molecules observed to inhibit those actions. One particular approach, genetic modifiers that increase hemoglobin in the fetus, has moved close to clinical trials to determine efficacy.

Lung Surfactant Replacement Program

A component of the National Heart, Lung, and Blood Institute's (NHLBI) Specialized Center of Research Program, "Respiratory Disorders in Infants and Children," this drug development program has sought new therapies since 1979 for respiratory distress syndrome (RDS), a breathing disorder that affects about 40,000 infants per year in the United States. Caused by a deficiency in surfactant, a substance produced within the lung during the final trimester of pregnancy, research within the program has produced a number of synthetic surfactants as well

¹Unless otherwise noted, the information on these programs were provided by the relevant agency (167,271,343).

Table K-1—Federal Targeted Pharmaceutical Development Programs

| Program | Agency | Component | Year begun | Fiscal year 1989 budget (\$ thousands) |
|--|-----------------|--|-------------------|---|
| Cancer Developmental Therapeutics | | | | |
| Program..... | NIH (DHHS) | NCI | | |
| Cancer Therapy Evaluation Program..... | NIH (DHHS) | NCI | 1955 ^a | \$305,101 ^b |
| Biological Response Modifiers Program..... | NIH (DHHS) | NCI | 1975 | |
| National Sickle Cell Disease Program..... | NIH (DHHS) | NHLBI | 1972 | 742 |
| Lung Surfactant Replacement Program..... | NIH (DHHS) | NHLBI | 1979 | 1,506 |
| National AIDS Drug Discovery Groups..... | NIH (DHHS) | NIAID | 1987 | 18,908 |
| Antimicrobial Chemistry Program..... | NIH (DHHS) | NIAID | 1981 | 3,493 |
| Antiviral Research Program (Non-AIDS).. | NIH (DHHS) | NIAID | 1969 | 9,722 |
| Anticonvulsant Drug Development | | | | |
| Program..... | NIH (DHHS) | NINDS | 1968 | 4,188 |
| Contraceptive Development Program..... | NIH (DHHS) | NICHD | 1971 | 13,833 |
| Drug Abuse Medications Development | | | | |
| Division..... | NIH (DHHS) | NIDA | 1972 | 30,216 |
| Antimalarial Experimental | | | | |
| Therapeutics Program..... | U.S. Army (DOD) | Walter Reed Army Institute of Research | 1963 | 1,900 |
| Total..... | | | | 389,609 |

a "Cancer therapies" programs began in 1955. No separate dates given for Cancer Developmental Therapeutics Program and Cancer Therapy Evaluation Program.

b All three NCI programs combined.

KEY: ADAMHA = Alcohol, Drug Abuse and Mental Health Administration; DHHS = U.S. Department of Health and Human Services; DOD = U.S. Department of Defense; NCI = National Cancer Institute; NHLBI = National Heart, Lung and Blood Institute; NIAID = National Institute of Allergy and Infectious Diseases; NICHD = National Institute of Child Health and Human Development; NIDA = National Institute on Drug Abuse; NIH = National Institutes of Health; NINDS = National Institutes of Neurological Disorders and Stroke.

SOURCE: Office of Technology Assessment, 1993.

as some derived from animals. NHLBI research has included testing of these compounds in both the laboratory and in humans through regular extramural grants and contracts as well as special grants to small businesses.

National Cooperative Drug Discovery Groups-AIDS

The National Institute of Allergy and Infectious Diseases (NIAID) set up its National Cooperative Drug Discovery Groups on Acquired Immune Deficiency Syndrome (NCDDG-AIDS) in order to promote collaboration among academic, industrial, and governmental scientists to increase the speed with which new and better AIDS treatments are discovered and developed. Although physically not centered in a single location, each NCDDG brings together three to seven senior scientists who represent expertise in different disciplines. As of February 1991, NIAID had established 34 NCDDGs with scientists drawn from 46

academic or nonprofit institutions and 27 for-profit firms. While some of the groups focus on HIV itself, others target their efforts toward treating opportunistic infections (OIs) to which people with HIV are susceptible and which represent the major causes of illness and death in this patient population.

These groups, which only conduct preclinical R&D, are part of a larger, coordinated effort within NIAID and other NIH institutes intended to bring about therapeutic developments in the treatment of HIV more rapidly than would otherwise occur.² NIAID has two clinical AIDS drug programs that are described in greater detail in the section below on Federal clinical drug R&D.

