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THE WHITE HOUSE

WASHINGTON

November 24, 1993

MEMORANDUM

TO: Victor Zanona

FROM: Kristine M. Gebbie, R.N., M.N. W. Steve Lee for
National AIDS Policy Coordinator

SUBJECT: Drug Development Task Force

Time to ACT

Where many forums

Over the past several months, representatives of the Department of Health and Human Services (DHHS) have participated in forums with academicians, AIDS advocacy groups, and the pharmaceutical industry on AIDS research improvement. Out of those sessions have come several ideas on public-private partnerships for information sharing and research that can speed the pace of discovery in our effort to stop the spread of HIV. The establishment of this new Drug Development Task Force is one example of the type of improvement anticipated by many of us.

By bringing together those conducting research on drugs to combat HIV infection from the pharmaceutical industry, the academic community, individuals with HIV infection and those advocating on their behalf, and key agencies of the federal government, DHHS formalizes channels of communication among the partners who must be involved to successfully bring new drugs into use. Working together, these partners can identify barriers to quick action or clear communication, and can act in common to eliminate those barriers.

The mere creation of a new committee does not halt an epidemic, and if this new group were allowed to become a mere bureaucratic space-filler, it could even become counter-productive. I am confident, however, that neither of those things will occur. Instead, the steadily strengthening collaboration among all parties concerned about AIDS gives me great confidence that this is one more important step toward our collective goal of stopping AIDS.

Roy Vagelos - Chairman/CEO Merck & Co.

Wall St. Jrnl.; 11-30-93

AIDS Panel to Slice Regulatory Red Tape

B6

By Marilyn Chase
Staff Reporter of The Wall Street Journal

On the eve of World AIDS Day, the Clinton administration is proposing to remedy the drought in new AIDS drugs by forming a task force to remove roadblocks that impede companies from moving new drugs from the test-tube through testing and into the marketplace.

Secretary of Health and Human Services Donna Shalala will announce today a new federal task force on AIDS drug development combining the National Institutes of Health and the Food and Drug Administration, with corporations and the communities hardest-hit by the epidemic.

"It is time to refocus . . . our best minds for a concerted attack on this killer," Dr. Shalala says in remarks prepared for delivery today. About one million U.S. citizens are infected with the human immunodeficiency virus that causes AIDS, or acquired immune deficiency syndrome. Another 340,000 people have already contracted the disease, of which 200,000 have died. World AIDS Day, tomorrow, is an annual global observation designed to take stock of the epidemic's inexorable progress and society's response to it.

Dr. Kessler's Fast Track

Dr. Shalala said she'll solicit nominations to the 15-member National Task Force on AIDS Drug Development over the next 30 days. While the committee's makeup isn't yet known, **Merck** & Co.'s Chairman and Chief Executive Officer P. Roy Vagelos – who has championed drug industry collaboration in AIDS drug development – is joining a list of backers at a news conference to be held today at the National Institutes of Health.

The move is greeted gingerly by AIDS activists. "I'm wary, but one can only hope," said New York playwright and AIDS activist Larry Kramer.

Led by HHS Assistant Secretary for Health Philip R. Lee, the task force is said to be the brainchild of FDA Comissioner David Kessler, who has long striven to cut regulatory red tape and speed approval of promising AIDS drugs.

But despite Dr. Kessler's fast track to market approval, Dr. Shalala notes there is a dearth of new drugs now emerging from the development pipeline and into the regulatory home stretch.

Filling the Pipeline

"The sad fact remains that not a single New Drug Application for an [AIDS antiviral drug] is currently before the FDA," she says in her prepared address. "No matter how much we shorten the pipeline, we cannot achieve our goal unless we start filling that pipeline with promising compounds."

Federal health officials have quietly floated the proposal for the so-called National Task Force on AIDS Drug Development before a number of AIDS activists in recent days – to mixed reviews.

"The burden will be on government to show this committee has teeth," said Martin Delaney of Project Inform. A panel of the prestigious Institute of Medicine has had an identical mission for four years, he noted adding the new initiative "doesn't warrant applause just because they're creating [another] committee. We need substance and action."

Dr. Shalala insists the new body won't simply add to the trail of passionate AIDS reports consigned to oblivion. "Let me be clear: This is not just another government panel appointed to study an issue and write a report that gathers dust," she says.

But there's no guarantee the task force will succeed in cutting through regulatory, proprietary, and financial roadblocks which discourage or delay companies from undertaking costly, high-risk drug development against the elusive AIDS virus.

"FDA doesn't have resources to do what it's charged to do," Mr. Delaney complained. Dr. Kessler's activism from the atop FDA sometimes seems slowed by conservative staff scientists within the agency, he added.

Complex research and development agreements, squabbles over who gets credit for a discovery, and government pressure on industry to restrain prices, further chill corporate involvement in the AIDS drug market, Mr. Delaney said.

'Where Are the Drugs?'

Even more daunted than larger and richer drug companies, small biotechnology companies may now risk scarce capital to develop a new AIDS therapy in cooperation with one federal agency, only to find their efforts hamstrung by another agency, he added.

"They've been sending mixed signals," Mr. Delaney said. "At least this committee will enable different agencies to work from a common deck."

For Mark Harrington, a member of the New York-based Treatment Action Group, the only question is: "Where are the drugs?" After 12 years of the epidemic, AIDS treatment has progressed little beyond AZT made by Wellcome PLC, and its sister drugs, DDI from Bristol-Myers Squibb Co. and DDC from Roche Holding Ltd.

"We've gotten a generation of drugs out, and quality of life has improved," Mr. Harrington said, "but [AIDS] is still a fatal disease."

Edward Scolnick = Merck Research Labs

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HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Tuesday, Nov. 30, 1993

Contact: Victor Zonana
(202) 690-6343

HHS Secretary Donna E. Shalala today announced the formation of a National Task Force on AIDS Drug Development to expedite the search for new therapies against AIDS and the underlying human immunodeficiency virus (HIV).

The expert panel will be highly focused, seeking new and innovative approaches to the development of AIDS drugs.

"The task force has a clear and critical mission: to identify, and remove, any barriers or obstacles to developing effective treatments," Shalala said.

The 15-member panel will be drawn from government, the pharmaceutical industry, academia, medicine and the AIDS-affected communities. "This represents unprecedented high-level collaboration among leaders in the field," Shalala said.

"It is time to refocus and re-energize our best minds for a concerted attack on this killer," Shalala said.

"None of us can guarantee success," Shalala added. "HIV is a vicious and cunning adversary. But history will judge us harshly if we fail to give it our best shot."

Shalala was joined at the announcement by Assistant Secretary for Health Dr. Philip Lee, who will chair the panel; Dr. P. Roy Vagelos, chairman and chief executive officer of Merck & Co. Inc.; Kristine M. Gebbie, national AIDS policy coordinator; and Moises

- More -

Agosto, research and treatment advocacy manager at the National Minority AIDS Council.

Also attending the National Institutes of Health press conference were Dr. David Kessler, commissioner of food and drugs; Dr. Harold Varmus, newly sworn in as director of the National Institutes of Health; and Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases.

"The FDA has made great strides in streamlining the approval process for drugs to treat life-threatening conditions, and the NIH has contributed mightily to our understanding of AIDS and HIV," Shalala said.

"In addition, the Clinton administration and Congress have raised the NIH AIDS research budget 21 percent this year, to $1.3 billion," she added.

"But the sad fact remains that not a single New Drug Application for an antiretroviral drug is currently before the FDA. No matter how much we shorten the pipeline, we cannot achieve our goal unless we start filling that pipeline with promising compounds," Shalala said.

At least one million U.S. citizens are infected with HIV. Some 340,000 have been reported to the CDC with full-blown AIDS, and over 200,000 have died.

"Unfortunately, none of the drugs we have today are curative," Dr. Lee said.

"The task force, which will be appointed by and report to the secretary, will bring together many of the top people in the field.

It will raise the level and intensity of collaboration," Dr. Lee continued.

"The group we envision will be constantly evaluating the process -- identifying obstacles, charting strategy, and asking: 'What are our options? Is anything falling through the cracks? Are we doing everything we possibly can?'" Lee said.

"We're not just talking about antivirals," Dr. Lee added. "We need an across-the-board strategy to develop drugs to treat all aspects of HIV disease. We need immune modulators, anticancer compounds, and agents to treat and prevent opportunitic infections."

"The Centers for Disease Control and Prevention inform me that AIDS and HIV, on average, kill 92 people in this country every day," Shalala said. "With so many people being held hostage by this virus, we must explore all possible options."

Shalala said she expects to begin receiving nominations for task force membership immediately.

Said Gebbie: "The mere creation of a new task force does not halt an epidemic, and if this new group were allowed to become a mere bureaucratic space-filler, it could even become counterproductive. I am confident, however, that neither of these things will occur."

Added Shalala: "This is is not just another government panel appointed to study an issue and write a report that gathers dust.

"I expect the task force to report to me personally, rapidly and regularly, and I pledge to work with all its members to eliminate any obstacles to finding effective treatments," she said.

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FOR RELEASE UPON DELIVERY
TUESDAY, NOVEMBER 30, 1993

*REMARKS BY

DONNA E. SHALALA

SECRETARY OF HEALTH AND HUMAN SERVICES

PRESS CONFERENCE/NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

BETHESDA, MARYLAND

*THIS TEXT IS THE BASIS OF SECRETARY SHALALA'S ORAL REMARKS. IT SHOULD BE USED WITH THE UNDERSTANDING THAT SOME MATERIAL MAY BE ADDED OR OMITTED DURING PRESENTATION.

GOOD MORNING:

Last week, HHS employees gathered in the Great Hall of the Hubert Humphrey Building to unveil 32 panels from the Names Project AIDS Memorial Quilt.

Today, we gather again -- not to remember the dead, but to fight for the living.