Antimicrobial Chemistry Program and the Non-AIDS Antiviral Research Program

NIAID has established these two research programs to develop new treatments for *viral* infections (other than HIV). Because viruses are parasitic organisms

² A recent report of the Institute of Medicine, *The AIDS Research Program of the National Institutes of Health (208)*, describes the continuum of HIV research efforts within the NIH in much greater detail.

that exist within cells and whose replication is closely tied to that of the host cell, most antiviral agents have profound toxic effects on the host cell. While the Antimicrobial Chemistry Program focuses only on drug discovery and preclinical evaluation (including an intramural program to screen compounds submitted by researchers outside the government as well as research support for designing and testing new compounds), the Antiviral Research Program includes both laboratory and clinical R&D. Among the recent clinical trials supported by the Antiviral Research Program are a Phase I/II dose-response study of the drug ganciclovir in treating congenital cytomegalovirus infections in babies with central nervous system symptoms, and a Phase I/II study of acyclovir as a treatment for neonatal herpes simplex infections in infants in whom the disease is limited to the skin, eye and mouth.

Anticonvulsant Drug Development Program

The National Institute of Neurological Disorders and Stroke's (NINDS) Anticonvulsant (or Antiepileptic) Drug Development (ADD) Program supports both preclinical and clinical investigations into new therapies for the treatment of seizures in the hopes of finding drugs that are more effective and less toxic than existing interventions. In addition to supporting intramural and extramural research, the ADD Program serves as a clearinghouse for R&D efforts aimed at treating seizure disorders. It monitors worldwide patents on potential compounds, maintains regular contacts with pharmaceutical firms doing central nervous system (CNS) research, and facilitates collaborative arrangements between NINDS and commercial suppliers to evaluate potential compounds for anticonvulsant activity. NINDS and an *ad hoc* advisory committee meet to determine NINDS priorities for promoting the development of promising compounds.

Contraceptive Development Program

Since 1971, the National Institute of Child Health and Human Development (NICHD) has provided support largely through contracts (currently at about \$1.3 million per year) for a Contraceptive Development Program to discover, develop, and clinically evaluate new potential pharmaceuticals. Included among the possible contraceptive strategies researched are drugs that block the production of viable ova (eggs) in women or spermatozoa in men or drugs that interfere in the ability of ova and spermatozoa to undergo

fertilization. This latter strategy includes spermicides for use in the female reproductive tract. Among the pharmaceutical approaches to contraception pursued by the NICHD are drugs that block the action of gonadotropin-releasing hormone (GnRH), which is necessary for the functioning of both the testis and the ovary. Development of contraception within this program may also provide advances in the treatment of diseases such as precocious puberty, endometriosis, and certain cancers that stem from improper GnRH activity.

Drug Abuse Medications Development Program

Although the National Institute on Drug Abuse (NIDA) has supported research for the development of medications to treat substance abuse since 1972, the current incarnation of the Drug Abuse Medications Development Program received its authorization from Congress in the Anti-Drug Abuse Act of 1988 (Public Law 100-690). The program draws a distinction between drugs to treat opiate and cocaine addiction, although NIDA indicates the distinction may be somewhat artificial for several reasons: 1) some opiate compounds have shown promise in treating cocaine addiction; 2) co-addiction to both types of substances is not uncommon; and 3) many potential medications may be useful in treating both types of dependence. As mentioned earlier in Chapter 9, a major justification for Federal support of this program cited by NIDA has been the historical reluctance of pharmaceutical firms to invest in R&D for medications to treat drug abuse. In fiscal year 1989, this program funded \$22.8 million in R&D, about two-thirds designated for narcotics dependence and one-third for cocaine. Of the total, about \$16.5 million was for clinical investigations.

Antimalarial Experimental Therapeutics Program

Since the early 1960s, when U.S. military personnel stationed in Southeast Asia became infected with strains of malaria resistant to existing treatments, the U.S. Army's Walter Reed Army Research Institute has supported antimalarial research in its Division of Experimental Therapeutics (272). With an increase in the number of Americans traveling and living in parts of the world where such malarias are common, the public health need for new drugs has increased while pharmaceutical company interest in antimalarial R&D has remained historically minimal. The Walter Reed

Program maintains an in-house capability to study the malaria parasite itself, to discover, develop, and evaluate new compounds, and to develop collaborative agreements with other public organizations such as the World Health Organization (WHO) and private pharmaceutical firms for clinical testing and potential marketing successful compounds.