We are here to take a major step toward one of our most important national goals -- the development of effective drugs for the epidemic known as AIDS.

For twelve years, we have lived with a disease that robs us of our future.

AIDS kills our sons and daughters; our husbands and wives; our mothers and fathers; our friends, lovers and loved ones.

The CDC maintains the grim tally: In this country, HIV and AIDS kill 92 people a day, on average. That's right: one AIDS-related death every 15 minutes.

AIDS also kills something in each of us.

It kills our belief that the future will be better than the past.

It kills our hope that our children will lead full and secure lives.

It kills our dreams that we can leave behind a better world.

But we must not despair.

AIDS has not killed our resolve.

AIDS has not killed our determination.

AIDS has not killed our conviction that our collective will, energy and imagination can bring forth a solution.

The Clinton Administration and the Congress have earmarked considerable new resources toward the quest for a cure. For research alone, we've increased the NIH AIDS budget 21% this year, to $1.3 billion.

It is now time to refocus and re-energize our best minds for a concerted attack on this killer. We must lock arms and move forward.

The National Task Force on AIDS Drug Development, which I am announcing today, has a clear and critical mission: to identify, and remove, any barriers or obstacles to developing effective treatment. It will make certain that all possible productive avenues are pursued with vigor.

The members of the task force will be drawn from government, the pharmaceutical industry, academia, medicine and the AIDS-affected communities.

This represents an unprecedented high-level collaboration among leaders in the field.

I'm especially pleased to be joined for this announcement by Dr. P. Roy Vagelos of Merck and Moises Agosto of the National Minority AIDS Council, who in a moment will share their perspectives on this undertaking.

The FDA, represented by its commissioner Dr. David Kessler, has made great strides in streamlining the approval mechanism for drugs against life-threatening conditions.

The NIH, represented by its new leader Dr. Harold Varmus and by N.I.A.I.D. director Dr. Tony Fauci, has contributed mightily to our understanding of HIV and AIDS.

But the sad fact today is that not a single New Drug Application for an anti-retroviral agent awaits FDA approval.

No matter how much we shorten the pipeline, we cannot achieve our goal unless we start filling that pipeline with promising compounds. That is the purpose of the new panel.

I expect to begin receiving nominations for the task force immediately and to name its members promptly.

Let me be clear: This is not just another government panel appointed to study an issue and write a report that gathers dust.

I expect the task force to report to me personally, rapidly and regularly, and I pledge to work with all its members to achieve our objectives.

None of us can guarantee success. HIV is a vicious and cunning adversary. But history will judge us harshly if we fail to give it our best shot.

Now, I'd like to introduce the person I've selected to chair this important task force.

Dr. Phil Lee, the assistant for secretary for health, is one of the greats of public health. He brings to this task force both a comprehensive knowledge of the pharmaceutical industry and a thorough understanding of the complexities of AIDS.

Before joining government, Dr. Lee served as policy coordinator for the Center for AIDS Prevention Studies at UCSF; was chair of the Policy Committee at the American Foundation for AIDS Research; and served as President of San Francisco's Health Commission during four critical years of the epidemic.

Phil will summarize the responsibilities of the task force for you:

REMARKS

PHILIP R. LEE, M.D.

ASSISTANT SECRETARY FOR HEALTH

ADMINISTRATOR OF THE U.S. PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PRESS CONFERENCE ANNOUNCING

THE TASK FORCE ON AIDS DRUG DEVELOPMENT

NOVEMBER 30, 1993

BETHESDA, MARYLAND

Attached is the text prepared for delivery; however, some material may have been added or omitted at the time of delivery.

Thank you. Over the years a number of innovative and creative approaches have been introduced to advance our progress in the search for effective drugs to treat HIV infection and HIV related diseases. However, despite the advances that have been made, it is a fact that no cure has been found and the treatments available are limited in their effect. We can and must do better in developing new drugs needed for persons who are infected with HIV and those who have AIDS and making them available to those who need them.

The Secretary has established a Task Force on AIDS Drug Development to deal both comprehensively and expeditiously with the problem. This is a creative new approach to bring the public and private sectors together to solve one of our most difficult tasks in medicine and public health. As chair of the Task Force, I will do everything possible to assure success in the effort.

The Task Force will have the responsibility of ensuring that all aspects of AIDS drug development are effectively coordinated, that all appropriate avenues of research are pursued, and that all unnecessary barriers to the development of new molecules, new compounds, and new combinations to treat and control HIV infection and HIV-related disease. Every aspect of AIDS Drug Development – from drug discovery, selection of candidates for screening, early clinical development, data-sharing, to the clinical trial process – will come under scrutiny.

The Task Force will establish subcommittees or working groups of experts to take an intensive look at key issues and to return to the task force with specific recommendations. If the recommendations are adopted by the task force, the recommendations will be forwarded to the Secretary for review and implementation.

To continually evaluate strategies and tactics and to build consensus, collaboration is required. Full participation is needed between government agencies, industry, the medical community, academia, and individuals who are HIV infected, as well as those affected by the epidemic. Too often in the past needed links have been missing or relationships have been adversarial, resulting in unnecessary duplication of efforts or potential drugs not being developed and evaluated as rapidly as they might or utilized most effectively.

While working to remove the barriers, the Task Force will not scrap innovative and creative approaches used in the past. The Task Force will build on them. It will build on the innovations that have taken place at NIH. It will build on the regulatory initiatives implemented by the FDA. It will build on community-based efforts to improve the quality and direction of clinical research. And it will build on efforts to bring together people working to find effective treatments of AIDS and HIV-related disease.

From the start, the Task Force will seek input from numerous groups including the Institute of Medicine, the Future Direction of AIDS Research Project, and the many Federal Advisory Committees that have done ground-breaking work in AIDS drug development. Open collaboration and communication are essential to move forward.

The first meeting of the Task Force will be held this winter – or at the latest – in early spring. Over the next thirty days, nominations will be sought from the public as to who should serve. Public nominations will help create a task force that is composed of people with both competence and compassion and the diversity that is reflective of the epidemic.

The Task Force represents a very important step forward and I hope it may be a model for other issues. For the first time in the fight against HIV related disease, the United States will have a systematic over-arching effort to coordinate drug development to treat HIV infection and HIV-related diseases. The Task Force will serve as an example of how government and private leadership can be used to focus national resources on national problems. By working in partnership – the pharmaceutical industry, the not-for-profit sector, private citizens and the government can and will get results.

# # # # #

SELECTED ARTICLES ON HIV INFECTION AND AIDS

PHILIP R. LEE, M.D.
Assistant Secretary for Health
Department of Health and Human Services
Washington, DC

Peter S. Arno, Ph.D.; Douglas Shenson, M.D., M.P.H.; Naomi F. Siegel, M.S.PH; Pat Franks; and Philip E. Lee, M.D., "Economic and Policy Implications of Early Intervention in HIV Disease" JAMA, September 14, 1989-Vol 262, No. 11, pp. 1493-1498.

A.E. Benjamin and Philip R. Lee, "Public Policy, Federalism, and AIDS" Institute for Health Policy Studies, University of California, San Francisco, Death Studies, 12:573-595, 1988.

A.E. Benjamin, Philip R. Lee, and Sharon N. Solkowitz "Case Management of Persons with Acquired Immunodeficiency Syndrome in San Francisco" Health Care Financing Review 1988 Annual Supplement, pp. 69-74.

Anne A. Scitovsky, M.A.; Mary Cline; and Philip R. Lee, M.D. "Medical Care Costs of Patients with AIDS in San Francisco" JAMA, December 12, 1986-Vol 256, No. 22, pp. 3103-3106.

Peter S. Arno, Ph.D. and Philip R. Lee, M.D., Institute for Health Policy Studies, School of Medicine, University of California, San Francisco, CA, "The Federal Response to the AIDS Epidemic" Health Policy, 6 (1986), pp. 259-267.

PHILIP R. LEE, M.D.

Head of the U.S. Public Health Service
and Assistant Secretary for Health
Department of Health and Human Services

Department of Health and Human Services Assistant Secretary Philip Randolph Lee, M.D., leads the U.S. Public Health Service at a time when this country's major national issue is health care reform – how to promote the health of the public through health care reform, how to ensure universal access, how to ensure quality, how to contain rapidly rising costs and how to pay for it. The programs of the Public Health Service that Dr. Lee directs contribute to virtually all those objectives.

Dr. Lee was sworn in as HHS assistant secretary for health on July 2, 1993, after being nominated by President Clinton May 14, 1993, and confirmed by the Senate July 1, 1993.

Dr. Lee brings to his new post more than four decades of involvement in health care and public health policy.

Twenty-eight years ago (November 1965), Dr. Lee was sworn in as assistant secretary for health and scientific affairs under President Johnson. In his first two years as assistant secretary, from 1965 to 1967, Congress enacted more health legislation than all the previous Congresses put together. Not since that period has the public's health and health care reform been such a huge priority on the nation's agenda.

Among his activities as assistant secretary in the 1960s, Dr. Lee helped fashion health manpower, family planning, health care, consumer protection, environmental health and biomedical research policies.

Before his first appointment to the top Public Health Service role, Dr. Lee served as director of health services in the Agency for International Development. Prior to his government service, he was a staff member at the Palo Alto Medical Clinic in California, and before that a fellow at the Mayo Clinic and Bellevue Medical Center. Dr. Lee's clinical experience enhances his commitment to public health policy and improving both care and access to care.

Dr. Lee has served with distinction as director of the Institute of Health Policy Studies, School of Medicine, at the University of California, San Francisco, for the past 21 years. In these years, he has, as a colleague recently said, worked with and influenced *hundreds* of health care policymakers and researchers, many of whom name Dr. Lee as their mentor. Since 1969, Dr. Lee has been a professor of social medicine at UCSF.