Among potential malarial treatments attributable to the program are: 1) mefloquine, 2) halofantrine, 3) artemisinin, and 4) a compound currently known as WR238605. Mefloquine was developed jointly by Walter Reed, WHO, and Hoffman-LaRoche, Inc., and was recently approved for U.S. marketing by the U.S. Food and Drug Administration (FDA). Halofantrine is a potential prophylactic jointly developed by Walter Reed and SmithKline Beecham that may be effective in parts of the world where malarias are proven resistant to mefloquine and is currently undergoing studies of chronic toxicity. Artemisinin is a drug based on traditional Chinese medicine and is in the early stages of development in cooperation with WHO as a treatment for severe forms of malaria. WR238605 will soon go into Phase I clinical testing as a replacement for the drug primaquine in treating malaria and possible *Pneumocystis carinii* pneumonia (PCP), a common opportunistic infection in HIV patients.

Pharmacological Research in the National Institute of General Medical Sciences (NIGMS)

Because NIGMS's sole research mission is to support work "the sciences basic to medicine" (rather than to focus on a particular disease or organ system), it plays a unique role among agencies in the Federal Government supporting basic biomedical investigation. It "helps supply new knowledge, theories, and concepts" that can then be used in disease-specific research undertaken by other parts of NIH³ (477). A large part of this fundamental scientific research portfolio is relevant to pharmaceutical R&D.

Among the institute's activities is the Pharmaceutical Sciences Program, which is charged with supporting "research and research training leading to increased understanding of the interactions of drugs with living systems in order to produce new, safer, and more efficacious therapeutic agents." While the program's work is interdisciplinary, drawing on the fields of genetics, molecular biology, chemistry, computer

science, and more traditional pharmacological investigation, most grants given by the Pharmaceutical Sciences Program are in three areas: anesthesiology, pharmacology, or bio-related chemistry (486a). The Pharmaceutical Sciences Program's extramural research budget totaled just under \$86 million in fiscal year 1989, representing 15 percent of the institute's total extramural research funds,

■ Clinical Evaluation Programs

NCI's Cancer Therapy Evaluation Program

NCI is one of two NIH institutes that maintains targeted drug development programs focused solely on clinical testing. NCI's Cancer Therapy Evaluation Program is responsible for funding and coordinating most extramural trials within the NCI's Division of Cancer Therapy, including those involving anticancer and anti-HIV pharmaceuticals. Through a network of clinical cooperative groups the program's Investigational Drug Branch sponsors trials to determine the efficacy and toxicity of new investigational drugs and maintains close contact with the pharmaceutical industry to promote efficient, coordinated drug development.

The program also maintains a Regulatory Affairs Branch that has responsibility for preparing and submitting investigational new drug (IND) applications to the FDA for human trials (particularly for those drugs lacking a commercial sponsor to fulfill that function). The Branch also cooperates with pharmaceutical companies in providing data and other information needed for a pharmaceutical firm to receive approval of new drug applications (NDAs).

NIAID's AIDS Clinical Trials Groups Program and the Community AIDS Program

Begun in 1986, the NIAID's AIDS Clinical Trials Groups (ACTGs) involves active trials of drugs at every stage of clinical development at many research sites around the country (208). Because of the intense scrutiny of ACTG trial protocols by patient groups, trials are designed through a process of consensus coordinated by NIAID and involving NIAID staff, AIDS advocates, and the potential investigators. Data collection at multiple sites is similarly coordinated with the help of an NIAID research contract.

³NIGMS is also charged with supporting doctoral and postdoctoral training toward the same ends and coordinates many of the NIH-administered training programs outlined in chapter 9.

A more recent initiative within NIAID is the Community Programs for Clinical Research on AIDS (CPCRA), launched in 1989 in an attempt to involve a greater number and broader cross-section of people with AIDS in the clinical research process than was the case with the ACTGs alone. According to NIAID comments to the trade press at the time the program was begun, CPCRA also differs from the ACTG program in that while “many of the [ACTG] trials have clinical endpoints (e.g., development of opportunistic infection or death) and require stringent

monitoring of immune responses to experimental drugs, CPCRA endpoints will include ‘indications of drug efficacy that are relevant to and easily obtainable in the day-to-day practice of medicine’ and which do not require the “sophisticated viral or cell-culturing capability or technically intense monitoring of typical ACTG studies” (375). In fiscal year 1990, CPCRA awarded \$9 million to 18 community-based projects in 14 cities, leaving another \$3 million to support statistical analysis and administrative coordination of the trials.