Dr. Lee has frequently advised federal and state health groups, and served on numerous advisory boards and planning committees. In 1985, then-San Francisco Mayor Dianne Feinstein named him as the first president of the city's Health Commission, which was the governing body in the city/county health department that included public health, mental health and substance abuse services, as well as the San Francisco General Hospital (the major AIDS care facility in the city), and a 1,000-bed long-term care facility.

In 1986, when Congress set up the Physician Payment Review Commission to examine reimbursement of physicians under Medicare, Dr. Lee was named to head the commission. The commission worked closely with Congress and many physician groups, consumer groups and others in shaping the physician payment reform adopted by Congress in 1989. Dr. Lee resigned from the commission early this year after being asked by President Clinton to serve as assistant secretary for health.

Until 1993 and his confirmation as assistant secretary, Dr. Lee served on the board of trustees of several California-based organizations representing a variety of public interests: the Henry J. Kaiser Foundation, Jenifer Altman Foundation, World Institute on Disability, and the Glide Foundation of the Glide Memorial United Methodist Church. Also, from 1971 to 1979, Dr. Lee served on the Board of Trustees of the Carnegie Corporation of New York.

Dr. Lee was a member of the editorial boards of the health policy journal *Milbank Quarterly* and of the *Annals of Internal Medicine* until assuming his recent Public Health Service responsibilities.

The Public Health Service includes eight agencies that lead the world in health care for the underserved, in biomedical research, in food and drug safety and in disease control. These agencies are the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Agency for Toxic Substances and Disease Registry, the Health Resources and Services Administration, the Indian Health Service, the Substance Abuse and Mental Health Services Administration, and the Agency for Health Care Policy and Research.

Also located in the Office of the Assistant Secretary are the Office of the Surgeon General, the National Immunization Program Office, the Office of Population Affairs, the Office of Minority Health, the Office of Women's Health, the Office of Disease Prevention and Health Promotion, the Office of International Health and the National AIDS Program Office.

Dr. Lee also advises and assists HHS Secretary Donna Shalala on health policy and on all health-related activities of the department. He has played an active role in the health care reform task force.

Dr. Lee received an A.B. from Stanford University in 1945, an M.D. from Stanford in 1948, an M.S. from the University of Minnesota in 1955, and an honorary Sc.D. from MacMurray College in 1967.

Dr. Lee lives in Washington, D.C. His wife, Professor Carroll Estes, also of the University of California, is a world-recognized expert in aging and long-term care policy. Dr. Lee has five children, a stepdaughter and five grandchildren.

July 1993

FOOD AND DRUG ADMINISTRATION

AIDS DRUG DEVELOPMENT INITIATIVES

I. EXPANDED ACCESS AND ACCELERATED PROCEDURES

FDA has taken significant steps toward making experimental drugs for HIV/AIDS more widely available and has initiated expedited procedures to speed the review and approval of promising therapies for HIV/AIDS.

1. Expanded Access Mechanisms

Expanded access mechanisms are designed to make promising products available as early in the drug evaluation process as possible. Expanded access mechanisms include Treatment IND protocols and parallel track protocols. In addition, the ordinary development of drugs under an IND includes a variety of open studies that also provide access to drugs. To date, tens of thousands of people have received products under expanded access mechanisms.

- o Treatment INDs

  Final regulations were issued in May of 1987 establishing conditions under which promising new drugs and biologics that have not yet been approved or licensed may be made available to persons with serious or life-threatening illnesses. Treatment INDs have generally been granted when the product is well into the clinical testing phase or when all clinical trials have been completed, after the development of some reliable evidence that the product is effective. Nine Treatment IND protocols for promising AIDS-related products have been allowed to proceed since the Treatment IND regulations became effective.

- o Parallel Track

  The final PHS policy statement on the parallel track mechanism was published in the Federal Register on April 15, 1992. The purpose of the parallel track policy is to expand the availability of promising investigational drugs to those persons with AIDS and HIV-related diseases who are without satisfactory alternative therapy and who cannot participate in controlled clinical trials. Stavudine (d4T) was the first drug submitted for consideration under the parallel track policy. The protocol was allowed to proceed on October 5, 1992.

2. Expedited Procedures

- In 1987, FDA created a "AA" priority category to classify all applications for potential AIDS therapies to ensure that these products receive the highest priority in the review process.

- In October, 1988, FDA issued interim regulations designed to expedite marketing approval of new drugs intended for life-threatening and severely-debilitating diseases, by facilitating the clinical testing and evaluation processes. Under the expedited procedures, early consultation with FDA by drug manufacturers, with agreement on the proper design of clinical trials, can lead to phase 2 studies with adequate data to support approval. In some instances, then, the need for Phase 3 testing can be virtually eliminated.

- On December 11, 1992 FDA published the final rule to accelerate the approval of new drugs for serious and life-threatening diseases when the drug provides meaningful therapeutic benefit over existing products. Under these procedures FDA may approve drugs based on surrogate endpoints that reasonably predict that a drug provides clinical benefit. This clinical benefit is then confirmed through additional human studies that will be carried out after marketing approval. The accelerated approval approach provides for removal of the drug from the market if further studies do not confirm the clinical benefit of the therapy.

II. STATUS OF AIDS PRODUCTS UNDER REVIEW

As of September 30, 1993, FDA had received over 500 IND applications for more than 150 products to be used in the treatment of HIV/AIDS. Many of the ongoing clinical trials are using combinations of two or more agents.

III. APPROVED THERAPIES FOR AIDS OR AIDS-RELATED CONDITIONS

FDA has approved 14 applications for products to treat HIV/AIDS. Three drugs are to treat HIV infection and eleven are to treat HIV/AIDS-related illnesses. There are no antiretroviral new drug applications pending review at FDA.

- Zidovudine (formerly AZT) - the first drug to go through the "AA" priority review designation, approved March, 1987 to treat AIDS.

- Human Interferon alpha, approved November, 1988 for the treatment of Kaposi's Sarcoma, a cancer affecting many

persons with AIDS.

- **Aerosolized pentamidine**, approved June, 1989, for the prevention of Pneumocystis carinii pneumonia in immunocompromised patients.

- **Ganciclovir**, approved June 1989, for the treatment of cytomegalovirus retinitis, a sight-threatening opportunistic infection from AIDS.

- **Fluconazole**, approved January, 1990, for use in the treatment of candidiasis and cryptococcal meningitis which are fungal infections.

- **Erythropoietin**, approved December, 1990, for the treatment of zidovudine-related anemia.

- **Foscarnet**, approved September, 1991, for use in the treatment of cytomegalovirus retinal infections in persons with AIDS.

- **ddI (didanosine)**, approved October 1991, for the treatment of adult and pediatric patients (over 6 months of age) with advanced HIV infection who are intolerant of zidovudine therapy or who have demonstrated significant clinical or immunologic deterioration during zidovudine therapy.

- **ddC (zalcitabine)**, approved June 1992, 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.

- **Itraconazole**, approved September 1992, for the treatment of blastomycosis and histoplasmosis in immunocompromised and non-immunocompromised patients.

- **Atovaquone**, approved November 1992, for the treatment of mild to moderate PCP in patients who are intolerant of trimethoprim-sulfamethoxazole, the standard therapy.

- **Dronabinol**, approved December 1992, (supplemental application) for anorexia and weight loss associated with AIDS.

- **Rifabutin**, approved December 1992, for the prophylaxis of Mycobacterium avium complex, a severe infection that often afflicts AIDS patients.

- **Megestrol acetate**, approved September 1993, (supplemental application), for anorexia, cachexia, or an unexplained weight loss in patients with AIDS.

NATIONAL INSTITUTES OF HEALTH

AIDS DRUG DEVELOPMENT AND EVALUATION INITIATIVES

Drug Development

The clinical evaluation of drugs against HIV, HIV-associated opportunistic infections (OIs), and HIV-associated malignancies requires an active preclinical drug discovery and development program. The NIH supports two major approaches in the area of drug development, including screening and rational (targeted) drug programs. The screening approach involves the testing of natural and synthetic compounds for anti-HIV activity. Rational (targeted) drug development involves characterization and delineation of the structural biology of HIV for the purpose of developing agents targeted to inhibit specific steps in the HIV life cycle. These programs have resulted in the discovery and development of AZT, ddI, ddC, d4T, and recombinant soluble CD4.

During the past year, the National Cancer Institute (NCI)-sponsored Preclinical AIDS Drug Screening Program has approved six new drugs for Phase I clinical studies. Approximately 137,000 agents have been screened for anti-HIV activity to date through this program. A new panel of screening cell lines is being developed for screening agents for activity against HIV-related malignancies, in particular HIV-related lymphomas.

The National Cooperative Drug Discovery Groups (NCDDG) and the National Cooperative Drug Discovery Groups for the Treatment of the Opportunistic Infections Associated with AIDS (NCDDG-OI) have expanded efforts to discover and develop potential treatments for HIV infection and HIV-associated OIs. The Targeted Antiviral Program provides extramural investigators with access to sophisticated techniques, while a similar program has been established for NIH intramural scientists through the Intramural AIDS Targeted Antiviral Program.

Planned programs:

- continue to screen, discover, develop, and preclinically test novel therapeutic agents that demonstrate activity against retroviruses, HIV-associated malignancies, and TB;
- bring the most promising new drugs into clinical testing;
- expand the development and validation of *in vitro* and animal model testing systems for evaluation of combination therapeutic agents;
- develop *in vitro* systems to evaluate novel combination therapies to overcome single drug resistance;

- develop therapies and interventions to prevent maternal-fetal transmission;
- perform preclinical testing of immune-based therapies in combination with traditional antiretroviral therapies; and
- delineate the crucial issues in advancing gene therapy into clinical trials.

Drug Development and Evaluation of Agents to Treat Opportunistic Infections

The NIH, through its intramural and extramural programs, has developed a multifaceted approach for the discovery, development, and preclinical and clinical evaluation of anti-OI drugs. Priority is placed on the identification of effective agents where established therapies do not exist and on the evaluation of new agents with the potential to improve efficacy or reduce toxicities of existing treatment or prophylactic regimens. OIs represent the most common cause of morbidity and mortality of HIV-infected patients. Approximately 26 percent of the current National Institute of Allergy and Infectious Diseases (NIAID)-funded AIDS Clinical Trials Group (ACTG) protocols are evaluating anti-OI therapies. There are 11 active OI protocols in the Community Programs for Clinical Research on AIDS (CPCRA). The increasing incidence of TB in HIV-infected populations is a public health priority. (A separate report has been prepared describing the NIH planned research activities on tuberculosis.)

The priority scheme for both preclinical and clinical activities associated with OIs is as follows:

Level 1 Priority	*Mycobacterium tuberculosis* *Mycobacterium avium* complex (MAC) Multiple Opportunistic Pathogens Prophylaxis Study (MOPPS) *Cryptosporidium*, Microsporidia, and other infectious causes of wasting
Level 2 Priority	Cytomegalovirus *Toxoplasma gondii* *Pneumocystis carinii*
Level 3 Priority	Pathogenic fungi (*Cryptococcus*, *Histoplasma*, and Candida)
Level 4 Priority	Other viral opportunists, other selected endemic mycoses, and serious bacterial infections.

Changes in Developing Agents for Treating Opportunistic Infections

Biomedical research on opportunistic infections (OIs) is challenged by the limited knowledge of the basic biology and natural history of these micro-organisms; the need for *in vitro* culture systems for susceptibility testing and biochemical studies; the lack of targeted screens or rational design of new agents; the need for optimization of animal models for testing treatment and prophylactic regimens; the need for evaluation of drug combinations for efficacy and safety, drug interactions, pharmacology, and immunotoxicology; and the relatively low level of interest shown by pharmaceutical manufacturers in the development of anti-OIs.

Planned activities:

- target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs;
- intensify basic biological studies on OIs;
- improve anti-OI drug evaluation methods such as rapid susceptibility testing, animal models, and outcome assessments;
- develop and standardize rapid diagnostic assays for OIs; and
- development valid animal and *in vitro* models of OIs for use in evaluating potential therapeutic agents administered singly and in combination.

Specific preclinical and clinical projects planned for each of the prioritized OIs are as follows:

MAC - discover and develop improved therapeutic modalities; determine the correlation between mycobacteremia and tissue organ burden; characterize the natural history of infection; and determine the optimal timing for treatment and prophylaxis assessing selected drug combinations.

MOPPS - including *Mycobacterium avium, Pneumocystis carinii,* the pathogenic fungi, *Cryptosporidium*) - establish the methods and procedures for evaluating the compatibility and effectiveness of agents (e.g., fluconazole, itraconazole, atovaquone, rifabutin, dapsone, TMP/SMX, ganciclovir, clarithromycin, and azithromycin) likely to be used in combination; assess drug resistance development; and initiate prophylaxis studies on multiple opportunistic pathogens.

Infectious Causes of Wasting Syndrome - identify and develop effective treatments (e.g., paromomycin, letrazuril and albendazole) for *Cryptosporidium*, Microsporidia, and other infectious causes of this syndrome; and develop *in vitro* and *in vivo* models for evaluation of drugs.

Cytomegalovirus - evaluate new, improved therapies (e.g., atovaquone, oral ganciclovir, and foscarnet) singly and in combination for the prevention and suppression of CMV infection including CMV retinitis and CMV colitis.

Toxoplasma gondii - establish an animal model for encephalitis; focus drug discovery efforts on the *Toxoplasma* bradyzoite; identify effective therapies including azithromycin + pyrimethamine, atovaquone + new macrolides for the prevention and treatment of toxoplasmosis.

Pneumocystis carinii - further define the biology and natural history of this infection; support targeted projects in drug discovery; develop new diagnostic techniques; and support prophylaxis and treatment trials with new approaches.

Pathogenic Fungi - identify diverse fungal targets for development of antifungal agents; optimize therapies for the treatment and prophylaxis regimens including evaluation of fluconazole, amphotericin B, and clotrimazole; monitor development of drug resistance; and optimize treatment strategies for cryptococcal meningitis.

Other Opportunistic Infections - Continue ongoing research efforts with other opportunistic micro-organisms; and initiate treatment and prophylaxis studies of selected opportunistic micro-organisms, such as viruses, bacteria, mycoplasma, and endemic mycoses.

Clinical Trials

The NIH has the primary responsibility for the federally supported clinical trial efforts to evaluate potential therapies for the treatment of HIV infection and its sequelae. These trials are conducted at 57 AIDS Clinical Trials Units (ACTUs) supported by the NIAID-funded ACTG (including 22 NIAID-funded Pediatric ACTUs), 17 NIAID-funded CPCRAs, 50 Division of AIDS Treatment Research Initiative (DATRI) sites, 28 NICHD-funded sites, and 3 NIH Intramural sites. Over 40,000 patients have been enrolled in these studies, which have involved the evaluation of more than 70 agents.

Accomplishments in NIH-sponsored clinical trials include demonstration of the efficacy and clinical benefits of AZT for adults and children with early and asymptomatic infection; the benefits of ddI resulting in expanded approval for patients who have been on AZT for prolonged periods of time; the benefits of interferon-alpha for reducing Kaposi's sarcoma lesions; early evidence of the benefits of nimodipine for the treatment of AIDS dementia complex; and the therapeutic benefits of ddC plus AZT combination therapy and FDA approval of the regimen. ddI and d4T have been made available through expanded access programs.

Accomplishments in combating HIV-associated OIs include demonstration of the efficacy of atovaquone (566C80) for treatment of *Pneumocystis carinii* pneumonia (PCP) in patients seriously intolerant of trimethoprim-sulfamethoxazole (TMP-SMX); TMP-SMX for prophylaxis of recurrent PCP; aerosolized pentamidine for prophylaxis and treatment of PCP; fluconazole for the treatment of cryptococcal meningitis; foscarnet for the treatment of CMV retinitis; IV gamma globulin for reducing OIs in HIV-infected children with CD4 + counts >200/mm3; early evidence on the combination of pyrimethamine and clindamycin for toxoplasmic encephalitis; and itraconazole for disseminated histoplasmosis.

Planned Clinical trials:

- evaluate multi-drug regimens, tat antagonists, reverse transcriptase inhibitors, protease inhibitors, potential immune-based therapies, passive immunotherapy, and chemotherapeutic agents against HIV-associated malignancies;
- evaluate interventions targeted at acute/early infection with the goal of building the infrastructure for primary infection intervention trials;
- evaluate potential therapies for treating and preventing CNS impairment and AIDS dementia complex (ADC);
- evaluate agents against the HIV-related wasting syndrome;
- evaluate novel therapies, upon their availability, to block maternal-fetal transmission; and
- identify, develop, and validate surrogate markers for demonstration of efficacy of therapeutic agents.

Participation of Under-represented Populations

The participation of specific populations in NIH-funded clinical trials reflects the changing demographics of HIV infection, an illness initially affecting homosexual and bisexual men but currently appearing with increasing incidence in women, children, adolescents, IDUs, and minority populations. Ongoing efforts within the ACTG are designed to assure participation of under-served and underrepresented populations in NIH-funded clinical trials. Other efforts to increase the participation of these populations include implementation of the CPCRA, which has dramatically increased NIAID's enrollment of underrepresented minorities and women in HIV therapeutic trials; establishment of Women's Health Committees within the ACTG and CPCRA organizations; provision of supplements to the ACTG for outreach activities toward these populations; addition of four minority institutions as fully functional ACTUs; implementation of institutional evaluations of ACTG and CPCRA sites to ensure participation of underrepresented populations; establishment of community advisory boards for each ACTG and CPCRA site. In addition, the recent recompetition of the ACTG adult and pediatric units required plans for enrollment representative of the population served by the applicant institution.

Planned initiatives:

- increase participation of urban poor, minorities, women, children, adolescents, IDUs, and rural residents in clinical trials.

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Deliver To: Victor Zanona

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____ Kristine Gebbie, RN, MN, National AIDS Policy Coordinator

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✓ Steve Lee

Number of Pages: 1 + Cover Fax Number: 690 6247 Date: 11/24

Message:

Victor- If you need anything else, please contact me directly.

Steve

DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
Washington, D.C. 20201

November 17, 1993

NOTE TO PARTICIPANTS, DRUG DEVELOPMENT MEETING:

This is to put in writing the steps discussed between now and Nov. 30:

1) Reschedule participants. Participants should convene at NIH by 9:30 a.m. Tuesday to go over the materials and format. Please notify Zonana of confirmed resched for your principal. Secure approriate room for pre-brief (Flavin).

2) OMB approval must be secured. Avis may want to raise this with the Deputy Secretary or Chief of Staff.

3) Draft statements for Secretary (Overview of the need for and purpose of the task force -- Sorian, Zonana), Dr. Lee (Overview on what the Task Force will do and how -- Wykoff, Davis), Gebbie (overview on Clinton Administration commitment and how the Task Force fits in to a bigger strategy -- Gurrola) due to Victor Zonana Monday Nov. 22, c.o.b. (Fax-690-6247) (Review of draft statements by industry and community reps is TBD.)

4) Press release (Zonana) will go into clearance by early next week.

5) Fact Sheet on Clinton Administration and AIDS (Zonana) will go into clearance by early next week.

6) Fact Sheet on PHS actions to date supporting drug development and approval (Wykoff, O'Hara with Flavin) will be supplied to DA Henderson for transmittal to Zonana as early as possible next week.

7) Briefing for Secretary (Henderson, Wykoff, w/Gardett) due Wednesday noon, Nov. 24.

8) Daybook (Gardett) by Wed, Nov. 24, with reminder calls (ASPA, FDA, NIH) Monday.

9) Prepare for satellite interviews or other video (Becker).

Victor Zonana Victor Zonana